

# **Vail Health Hospital Policies & Procedures for Human Subjects Research Protection**

**Institutional Review Board  
Human Research Protection Program**

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# 1. Mission

Vail Health Hospital (“VHH”) fosters a research environment that promotes respect for the rights and welfare of individuals recruited for or participating in research conducted by or under the auspices of VHH. All human research conducted under the auspices of VHH will be guided by: the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (often referred to as the “*Belmont Report*”); and will be performed in accordance with the Department of Health and Human Services (“DHHS”) policies and regulations at 45 CFR 46 (also known as the “Common Rule”), and also the Food and Drug Administration (“FDA”) policies and regulations at 21 CFR 50 and 21 CFR 56. The foregoing Principles emphasize factors such as respect for persons, beneficence and justice. All research conducted under the auspices of VHH will also conform to all other applicable federal, state, and local laws and regulations.

In order to effectively conduct research, VHH maintains a Human Research Protection Program (IRB), which reviews research protocols involving human subjects and evaluates both the risk to and protection of those subjects.

The mission of the IRB is to:

- safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected
- determine and certify that all projects reviewed by the IRB conform to the policies and procedures set forth in this document, including all applicable regulations regarding the health, welfare, safety, rights, and privileges of human subjects
- safeguard patient privacy and protection of personal health information
- provide timely and high quality education, review and monitoring of human research projects
- facilitate excellence in research involving human participants

The purpose of the IRB that will achieve the following policies and procedures is to:

- establish a formal process to monitor, evaluate and continually improve the protection of human research participants
- dedicate resources sufficient to do so
- exercise oversight of research protection
- educate investigators and research staff about their ethical responsibility to protect research participants
- assist the investigators in complying with federal and state regulations
- allow for intervention in research and for a direct response to concerns of research participants

## 1.1. Introduction

The *VHH Policies and Procedures for Human Subjects Research Protection* details not only the policies and regulations governing research with human subjects, but also the requirements for submitting research proposals for review by the IRB. These policies and procedures apply to all research involving human subjects at VHH entities as applicable.

VHH IRB is guided by the ethical principles regarding all research involving humans, as set forth in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, (*National Commissions for the Protection of Human Subjects of Biomedical and Behavioral Research*, April 1979) (or “Belmont Report”).

All institutional and non-institutional performance sites for VHH IRB approved research are obligated to conform to the ethical principles as may be determined by VHH, the IRB or the DHHS Secretary.



## 1.2. Ethical Principles: The Belmont Report

It is the duty of the IRB to review and make decisions on all protocols for research involving human subjects. The twofold principal responsibilities of the IRB include (1) the protection of research subjects from undue risk, and (2) protection of research subjects from deprivation of personal rights and dignity. This protection is best assured by consideration of three Principles as set forth in the Belmont Report, the touchstones for ethical research are:

- Voluntary participation by the subjects through free and informed consent, is assured;
- Appropriate balance exists between the potential benefits of the research to the subject or to society and the risks assumed by the subject; and
- There are unbiased and fair procedures in place in the selection of research subjects.

**These principles maintain Respect for Persons, Beneficence, and Justice.**

### ***Respect for Persons: Voluntary Participation and Informed Consent***

One of the most important elements in any research involving human research subjects is the assurance of voluntary, informed consent. Any person who is to be a research subject, whether designed for the person's own direct benefit or for the advancement of scientific knowledge in general, must understand, as completely as possible, what the study entails and the potential risks to the individual and benefits of the study to the individual or society as a whole. The person must give consent freely, without pressure or inappropriate inducement. The IRB strives to ensure voluntary, informed consent of research subjects through a careful review of the recruitment and consent process, and a thorough review of the details of the consent form and accompanying information sheets.

The need for voluntary, informed consent includes those studies in which the subjects are not able to give personal consent for themselves. In this situation, the consent document is presented to those who have been designated responsible for the research subject's wellbeing (e.g. parent of a child). The IRB's role is to verify that the consent process and all documents accompanying the consent form are likely to assist those responsible for such persons in making an informed decision as to the best interests of the research subject. The capacity for truly informed and voluntary participation in research varies widely among study populations. At one extreme, there may be ample understanding and manifest freedom from coercion; at the other, there may be degrees of understanding and freedom that affect the consent of potential subjects. The IRB must exercise special care when considering subjects whose ability to give free and informed consent may be compromised in any way.

### ***Beneficence: The Risk-Benefit Ratio***

The IRB maintains decisional authority, for any proposed activity that falls under its jurisdiction, whether:

"The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept (those) risks."

*(Federal Register, May 30, 1974)*

The assessment of the risk/benefit relation is a complex task. The potential risks include injury or discomfort to the individual that can be physical, psychological, financial or social. Conversely, there may be potential benefits to the individual, to a group to which the individual belongs or to society. During the review of applications, the IRB must carefully assess the types and degrees of both risks and benefits for a given subject population, as well as the investigator's communication of these risks and benefits to the subject in the consent process and consent form. While the IRB is not charged with

reviewing scientific design per se, it must occasionally do so in order to assess the risk/benefit ratio. If a study design seems inadequate in attainment of the stated aim of the investigation, then no benefit can be anticipated from conducting the study. Thus, there would be no justification for placing any research subject at risk, however minimal. Therefore, the design of the study must be sound, and the nature and likelihood of all risks and benefits must be made clear in any application to the IRB.

### ***Justice: The Fair Selection of Research Subjects***

Both the risks and the potential benefits of research should be spread fairly among potential research subjects and research subject groups. Study design and selection of subjects should avoid bias for or against any particular group based on such factors as gender, sexual orientation, socioeconomic status, immigration status, race, or social group.

### ***Sharing Research Risks***

The guiding Principle in the ethical selection of research subject groups is that any risks of the research should fall upon the groups who might benefit from the research. If the results of a risky protocol might benefit the general population, it would be unethical to focus subject recruitment on vulnerable or disadvantaged groups (e.g. institutionalized people or prisoners; patients at free clinics primarily patronized by people unable to afford other medical care) simply because this population is easily accessible or can be persuaded to participate. Further, an undue share of research risks should not burden groups already burdened by other factors. Rather, attempts will be made to include a fair sampling of the populations who might benefit from the study. When research involves persons whose autonomy is compromised, it is expected that the research bear some direct relationship to the conditions or circumstances of the research subject population. In addition, groups fully able to consider the research risks and informed consent process should be considered for selection in a study prior to involvement of the more vulnerable populations. For example, investigational drugs are typically tested in adults prior to being tested in children. Certain investigational drugs and procedures may be tested in healthy volunteers prior to being tested in patients.

### ***Sharing Research Benefits***

In recent years, increasing attention has been paid to the rights of various groups to be included in research. Through advocacy groups, many patients have come to insist on having access to experimental treatments, as these experimental treatments may potentially provide the best medical care available. In addition, researchers, ethicists and public officials have recognized that because many clinical trials focus primarily on white middle-class research subject groups, the results of certain trials were of questionable value for members of other social, racial, sexual, and ethnic groups. As a result, both the National Institutes of Health and the FDA now require that a study design include as broad a range of research subjects as feasible, and further that the data be analyzed to uncover responses that differ between groups. For example, where women of child-bearing potential, pregnant and nursing women were previously routinely excluded from new drug trials, it is now required that, whenever possible, these women be asked to make their own choices after being fully informed of the risks of the research.

## **2. Definitions**

### **Agent**

Agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

## **Certification**

The official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance

## **Clinical Investigation**

Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA, or need not meet the requirements for prior submission to the FDA, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

## **Common Rule**

The Common Rule refers to the “Federal Policy for the Protection of Human Subjects” adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

## **Engagement**

Institutions are considered to be engaged in a research project when the involvement of their employees or Agents in that project includes any of the following:

- Intervention for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
- Intervention for research purposes with any human subject of the research by manipulating the environment.
- Interaction for research purposes with any human subject of the research.
- Obtaining the informed consent of human subjects for the research.
- Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
  - observing or recording private behavior;
  - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.
- 

## **Generalizable Knowledge**

Generalizable knowledge means that (1) conclusions are drawn from particular instances, and (2) the information from the investigation is to be disseminated.

Activities that meet this definition may be funded or unfunded, or may be conducted as a component of another program not usually considered research. For example, demonstration and service programs may include evaluation components, which constitute research activities under this definition.

For the purposes of this policy, a “systematic investigation” is defined as a methodical planned inquiry to obtain or ascertain facts.

Research as defined by FDA regulations is any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under Section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these Sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. An experiment, as defined in 21 CFR 312, includes any use of a drug other than the use of a marketed (approved) drug in the course of medical practice, and as defined in 21 CFR 812, includes any activity that evaluates the safety or effectiveness of a medical device. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Research that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

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

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

### **Human Subject**

(as defined by DHHS regulations) a living individual about whom an investigator (whether professional or student) conducting research obtains:

- data through intervention\* or interaction\*\* with the individual, or
- identifiable\*\*\* private information

Human Subject as defined by FDA regulations:

An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. In the case of a medical device, a human subject/participant is also means a human on whose specimen an investigational device is used.

*\*Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.*

*\*\*Interaction includes communication or interpersonal contact between investigator and subject.*

*\*\*\*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 (for example, a medical record). Private information*

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

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### **Institutional Official (IO)**

The IO is responsible for ensuring that the IRB at the Organization has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance.

### **IRB**

An Institutional Review Board established in accord with and for the purposes expressed in this policy

### **IRB Approval**

The determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements

### **Letter of Support**

Letters of support must be printed on the facility's letterhead, signed by the site's administrator, and include the following:

- A statement that the site administrator has reviewed the research and has found it appropriate for the population of that facility;
- A statement allowing the investigator to conduct the research activities on site and if applicable, indicating there are appropriate resources available to conduct the research;
- Contact information for an individual who will represent the facility in matters related to the conduct of human subjects research; and
- A statement that based on the risks associated with the research, there are adequate provisions to effectively manage unanticipated problems and/or adverse events to minimize potential harm to research subjects.

### **Minimal Risk**

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests

### **Research**

(as defined by DHHS regulations)—a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

### **Research under the Auspices of the Organization**

Research under the auspices of the institution includes research conducted at VHH, conducted by or under the direction of any employee or agent of VHH (including students and fellows) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, or involving the use of this institution's non-public information to identify or contact human subjects.

## Test Article

Test articles covered under the FDA regulations include:

- **Human Drugs**  
the primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary: A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; A substance (other than food) intended to affect the structure or any function of the body; A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>
- **Medical Devices**  
A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>
- **Biological Products**  
include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.  
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>
- **Food Additives**  
In its broadest sense, a food additive is any substance added to food. Legally, the term refers to "any substance the intended use of which results or may reasonably be expected to result – directly or indirectly – in its becoming a component or otherwise affecting the characteristics of any food." This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food.
- **Color Additives**  
A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. <http://www.fda.gov/Food/FoodIngredientsPackaging/ucm094211.htm#foodadd>
- **Foods**  
including dietary supplements, that bear a nutrient content claim or a health claim
- **Infant Formulas**

## 3. Institutional Authority

The VHH Human Research Protection Program operates under the authority of the Organization policy "IRB Policies & Procedures for Human Subjects Research Protection IRB adopted by the VHH Board on September 16, 2016 as amended from time to time. As stated in that policy, the operating procedures in this document "...serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the IRB." The IRB Policy and these operating

procedures are made available to all IRB investigators and research staff and are posted on the IRB website (<https://VHH.boardeffect.com>).

The VHH Board designated the VHH President/CEO as the Institutional Official (“IO”) for carrying out VHH’s human research protections program.

The IO may delegate tasks and responsibilities to qualified person[s]. Further, the IRB Chair and Co-Chair with support from IRB Administrator have been delegated responsibility for administrative oversight of the individual components of the human research protection program.

The IRB has jurisdiction over all human subject research (as defined above) conducted under the auspices of VHH. Assurance of Compliance

VHH holds a Federal-wide Assurance (FWA). The FWA is an assurance of compliance with the federal regulations for the protection of human subjects in federally funded research. The FWA is also approved by OHRP, thereby permitting other departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects to rely upon the FWA for the research that they conduct or support. VHH IRB maintains these same standards for all human research regardless of funding status.

### **3.1. Regulatory Compliance**

The IRB is responsible for ensuring compliance with federal regulations, state law and institutional policies. All human subjects’ research at the IRB is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of IRB will also conform to all other applicable federal, state, and local laws and regulations.

The IRB voluntarily applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) only to the extent that they are compatible with FDA and DHHS regulations.

### **3.2. IRB Office**

The IRB Office reports directly to Chair or his or her designee and is supervised by the Chair or his or her designee. The Chair and his or her designee have expert knowledge in regulatory issues regarding human subjects, and further serves as the Human Protections Administrator. The Chair or his or her designee is the principal contact at VHH for the IRB Office. The IRB Director has day-to-day responsibilities for the operation of the IRB. This includes responding to inquiries with respect to human subjects’ research, as well as organizing and documenting the review process.

The IO works closely with the Chair of the IRB and the IRB Director in the development of policy and procedures. VHH employees staff the Office. The duties and responsibilities for all IRB staff are found in their respective job descriptions, and their performance is evaluated on an annual basis.

The criteria for selection of the IRB Chair and staff includes: (1) the requirement of a background in clinical research, (2) high-level organizational, analytical and administrative abilities, and (3) customer service-oriented skills. IRB staff report to the IRB Chair and the VHH President. On an annual basis, the IRB Chair and the VHH President or their designees meet with all staff members to review individual performance, identify need for supplemental education and to further professional development.

### 3.3. Colorado State Law

VHH and the IRB rely on legal counsel for the interpretation and application of Colorado State Law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. When there are any conflicts between federal or national law and other applicable laws, legal counsel will determine the appropriate resolution. All consent forms must be consistent with applicable state and local laws.

## 4. VHH Institutional Review Board

The VHH IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of this institution. The IO and the Chair of the IRB review the activity of the IRB on at least an annual basis.

### 4.1. Authority of the IRB

The IRB reviews and has the authority to approve, require modifications in, or disapprove all research activities conducted under the auspices of VHH. The IRB also has the authority to suspend, place restrictions on, or terminate approvals of research activities that fall within its jurisdiction that are not being conducted in accordance with IRB requirements, or that have been associated with unexpected harm or serious harm to subjects.

The IRB ensures that appropriate safeguards exist to protect the rights and welfare of research subjects [45 CFR 46.111]. In fulfilling these responsibilities, the IRB reviews all research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. Examples of IRB review documentation include, *inter alia*: protocols, consent/assent document(s) and, for studies conducted under the Investigational New Drug (“IND”) regulations, the investigator's brochure(s), tests, surveys, questionnaires and similar measures, and recruiting documents.

Before any human subject becomes involved in research at VHH, an IRB will properly consider:

- risks to the subject
- anticipated benefits to the subject and others
- importance of the knowledge that may reasonably be expected to result from the study
- informed consent process to be employed

The IRB has the authority to suspend, place restrictions upon, or terminate approval of research activities that fall within its jurisdiction that:

- are not being conducted in accordance with IRB requirements, or
- that have been associated with unexpected or serious harm to subjects

The IRB has the authority to observe (or delegate a third party to observe) the consent process and the research if the IRB deems this necessary.

### 4.2. Jurisdiction of the IRB

The IRB jurisdiction extends to all research (funded and unfunded) involving human subjects conducted at VHH, as well as research reviewed by the IRB conducted elsewhere, excluding research where involvement of human subjects falls within one or more exempt categories (see [Categories of Research Permissible for Exemption](#)).



If an IRB chair, member, or staff person believes the IRB to have been unduly influenced by any party, a confidential report shall be made to the IO. The IO will authorize the VHH Ethics and Compliance Officer to conduct an investigation, in addition to instituting corrective action to prevent additional occurrences.

### **4.3. IRB Relationships**

The IRB functions independently of, but in coordination with, other institutional regulatory committees. The IRB, however, makes independent determinations regarding approval or disapproval of a protocol based upon whether or not human subjects are adequately protected. The IRB retains review jurisdiction over all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that adopted the human subjects' regulations.

The VHH Compliance Officer, CEO, and Chair will meet as required in order to ensure that communication is maintained between the various compliance entities at VHH. The committee will act in an advisory capacity to monitor the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

Research previously reviewed and approved by the IRB may be subject to review and disapproval by officials of VHH. However, officials of VHH have no authority to approve research previously disapproved by the IRB.

#### ***Relationships with Other Institutions***

VHH may choose, on a case-by-case basis, to provide human research protection oversight for other institutions. In providing such oversight, a formal relationship must be established between VHH IRB and the institution through either a Cooperative Agreement or a Memorandum of Understanding. This relationship must be formalized prior to VHH IRB's acceptance of any human research proposals from the other institution.

In the conduct of cooperative research projects, VHH IRB acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects, and further for ensuring compliance with the applicable federal regulations. When a cooperative agreement exists, VHH IRB may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

When VHH IRB relies on another IRB, the IRB Chair or Vice Chair will review the policies and procedures of the IRB to ensure that they meet VHH IRB standards. If the other IRB is part of an accredited IRB, then it will be assumed that the VHH IRB standards are being met.

When VHH IRB reviews research conducted at an unaffiliated institution, the particular characteristics of the unaffiliated institution's local research context must be considered, either (1) through prior knowledge of the unaffiliated institution's local research context, or (2) through subsequent review by appropriate designated institutional officials, such as the Chairperson and/or other IRB members.

When an investigator plans to conduct research at sites external to VHH and the site's IRB plans to defer review to the VHH's IRB, arrangements must be made for the VHH's IRB to be the IRB of record for the project and arrangements must be made for communication between the IRB and the site.

When VHH is the coordinating center for a multi-center protocol, the IRB will require that VHH ensure that IRB approval has been obtained at each participating site prior to initiation of the research at that site. At the time of initial review, the IRB will assure that the procedures for dissemination of protocol

information to all participating sites are in place and followed. Assessment of protocol information includes, *inter alia*, unanticipated problems involving risks to participants, protocol modifications and interim findings.

## 4.4. Roles and Responsibilities

### ***Institutional Official***

The ultimate responsibility of the IRB resides with the VHH Board of Directors and the VHH President/CEO who serves as the Institutional Official (IO) of the program. The IO is responsible for ensuring the IRB has the resources and support necessary to comply with all institutional policies and with federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the IRB.

The IO also holds ultimate responsibility for oversight over the:

- Institutional Review Board (IRB); and
- conduct of research conducted by all IRB investigators;

### ***Institutional Review Board (IRB)***

The IO in accordance with directives of this Policy appoints IRB Members. The IRB prospectively reviews and makes decisions concerning all human research conducted at VHH facilities by its employees or agents, under its auspices. The IRB is responsible for the protection of rights and welfare of human research subjects at all VHH facilities. It discharges this duty by complying with the requirements of the Common Rule; state regulations, the FWA and institutional policies.

### ***Legal Counsel***

The IRB relies on the Legal Counsel for the interpretations and applications of Colorado State law and the laws of any other jurisdiction as needed.

### ***Chairperson of the IRB***

The IO will appoint a Chair and Vice Chair of the IRB to serve for renewable terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual at VHH who is fully capable of managing the IRB and the matters brought before it with fairness and impartiality. Moreover, the IRB Chair must be immune to pressure from the institution's administration, the investigators whose protocols are brought before him/ her, and other professional and nonprofessional sources.

The IRB Chair is responsible for conducting convened IRB meetings.

The IRB Chair may designate other IRB members to perform duties, as appropriate, for review, signature authority, and other IRB functions, e.g., the Vice Chair, Primary Reviewer.

The IRB Chair will advise the IO and the IRB Director about IRB member performance and competence.

The performance of the IRB Chair will be reviewed on an annual basis by the IRB Director in consultation with the IO. The IRB Director will convey formal feedback based on this evaluation of the Chair in writing with an opportunity to discuss in person. Should the determination be made that an IRB Chair (1) failed to act in accordance with the IRB's mission, (2) failed to follow the policies and

procedures set forth herein and in the federal rules and regulations, (3) has an undue number of absences, and/ or (4) failed to fulfill the designated responsibilities of the IRB Chair, he/ she will be removed by the IO.

Duties of Chair or designee may include:

- Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the IRB program
- advising the IO on matters regarding research at IRB
- implementing the institution's IRB policy
- assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations
- assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations
- the development and implementation of an educational plan for IRB members, staff and investigators
- submitting, implementing and maintaining an approved FWA through the IO, Vice President for Research and the Department of Health and Human Services Office of Human Research Protection (OHRP)
- managing the finances of the IRB
- Assisting investigators in their efforts to carry out Organization's research mission.
- developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program
- developing training requirements as required and as appropriate for investigators, subcommittee members and research staff, and ensuring that training is completed on a timely basis
- serving as the primary contact at IRB for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services and other federal regulatory agencies
- day-to-day responsibility for the operation of the IRB office, including supervision of IRB staff
- responding to questions
- working closely with the Chair of the IRB and on the development of policy and procedures, as well as organizing and documenting the review process

### ***Vice Chair(s) of the IRB***

A Vice Chair(s) serves as the Chair of the IRB in the absence of the Chair, and maintains the same qualifications, authority, and duties as the IRB Chair.

### ***Subcommittees of the IRB***

The IRB Chair, in coordination with the Vice Chair(s), may establish subcommittees consisting of one or more IRB members.

Duties of a subcommittee may include the following:

- Serve as designees by an IRB Chair for the expedited review of new or continuing protocols, and/ or modifications of continuing protocols. The subcommittee must be experienced (in terms of seniority on the IRB), and must be matched as closely as possible with their field of expertise to the study.
- Review and approve revisions of protocols previously given provisional approval ("Conditional Approval") by the convened IRB.
- Conduct an inquiry into allegations of non-compliance. The subcommittee is given a charge by the IRB, which can include any or all of the following:
  - review of protocol(s) in question
  - review of FDA audit report of the investigator, if appropriate
  - review of any relevant documentation, including, *inter alia*, consent documents, case report forms, and a subject's investigational and/ or medical files, as the documentation relates to the investigator's execution of her/ his study involving human subjects

- interview of appropriate personnel if necessary
  - preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting
  - recommend actions if appropriate
- Conduct on-site review. Determination of the review interval and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, an on-site review by an IRB subcommittee might occur in a particularly risky research study, or approval might be subject to an audit of study performance where an investigator recently had a protocol suspended by the IRB due to regulatory concerns.

### ***The Investigator***

The Investigator is the ultimate protector of the human subjects who participate in research. The Investigator is expected to abide by the highest ethical standards and for developing a protocol, which incorporates the principles of the Belmont Report. He/she is required to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process.

All subjects must give informed consent and the Investigator must establish and maintain an open line of communication with all research subjects within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the Investigator must comply with institutional and administrative requirements for conducting research. The Investigator is responsible for ensuring that all research staff completes appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the Investigator is responsible for providing written procedures for their storage, security, dispensing and disposal.

The IRB is responsible for ensuring that the Principal Investigator (PI) is qualified by training and experience to conduct the proposed research. In addition, the IRB is responsible for ensuring that the Principal Investigator has sufficient resources and facilities to conduct the proposed research. For each protocol submitted to the IRB for approval, the Investigator must certify that s/he accepts responsibility for assuring adherence to the federal and state regulations and institutional policies governing the protection of human subjects of research, including applicable institutional credentialing requirements.

### ***Relationship with VHH***

The IRB functions independently of (but in coordination with) other VHH regulatory committees. The IRB, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected. The IRB has review jurisdiction over all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that has adopted the human subject's regulations conducted under the auspices of VHH.

The IRB will ensure a dialogue is maintained between the various compliance entities at VHH.

VHH will monitor the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the IRB as needed.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of VHH. However, VHH officials may not approve human research that has not been approved by the IRB.

### ***Protocol-Specific Coordination***

The *Health Biological Medical Research Application*, which must be submitted for every new protocol, requires PIs to indicate institutional support required for the research, including as applicable:

- Laboratory
- Medicine
- Pharmacy
- Radiology
- Nuclear Medicine
- Nursing
- Psychiatry
- Outpatient
- Surgery
- Other

For any that are indicated, a letter of support or collaboration must be included and the relevant Department Representative or site administrator must sign the letter of support.

## **4.5. IRB Operations**

In addition to the leadership structure described above, other support staff members are listed below. The IRB Staff for VHH must comply with all ethical standards and practices.

### ***IRB Administrative Staff***

The IRB Administrative Staff report to the Chair or his or her designee, who has day-to-day oversight for their daily responsibilities.

The duties and responsibilities for all staff are located in their respective job descriptions and their performance is evaluated on an annual basis.

### ***Selection, Supervision and Evaluation of IRB Supporting Staff***

#### **Selection Process**

All IRB staff are selected by the IO according to these Policies and Procedures.

Depending on the position to be filled, qualification to be considered in the selection of IRB staff include prior experience in IRB administration or another position within an IRB (e.g., study ), or, at the assistant or clerical levels, a desire to learn and be an active participant in the regulatory, ethical, and procedural aspects that support an IRB.

#### **Supervision**

IRB staff are supervised by the IO or designee.

#### **Evaluation**

All IRB staff are evaluated on an annual basis consistent with these Policies and Procedures.

## **4.6. Resources for the IRB**

VHH provides resources to the IRB and IRB Office, including adequate meeting and office space, and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines (etc.) will be made available to the IRB and staff.

On an annual basis, the IO will review the activity, workload and resources of the IRB and the IRB Office with the Chair and will make a recommendation with regard to resources to the VHH Board. The resources provided for the IRB and IRB Office will be reviewed during the VHH annual budget review process.

#### **4.7. Conduct of Quality Assurance/Quality Improvement Activities for IRB Operations**

The Quality Assurance methods whereby the IRB processes, are reviewed and tracked internally, are described in *VHH Quality Assurance / Quality Improvement Plan*. The QA&I staff will conduct investigations and audits of ongoing research in the following instances: (1) when the IRB directs an audit be conducted, (2) when a complaint or allegation of non-compliance is received. (3) routine compliance audits of research.

### **5. IRB Membership**

The VHH IO, in coordination with the Institutional Review Board (“*IRB*”) and the IRB Chair, will identify and screen potential candidates for IRB membership. Candidates for appointment to the IRB may be proposed by IRB Members, Medical Staff Members, VHH administrative staff, the VHH Board of Directors (“*Board*”), or any interested party. Appointments to the IRB are made by the IO.

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, and specific community concerns, in addition to representation by multiple, diverse professions, knowledge and experience with vulnerable subjects, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is being reviewed. Every effort will be made to have member representation with an understanding of the areas of specialty that encompass most of the research reviewed by the IRB.

The IRB will include members who are knowledgeable about and experienced working with vulnerable populations.

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and possess the professional competence necessary to review specific research activities.

#### **5.1. Composition of the IRB**

The IRB will at all times consist of a minimum of five members (the “*Principal Members*”). There is no maximum number of members. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes.

In addition to possessing the professional competence necessary to review specific research activities, the IRB should be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.

Since the IRB may review research that involves a vulnerable category of subjects, including, for example, children, prisoners, pregnant women, and/or handicapped or mentally disabled persons, consideration is given to the inclusion of one or more individuals on the IRB who are knowledgeable about, and experienced in, working with vulnerable populations. When protocols involve vulnerable populations, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the IRB or as consultants.

Prior to IRB meetings, the IRB Chair or his or her designee shall review the agenda to ensure that the membership present for the meeting has the appropriate expertise and experience with any vulnerable populations that are included in the protocols being reviewed.

Every effort will be made to ensure that the IRB is diverse and does not consist entirely of only men or only women; however, no selection is made to the IRB on the basis of gender. The IRB shall not consist entirely of members of one profession. The IRB includes at least one member whose principal concerns are in scientific areas and at least one member whose principal concerns are in non-scientific areas. The IRB includes at least one member who is not otherwise affiliated with VHH and who is not part of the immediate family of a person who is affiliated with VHH. One member may satisfy more than one membership category.

The IO and a member of the VHH Board may be voting members of the IRB. On an ongoing basis, the IRB Chair and the IO will monitor the membership and composition of the IRB and make changes regarding the appointment of members in order to meet regulatory and organizational requirements. Proposed revisions to IRB membership will be made as needed.

Individuals with conflicts of interest or the appearance of conflicts of interest (“*Conflicts of Interest*”) are prohibited from voting in a protocol or carrying out day-to-day operations of the review process, when protocols are being reviewed, where there may be a Conflict of Interest. However, individuals with Conflicts of Interest may provide information to the IRB and attend IRB meetings as guests, when invited by the IRB Chair.

## **5.2. Appointment of Members to the IRB**

Appointments are made for one- to three-year periods of service and are renewable. No person may serve as a Member of the IRB for longer than seven consecutive years, unless a written exception is made by the IO, due to extraordinary circumstances. Any change in appointment, including reappointment or removal, requires written notification by the IO to the Member. Members may resign by written notification to the IO.

On an ongoing basis, the IRB Chair will monitor the membership and composition of the IRB and make recommendations on the appointment of members to the IO in order to meet regulatory and organizational requirements.

## **5.3. Alternate Members**

The appointment and function of alternate members is the same as that for Principal Members, and the alternate’s expertise and perspective should be comparable to those of the Principal Member. The role of the alternate member is to serve as a voting member of the IRB when a Principal Member is unavailable to attend a convened meeting. When an alternate member substitutes for a Principal Member, the alternate member will receive and review the same materials prior to the IRB meeting that the Principal Member received or would have received.

The IRB roster identifies the Principal Member(s) for whom each alternate member may substitute. The alternate member will not be counted as a voting member, unless a Principal Member is absent. The IRB minutes will document when an alternate member is substituting for a Principal Member.

#### **5.4. Use of Consultants (Outside Reviewers)**

When necessary, the IRB Chair or his or her designee may solicit individuals with competence in specialized areas to assist in the review of issues or protocols requiring scientific or scholarly expertise beyond, or in addition to, that available on the IRB. The need for an outside reviewer is determined in advance of the IRB meeting by the IRB Chair, or may be recommended by the primary reviewer. The IRB Chair or his or her designee will solicit an outside reviewer in consultation with the IO. The IRB Chair or his or her designee will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Written statements of outside reviewers will be kept in IRB records and filed with the relevant protocol. Key information provided by outside reviewers at convened meetings will be documented in the meeting minutes.

The IRB Chair or his or her designee reviews the conflict of interest policy for IRB members with consultant(s) (see Conflicts of Interest). The consultant(s) must confirm in writing that no Conflicts of Interest exist prior to review.

The consultant's findings will be presented to the IRB for consideration either in person, via telephone, or in writing. If in attendance, these individuals will provide consultation, but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full IRB) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular principal investigator and research protocol).

#### **5.5. Duties of IRB Members**

The agenda, submission materials, protocols, proposed informed consent forms, and other appropriate documents are distributed to members one week prior to the convened meetings at which the research is scheduled to be discussed. Members review the materials at least one week prior to the convened meeting in order to ensure full participation in the review of each proposed project. IRB members will treat the research proposals, protocols, and supporting data confidentially. All copies of the protocols and supporting data are returned to the IRB Chair or his or her designee at the conclusion of the review for document destruction.

#### **5.6. Attendance Requirements**

Members must attend a minimum of fifty percent (50%) of IRB meetings annually, and should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, that member should inform the IRB Chair or his or her designee in writing. If the inability to attend will be prolonged, a request for an alternate member to be assigned may be submitted to the IRB Chair or the IO. If an IRB member is to be absent for an extended period of time, he or she must notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the IRB. If the



member has a designated alternate (see Alternate Members), the alternate member can serve during the Principal Member's absence, provided that the IRB receives advance notice.

## **5.7. Training/Ongoing Education of Chair and IRB Members in Regulations and Procedures**

A vital component of a comprehensive human research protection program is an education program for the IRB Chairs and the IRB members. VHH is committed to providing training and an ongoing educational process for IRB members and the staff of the IRB office related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

### ***Orientation***

New IRB members and staff, including alternate members, will meet with the IRB Chair or his or her designee for a formal introduction to the IRB and members' responsibilities. At this session, the new members and staff will be given an IRB Handbook that includes:

- The Belmont Report
- VHH Policies and Procedures for the Protection of Human Subjects
- Federal regulations relevant to the IRB
- New members are required to complete the above education requirement prior to serving as a Reviewer.

### ***Education***

To ensure that oversight of human research is ethically grounded and that the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members and staff throughout their service on the IRB. Educational activities include, but are not limited to:

- NIH and/or CITI IRB Member Training
- in-service training at IRB meetings;
- training workshops;
- review of appropriate publications;
- identification and dissemination by the IRB Chair or his or her designee of new information that might affect the human research protection program, including emerging laws, regulations, policies, procedures, and ethical and scientific issues to IRB members via email, mail, or during IRB meetings; and
- unlimited access to the IRB Office resource library.

## **5.8. Liability Coverage for IRB Members**

Appropriate insurance coverage will be provided to any person authorized to act on behalf of the IRB, and any person who acts within the scope of their employment or authorized activity.

## 5.9. Review of IRB Member Performance

IRB Members' performance will be reviewed on an annual basis by the IRB Chair and the IRB Director utilizing the IRB Member Evaluation form. Members who are not acting in accordance with the IRB mission or policies and procedures, or IRB members who have an undue number of absences, will be subject to further review and recommendation for removal by the IRB Chair in consultation with the IRB Director and may be removed by the IO.

## 5.10. Reporting and Investigation of Allegations of Undue Influence

If an IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party; such party shall make a confidential report to the VHH Ethics and Compliance Officer who shall conduct a thorough investigation and ensure that corrective action will be taken to prevent additional occurrences, as needed.

# 6. IRB Records

The IRB must prepare and maintain adequate documentation of the IRB's activities including: copies of all items reviewed, including, but not limited to research proposals; investigators' brochures and recruitment materials; scientific evaluations (if any) that accompany the proposals; approved consent documents including DHHS-approved sample consent documents, if any; DHHS-approved protocols, if any; HIPAA Authorization documents, if separate from the informed sample consent documents; any proposed amendments and the IRB action on each amendment; reports of injuries to subjects and serious and unexpected adverse events; documentation of protocol violations, and documentation of non-compliance with applicable regulations.

IRB records must also include continuing review activities and copies of all correspondence between the IRB and investigators. Statements of significant new findings provided to subjects must be maintained with the related research proposal and, when reviewed at an IRB meeting, such statements must be documented in the minutes.

Documentation of verified exemptions consists of the reviewer's written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exemption category.

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; a description of action taken by the reviewer, and any determinations required by the regulations and protocol-specific findings supporting those determinations.

IRB records must document any determinations required by the regulations and protocol-specific findings supporting those determinations.

All records must be accessible for inspection and copying by authorized representatives of VHH the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

## 6.1. IRB Records

IRB records include, but are not limited to:

- Written operating procedures
- IRB membership rosters

- Training records, records listing research investigators, IRB members, and IRB staff that have fulfilled the facility's human subject training requirements.
- IRB correspondence (other than protocol related)
- IRB Study Files
- Documentation of Emergency Exemption from Prospective IRB Approval. (21 CFR 56.104(c))
- Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article ((21 CFR 50.23)
- Documentation of exemptions
- Documentation of convened IRB meetings minutes
- Documentation of review by another institution's IRB when appropriate
- Documentation of cooperative review agreements, e.g. Memoranda of Understanding (MOUs)
- Federal Wide Assurances
- Protocol violations submitted to the IRB
- Quality assurance reviews

Documentation for off-site IRBs include:

- On-line access to all applicable protocol documents
- MOU/Agreements of IRB Services
- Workflow/SOPs
- Notes/documents pertaining to administrative reviews

## 6.2. IRB Study Files

The IRB will maintain a separate IRB study file for each research application (protocol) that it receives for review. Protocols will be assigned a unique identification number by the IRB Administrative Staff and entered into the IRB tracking system.

Accurate records are maintained of all communications to and from the IRB. Copies are filed in the Principal Investigator's project file. The IRB maintains a separate file for each research protocol that includes, but is not limited to:

- Protocol and all other documents submitted as part of a new protocol application
- Protocol and all other documents submitted as part of a request for continuing review/termination of research application. This also includes progress reports, statements of significant new findings provided to participants, reports of injuries to patients
- Documents submitted and reviewed after the study has been approved, including reports of modifications to research/amendments and adverse event reports
- Copy of IRB-approved Consent Form
- DHHS-approved sample consent form document and protocol, when they exist
- IRB reviewer forms (when expedited review procedures are used) and scientific reviewer forms (where applicable)
- Documentation of type of IRB review
- For expedited review, documentation of any determinations required by the regulations and protocol-specific findings supporting those determinations, including:
  - waiver or alteration of the consent process
  - research involving pregnant women, fetuses, and neonates
  - research involving prisoners
  - research involving children
  - research involving persons with impaired cognitive function
- Documentation of all IRB review actions

- Notification of expiration of IRB approval to the Principal Investigator and instructions for submitting relevant continuing review materials
- Notification of suspension of research
- Correspondence pertaining to appeals
- Copies of approval letters and forms that describe what Principal Investigator must have before beginning the study
- IRB correspondence to and from research investigators
- All other IRB correspondence related to the research
- For devices, a report of prior investigations
- Reports of unanticipated problems involving risk to subjects or others and adverse events.

### **6.3. Minutes of an IRB Meeting**

Proceedings must be written and available for review by the next regularly scheduled IRB meeting date. After ratification of the minutes by the Board members, if it is determined that revisions/corrections are necessary, the Minutes will be amended and presented at the following IRB meeting.

Minutes of IRB meetings must contain sufficient detail to show:

- The basis for requiring changes in research
- The basis for disapproving research
- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document
- The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
- Attendance at the meetings, including documentation of those members or alternate members who are participating through videoconference or teleconference, including documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions
- Alternate members attending the meeting and for whom they are substituting
- Names of consultants present
- Name of investigators present
- Names of guests present
- The initial attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect those members present for the vote on that item
- Business items discussed
- Continuing education
- Actions taken by the IRB including those involving full review. The IRB must use the minutes to notify IRB members of actions taken through expedited review and those studies that have been determined to be exempt from IRB review
- Separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
- Documentation that the research meets each of the required criteria [45 CFR 46.116(d)] along with protocol-specific information containing justification as to why the IRB considers the research to meet each criterion when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent
- Documentation that the research meets each of the required criteria [45 CFR 46.117(c)] along with protocol-specific information justifying why the IRB considers the research to meet each criterion when the requirements for written documentation of consent are waived
- When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the IRB's protocol-specific justifications and findings regarding the determinations

stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms

- The vote on actions, including the number of members voting for, against, and abstaining. Number of those excused, Number of those recused
- Notations indicating an IRB member's conflicting interest with the research under review, as defined by VHH policy (see: [Conflicts of Interest](#))
- and further that the conflicted IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained)
- A written summary of the discussion of controversial issues and their resolution
- Review of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in IRB records
- For initial and continuing review, the frequency of continuing review of each proposal, as determined by the IRB, including identification of research that warrants review more often than annually and the basis for that determination
- Risk level of initial and continuing approved protocols
- Review of interim reports, e.g. unanticipated problems or safety reports; amendments; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.
- Review of Data and Safety Monitoring Board (DSMB) summary
- Review of Plans for Data and Safety Monitoring
- Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization
- Relevant information provided by consultants will be documented in the minutes or in a report provided by the consultant
- The rationale for significant risk/non-significant risk device determinations
- Determinations of conflict of interest management plans and that the IRB found it acceptable.
- Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research
- A list of research approved since the last meeting utilizing expedited review procedures

A copy of the IRB-approved minutes for each IRB meeting must be distributed to the IO and VHH Counsel upon ratification by the IRB.

## 6.4. Membership Rosters

A membership list of IRB members must be maintained and must identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list must contain the following information about members (IRB Membership Roster)

- Name
- Earned degrees
- Affiliated or non-affiliated status
- Status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist). For purposes of this roster, IRB members with research experience are designated as scientists. Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research.
- Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations
- Representative capacities of each IRB member; and naming the IRB members knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations locally involved in research
- Role within the IRB (Chair, Vice-Chair, etc.)
- Voting status (Any *ex officio* members are non-voting members)
- Alternate status, including the name of the member he/ she alternates with

- Relationship (e.g., employment) between the individual IRB member and the organization

The IRB Office must keep the IRB membership list current. The IRB Administrator must promptly report changes in IRB membership to the Office for Human Research Protections, DHHS.

## 6.5. Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's determination of a specific exemption category on the Checklist for Exempt Determination form and written concurrence that the activity described in the investigator's request for an exemption satisfies the conditions of the determined exemption category. The exempt determination is reported at the next convened IRB meeting and documented in the Minutes.

## 6.6. Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; that the activity described by the investigator satisfies all of the criteria for approval under expedited review (see: [Categories of Research Eligible for Expedited Review](#)); the approval period and any determinations required by the regulations including protocol-specific findings supporting those determinations. An Expedited Protocol Reviewer Checklist will be used by the Reviewer and documented in the IRB record. The approval letter for the expedited review will be reported at the next convened IRB meeting and documented in the Minutes.

## 6.7. Access to IRB Records

The IRB has policies and procedures to protect the confidentiality of research information:

- All IRB records are kept secure in locked filing cabinets or locked storage rooms. Doors to the IRB offices are closed and locked when the rooms are unattended
- Digital storage is maintained on password-protected secure hard disk drives conforming to the highest level of security available at any time
- Ordinarily, access to all IRB records is limited to the Director, IRB Chairs, IRB members, IRB Administrators, IRB staff, authorized institutional officials, and officials of Federal and state regulatory agencies (OHRP, FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access and may recommend additional procedures for maintaining security of IRB records. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and Chair.
- Records are accessible for inspection and copying by authorized representatives of Federal regulatory agencies during regular business hours
- Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested
- All other access to IRB study files is prohibited

## 6.8. Records Retention Requirements

The above-detailed records must be stored securely in the IRB Office and must be retained for at least three years.

Records pertaining to conducted research must be stored securely in the IRB Office and must be retained for at least three years after completion of the research. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least three years after closure.

All records must be accessible for inspection and copying by authorized representatives of the OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

Records are maintained in locked file cabinets and/or locked offices within the main IRB Office and are available only to those persons listed above.

Records associated with closed or terminated studies shall, after the three-year retention period expires, be electronically scanned and thereafter shredded or otherwise destroyed.

## 6.9. Written Policies and Procedures

This document details the policies and regulations governing research with human subjects, and further set forth the requirements for submitting research proposals for review by VHH. These procedures and guidelines apply to all research involving human subjects, regardless of sponsorship and performance site, conducted under the auspices of VHH.

These Policies and Procedures are frequently updated. The IRB Director will keep the VHH research community apprised of any new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues. Such notification may be via electronic mail, displayed on the Vail Health website and via the IRB's web-based Newsletter. The policies and procedures will be available on the VHH website.

On at least an annual basis, IRB Chair, Vice-Chair, and IRB Director shall review existing Policies and Procedures to determine if updates and modifications are required. Upon identification of any modifications, recommendations are presented to the IRB membership and thereafter to the Institutional Official for their review and approval.

## 7. IRB Review Process

### 7.1. Human Subjects Research Determination

The IRB, IRB Chairperson or Chair designee determines whether an application submitted to the IRB is human subjects research that meets the definition of "research", "human subject" and/or "clinical investigation" based on Federal regulatory definitions, 45 CFR 46.102(d), 45 CFR 46.102(f), 21 CFR 50.3(g), 21 CFR 56.102(e), 21 CFR 50.3(c), and 21 CFR 56.102(c). IRB Administration can assist investigators in determining whether or not research involves human subjects and is under the purview of the VHH IRB prior to submission of a research application.

All research determined to be human subjects research must apply protections for human participants as mandated by applicable laws and regulations, and standards set forth in federal, state and local laws and institutional policies. All proposed research activities must be submitted to the VHH IRB or relied upon IRB **prospectively** for review and approval. Investigators must obtain IRB approval prior to the commencement of any human subjects research activities. Conducting research without IRB approval can jeopardize the entire Human Subjects Protection Program at Vail Health and lead to serious penalties by federal authorities.

The VHH IRB utilizes the Office for Human Research Protections (OHRP) guidance entitled "Guidance on Engagement of Institutions in Human Subjects Research" to determine when the institution is engaged in human subjects research activities. The IRB staff will respond to investigators' formal

requests for determination of human subject research status in writing. A copy of the submitted materials and determination correspondence will be kept on file in the IRB Office.

## 7.2. Exempt Research

All research using human subjects must be approved by the IRB. However, certain categories of research (i.e., “exempt research”) do not require review and approval by the convened IRB. While Exempt research is subject to institutional review, it is reviewed, determined and approved by the IRB Chair, or designee of the Chair.

Reviewers will use the *Checklist for Exempt Determination* to determine and document whether or not the protocol meets the exemption criteria.

An exemption from IRB review does not equate to an exemption from the HIPAA requirement for authorization or waiver of authorization when the research involves a covered entity’s protected health information. Researchers who receive an exemption determination but whose research involves protected health information must still (1) submit a HIPAA authorization form (or a request for waiver of HIPAA authorization), or (2) if applicable, submit a HIPAA form for conducting research involving decedents’ information or research using a limited data set. Researchers who wish to review protected health information (e.g., medical records) to prepare a research protocol must submit the appropriate HIPAA form for IRB approval.

### ***Limitations on Research Subjects; Vulnerable Populations***

#### **Children**

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

#### **Prisoners**

Exemptions do NOT apply; IRB review is required.

### ***Categories of Research Permissible for Exemption***

The Exempt Reviewers are required to use the *Checklist for Exemption Determination* to make a determination that the research project is exempt from IRB review. Only the IRB Chair or designee of the Chair may deem a research project to be exempt from IRB review.

Research activities not regulated by the FDA (see: [FDA Exemptions](#)) in which the only involvement of human subjects will be in one or more of the following categories are exempt from federal regulations, but require IRB review.

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
  - research on regular and special education instructional strategies, or
  - Research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
  - information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and



- any disclosure of the human subjects' responses outside of the research setting could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
    - the human subjects are elected or appointed public officials or candidates for public office
    - Federal statute(s) require(s) that, without exception, the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter
  4. Research involving the collection or study of existing (reviewed materials existing at the time the research is proposed) data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
  5. Research and demonstration projects which are conducted by, or subject to, the approval of Federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
    - public benefit or service programs;
    - procedures for obtaining benefits or services under those programs;
    - possible changes in or alternatives to programs or procedures listed in the two bullet points above
    - possible changes in methods or levels of payment for benefits or services under those programs

Such projects must be conducted pursuant to specific federal statutory authority. There must be no statutory requirements for IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the funding agency.

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

### ***FDA Exemptions***

The following categories of clinical investigations are not regulated by DHHS or another federal agency and are exempt from the requirements of IRB review prior to commencement of the investigation:

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

### ***How to Submit an Exemption Application***

Any investigator submitting an IRB Application for Exemption Review must include in the application the following information:

- a summary of the research;

- a description of the research procedures;
- consent documents (if applicable);
- plan for privacy and confidentiality;
- plan for dissemination of findings;
- a copy of the proposal if the research is externally funded, and
- Expected date of completion date.

The exemption application must be signed and dated by the Principal Investigator.

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

To document the IRB reviewer's determination of the request for exempt research, he/she completes the Checklist for Exemption Determination Form. The IRB reviewer indicates whether the request for exemption was approved or denied, and if approved, the rationale for the determination and category under which it was permitted.

Exempt studies are communicated to the IRB and documented in the minutes at the next convened meeting after the approval of exemption.

The decision must be communicated in writing to the investigator and the IRB. Documentation must include the specific categories justifying the exemption.

Investigators will be given feedback as to the qualification of the application for exemption status via electronic mail. Upon the IRB's completion of the review, the IRB Administrator will inform the Principal Investigator of the results of the review via electronic mail.

### ***Additional Protections***

Although exempt research is not covered by the federal regulations, such research is not exempt from VHH policies on the responsible conduct of research or the ethical guidelines of the Belmont Report. The individual making the determination of exemption will use the *Checklist for Exemption Determination* to determine whether to require additional protections for subjects (including specifics of the informed consent procedures) in keeping with the guidelines of the Belmont Report.

## **7.3. Expedited Review of Research**

The IRB may use the expedited review procedure to review either or both of the following: (A) some or all of the research appearing on the categorical list below (see: [Categories of Research Eligible for Expedited Review](#)) and found by the reviewer(s) to involve no more than minimal risk, and/or (B) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in (i) the level of risks to subjects; (ii) the research design or methodology (e.g., an addition of a procedure which would increase risk to subjects); (iii) the number of subjects enrolled in the research (e.g., increases representing greater than 10%); (iv) the qualifications of the research team; (v) the facilities

available to support safe conduct of the research, or (vi) any other change in the research that would otherwise warrant review of the proposed changes by the convened IRB. Adding procedures that are not eligible for expedited review is not considered a minor change.

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more IRB reviewers designated by the Chair. The IRB Chair may also designate the IRB Vice Chair to assist the designees in review of Expedited reviews. The IRB Chair may appoint other designees from among the members of the IRB when a particular field of expertise is required for an expedited review. At the discretion of the reviewer, the reviewer(s) may forward expedited reviews to the IRB Chair or IRB Vice Chair when additional review is needed in order to evaluate minimal risk status and determine expedited status. IRB members eligible to conduct expedited review must have served on the IRB for at least three months.

When reviewing research under an expedited review procedure, the IRB Chair, or designees, should receive and review all documentation that would normally be submitted for a full-board review including the complete protocol, a Continuation review form summarizing the research to date (including modifications and adverse events), notes from the pre-screening conducted by the IRB Office staff, and the current consent documentation. The IRB Chair or designees shall determine the regulatory criteria for use of such a review procedure by using the Reviewers Checklist.

The Principal Investigator will indicate on the research application the specific category under which the investigator believes the research is eligible for expedited review. The reviewer(s) shall evaluate the Principal Investigator's request and determine whether the expedited review process is appropriate. If the research clearly qualifies for expedited review, the reviewer shall conduct the expedited review. If the research does not clearly qualify for expedited review, the reviewer shall refer the application to the IRB for full review at its next convened meeting

The reviewer(s) conducting the initial or continuing review will complete the appropriate *Reviewer Checklist* in order to determine whether the research meets the expedited procedure criteria and, if so, whether the research meets the regulatory criteria for approval. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the protocol will be placed on the next agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in [Review Process](#) and may exercise all of the authorities of the IRB but for disapproval of the research. A research activity may be disapproved only after full review is completed by the IRB Committee at a convened meeting.

Reviewers will indicate approval, required modifications or disapproval on the Reviewer Checklist and return it to the IRB Office,. If the reviewer marked the study for disapproval, the protocol will be reviewed by the full board at the next convened meeting. If modifications are required, the reviewer or IRB Staff will inform the investigator via electronic mail. If the modifications are minor, the reviewer(s) may determine if the investigator has sufficiently addressed the modifications. If the modifications are major and have been reviewed by the IRB Chair or IRB Vice Chair, the reviewer(s) may send the review back to the Chair or Vice Chair (s) for further review. Upon the discretion of the reviewer(s) and/or the IRB Chair or IRB Vice Chair, the protocol may be submitted to the IRB for full board review.

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

## Categories of Research Eligible for Expedited Review

[63 FR 60364-60367, November 9, 1998]

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

- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/ or subjects' responses would reasonably place them at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- The standard requirements for informed consent (or waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

Research Categories one (1) through seven (7) below pertain to both initial and continuing IRB review:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
  - research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. However, research on marketed drugs that significantly increase the risks or decrease the acceptability of the risks associated with the use of the drug is not eligible for expedited review.
  - research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared and/ or approved for marketing, and the medical device is being used in accordance with its cleared/ approved status.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
  - from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
  - from other adults and children, taking into consideration the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency in which blood samples will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
  - Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." [45 CFR 46.402(a)]
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples include, *inter alia*: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings, and (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical

devices are employed, such devices must be cleared and/ or approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples include, *inter alia*: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography, and (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual..

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).  
NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See [Categories of Research Permissible for Exemption](#) and [45 CFR 46 101(b)(4)]. This listing refers only to research that is not exempt.
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus groups, program evaluation, human factors evaluation, or quality assurance methodologies. Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.
8. Continuing review of research previously approved by the convened IRB as follows:
  - o a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions, and (iii) the research remains active only for long-term follow-up of subjects; or
  - o b. where no subjects have been enrolled and no additional risks have been identified, or
  - o c. where the remaining research activities are limited to data analysis.

*Note: for categories 8(a) and 8(b) the following applicability criteria apply: (1) the remaining activities must be minimal risk, (2) if identification of the subjects or their responses will reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal, and (3) the research may not be classified research. For category 8b the only applicability criterion is that the research may not be classified research.*

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

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

*Note: under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no*

*additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.*

If a research protocol has been initially approved through a full-board review procedure, the continuing review may not be performed under the expedited review procedure unless such protocol falls within the purview of categories 8 or 9, above. If the protocol was initially targeted for full board review but met the expedited review criteria outlined above, the reviewer(s) will document that an erroneous review had previously taken place and process the expedited review in accordance with this policy. The Principal Investigator will be notified of the change in status through electronic mail correspondence.

### ***How to Submit an Expedited Review***

The Principal Investigator should indicate on the *Research Application Form* the specific category under which the investigator believes the research is eligible for expedited review.

Investigators must submit a completed IRB *Research Application Form* and include the following documentation:

- a summary of the research;
- description of the research procedures;
- consent documents (if applicable);
- plan for privacy and confidentiality;
- plan for dissemination of findings;
- a copy of the proposal if the research is externally funded;
- a protocol;
- a current CV for each investigator listed on the study
- expected date of completion date, and
- any financial disclosure using the VHH *Conflict of Interest Disclosure Form*

The application must be signed and dated by the Principal Investigator.

### ***Informing the IRB***

All members of the IRB will be apprised of all expedited review approvals by means of the agenda for the next scheduled meeting. The expedited review approvals will be made available for any optional review at the request of any IRB member.

## **7.4. Convened IRB Meetings**

Except where an expedited review procedure is followed, the IRB must review proposed research at convened meetings (also known as "Full-Board meetings") at which a quorum is present.

### ***Schedule of IRB Meetings***

In general the IRB meets monthly. Meeting dates may be added as needed or changed due to holidays. The IRB meets on a regular basis throughout the year. The schedule for the IRB may vary due to holidays or lack of quorum. Special meetings may be called at any time by an IRB Chair and held via telephone conference.

### ***Quorum***

A quorum consists of a simple majority of the voting membership plus one, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate quorum is present before calling the meeting

to order. The IRB Chair will be responsible in ensuring that the IRB meetings remain appropriately convened.

Votes may only occur when a quorum is present. The IRB Chair or his or her designee takes note of arrivals and departures of all members to determine if a quorum is present. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated. All members present at a convened meeting have full voting rights, except in the case of a conflict of interest.

In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

While it is preferred that IRB members be physically present at the meeting, if physical presence is not possible, a member may be considered present if participation occurs via teleconference or videoconference. In such cases, the member must have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

### ***Pre-Meeting Distribution of Documents***

The location and time of each IRB meeting is set forth on the agenda cover sheet distributed to all IRB members.

The agenda, including all supporting documentation to be reviewed, are provided to IRB members approximately one week prior to each meeting. Updated information, such as revisions, may be distributed prior to a full Board meeting as needed.

### ***Meeting Procedures***

The IRB Chair, or Vice-Chair in the event that the IRB Chair is absent, will call the meeting to order, once it has been determined that a quorum is in place. The Chair or Vice-Chair will remind IRB members to recuse themselves from the discussion and vote where there is a conflict. The IRB will review and discuss the IRB Minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the Minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the Minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Primary and Secondary Reviewer present an overview of the research and lead the IRB through the completion of the regulatory criteria for approval in the *Institutional Review Board - Protocol Review/Initial Review* checklist.

All members present at a convened meeting have full voting rights, except in the case of a conflict of interest (see below) when the member is excused for that portion of the meeting when the item is under action. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB Chair or his or her designee to record the proceedings of the session. In addition, the IRB Chair or his or her designee is responsible for taking Minutes at each IRB meeting.

## **Guests**

At the discretion of the IRB, the Principal Investigator may be invited to the IRB meeting to answer questions about their proposed or ongoing research. The Principal Investigator may not be present for the discussion or vote on their research.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair. Guests may not speak unless requested by the IRB and must sign the IRB's *Confidentiality Agreement*. The IO, other VHH staff, consultants and legal counsel are not considered guests for purposes of this section.

## **Primary Reviewers**

The IRB Office staff assigns a primary and secondary for all protocols requiring initial full review, continuing full review and for all protocols requiring full review of modifications to previously approved research. When making reviewer assignments, IRB staff will assign a member or members of the IRB, and will take into consideration the vulnerable populations involved in the research and the scientific or scholarly expertise required to review the research. Such protocols will then be assigned to at least one IRB member who has the appropriate expertise. If the IRB Office staff cannot identify a primary reviewer with appropriate expertise, the IRB Chair or his or her designee will solicit consultants from the Institution or the community with competence in such specialized areas to assist in the review of the issues or protocols requiring appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB.

Prior to the convened IRB meeting, each protocol application (including background information, project protocol, and informed consent) is reviewed in depth by the assigned Primary reviewer(s). All other IRB members receive copies of aforementioned. They are expected to have reviewed all provided material in order to have a meaningful discussion of the presented information during the convened IRB meeting.

At the meeting, the Primary and Secondary Reviewers present an overview of the goals, design, study procedures, safety procedures, and qualifications of the investigators. The Primary and Secondary Reviewers, along with the IRB members, will review the regulatory criteria for approval.

## **7.5. Review Process**

### ***IRB Office Pre-review***

Applications are screened by the IRB Administrator for completeness, using the appropriate *Pre Review Checklist* and ensuring regulatory compliance prior to the placement of the application on the agenda. The IRB Chair or his or her designee will perform comprehensive pre-reviews of all new protocol full board submissions. The IRB Chair or his or her designee will check for completeness and accuracy of submissions and further identify the pertinent issues for the IRB Committee. The IRB Chair or his or her designee will identify and/ or clarify any substantive questions and deficiencies before the protocol is added to an agenda for full board review. Any required changes by the IRB Chair or his or her designee will be incorporated within the packet of materials sent to the board for full review. Changes to the protocol after the agenda packets have been delivered to IRB members will be forwarded to the full IRB board prior to the convened meeting.

Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by e-mail, phone or in person of missing materials and the necessary date of receipt for inclusion on that month's agenda. Questions about the IRB policies and procedures, determination of whether a particular protocol is human research or not and what particular forms are required for a



particular study can be submitted in writing to the IRB Chair or his or her designee for information and/or clarification.

### ***Materials Received by the IRB for the Initial Review of Research***

Each IRB member will receive the following documentation, as applicable:

- complete protocol application form
- protocol summary
- proposed consent / parental permission / assent form(s)
- recruitment materials
- subject information
- investigator CV's
- data collection instruments (including all surveys and questionnaires)
- letter of support if applicable

At least one Primary Reviewer must receive and review:

- any relevant grant applications
- the sponsor's protocol (when one exists)
- the investigator's brochure (when one exists)
- the DHHS-approved sample informed consent document (when one exists)
- the complete DHHS-approved protocol (when one exists)
- the investigator's current curriculum vitae or other documentation evidencing qualifications

If an IRB member requires additional information to complete the review, that member may contact the investigator directly or may contact the IRB Office to make the request of the investigator.

Protocol reviewers will use the *Reviewer's Checklists* as a guide to completing their review.

When a protocol is reviewed by the expedited procedure process, reviewers are provided with and expected to review all information that the convened IRB would have received. For expedited review protocols, any IRB member can request to review the full protocol by contacting the IRB Office.

### ***IRB Member Conflicts of Interest***

IRB members and consultants will not participate in any IRB action, including the initial and continuing review of any project, in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members are expected to self-identify conflicting interests. A Primary Reviewer or expedited reviewer with a conflict of interest must notify the IRB staff, and the IRB staff will, in turn, re-assign the protocol to another IRB member.

An IRB member is considered to have a conflicting interest when the IRB member or an immediate family member (defined as having a relationship to a person, whether by blood, law, or marriage, as a spouse, parent, child, grandparent, grandchild, stepchild, or sibling) of the IRB member:

- has an involvement in (or is directly supervising) a research project being reviewed by the IRB
- is the project director, or a member of the research team
- has a financial interest (for example, a financial interest in the sponsor or the product or service being tested) in the research whose value cannot be readily determined or whose value may be affected by the outcome of the research
- has a financial interest in the research with value that exceeds \$10,000 or 5% ownership of any single entity when aggregated for the IRB member and their immediate family
- has received or will receive any compensation whose value may be affected by the outcome of the study
- has a proprietary interest in the research (property or other financial interest in the research including, but not limited to, a patent, trademark, copyright or licensing agreement)

- has received payments from the sponsor that exceed \$10,000 in one year when aggregated for the IRB member and their immediate family
- is an executive or director of the agency or company sponsoring the research,
- any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a protocol

IRB members may be excused from the meeting room when the IRB reviews research in which the IRB member has a conflicting interest, except when otherwise requested to provide information to the IRB. The IRB Chair will allow for board discussion to commence upon the conflicted member's recusal from the meeting. The conflicted member is recused during the discussion and vote on the protocol will be noted in the IRB meeting minutes.

If the Conflict of Interest status of an IRB member changes during the course of a study, the IRB member is required to declare such conflict to the IRB Chair and/or IO.

### ***Possible IRB Actions Taken by Vote***

#### **Approved**

The study is approved as submitted.

#### **Conditionally Approved**

The IRB may approve research with conditions if, given scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

- Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (e.g., confirmation that research excludes children);
- Submission of additional documentation (e.g., certificate of training);
- Precise language changes to the study, consent, or other study documents; or
- Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes.

When the convened IRB approves research with conditions, the IRB may designate the IRB Chair (and/or other qualified individual(s)) to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review.

After verification, the following will be documented in IRB records and written communication to the investigator:

- The Approval date (The IRB approves human subjects research for a specific time interval not to exceed one year from the date of the convened meeting at which the study was approved or conditionally approved). For initial expedited review approval, the date when approval becomes effective (i.e., the date on which the investigator's response has been accepted by the Chair as satisfactory), and;
- The Study Expiration date by which continuing review must occur.

### **Deferred (Tabled) for Substantive Issues**

Substantive issues regarding the protocol and /or consent form must be addressed. This action is taken if substantial modification or clarification is required, or insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research will not occur by the convened IRB until subsequent review of the material submitted for by the Principal Investigator.

If the application is deferred the following will occur:

- the IRB Office informs the investigator in writing of the IRB's decision, setting forth the IRB's questions and concerns
- the investigator's response is sent to the IRB Office
- in order to receive approval for a deferred protocol, the protocol must be submitted for full IRB review at a subsequent, convened meeting of the same IRB. The IRB Office will provide to the IRB members the investigator's response, the revised protocol and/or consent with highlighted changes, all original submission materials (inclusive of changes, if any were required), and the previous IRB written decision (relayed to the Principal Investigator by the IRB Office) signed by the Principal Investigator. The deferred protocol is then placed on the agenda for the following meeting
- the amended protocol application is given full IRB review
- the outcome of the IRB's deliberations is once again communicated to the investigator in writing
- the IRB's determination concerning the subsequent amended submission will be documented in the minutes of that meeting

### **Disapproved**

Questions and issues are of such a magnitude that the IRB determines approval of the study is unwarranted. Approval of a previously disapproved protocol requires full IRB review.

### **Approval in Principle [45 CFR 46.118]**

There are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents:

- if study procedures are to be developed during the course of the research, but human subjects approval is required by the sponsoring agency
- if the involvement of human subjects depends on the outcomes of work with animal subjects

The IRB may then grant approval without having reviewed the, as yet undeveloped, recruitment, consent, and intervention materials. If the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests. Approval in Principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

### ***Determination of Risk***

Concurrent with the initial and continuing review process, the IRB will make a determination with respect to the risks associated with the research protocols. Risks associated with the research protocols will be classified as either "minimal" or "greater than minimal" based on the "absolute" interpretation of minimal risk. The meeting minutes will reflect the IRB's determination regarding risk levels.

### ***Period of Approval***

Concurrent with the initial and continuing review process, the IRB will make a determination with respect to the frequency of review of the research protocols. All protocols will be reviewed by the IRB at

intervals appropriate to the IRB's determination of the degree of risk, but no less than once per year. In certain circumstances, a shorter review interval (e.g. bi-annually, quarterly, or after accrual of a specific number of participants) may be required. The meeting minutes will reflect the IRB's determination regarding review frequency.

### ***Review More Often Than Annually***

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

- significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
- the involvement of especially vulnerable populations likely to be subject to coercion (e.g., institutionalized psychiatric patients, incarcerated minors); or
- a history of serious or continuing non-compliance on the part of the Principal investigator.
- the following factors will also be considered when determining which studies require review more frequently than on an annual basis:
  - The probability and magnitude of anticipated risks to subjects;
  - The likely medical condition of the proposed subjects;
  - The overall qualifications of the Principal Investigator and other members of the research team;
- the specific experience of the Responsible Investigator and other members of the research team in conducting similar research;
- the nature and frequency of adverse events observed in similar research at this and other institutions;
- the novelty of the research, thereby increasing the possibility of unanticipated adverse events, and
- any other factors that the IRB deems relevant.

In circumstances where the IRB mandates an approval period of less than one year, the IRB may define the review period (1) with a time interval, or (2) in circumstances where a specified number of subjects were studied or enrolled in the study. If a specified number of subjects were studied or enrolled in the study, it is understood that the approval period in no case may exceed 1 year. Further, the number of subjects studied or enrolled in the study will determine the approval period only when the specified number of subjects were studied or enrolled in the study for less than 1 year.

### ***Independent Verification Regarding Material Changes***

Protecting the rights and welfare of subjects may require the IRB to independently verify information about various aspects of the study utilizing sources other than the investigator. Independent verification includes, but is not limited to:

- adverse event reporting
- information in the scientific literature
- reports of drug toxicity
- drug approval status
- confirmation that no material changes occurred during the IRB-designated approval period

The IRB will determine the need for verification from outside sources on a case-by-case basis based upon the following criteria:

- protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources
- protocols conducted by Principal Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB
- protocols randomly selected for internal audit
- whenever else the IRB deems verification from outside sources is relevant

The following factors will also be considered when determining whether or not a study requires independent verification:

- the probability and magnitude of anticipated risks to subjects
- the likely medical condition of the proposed subjects
- the probable nature and frequency of changes that may ordinarily be expected in the type of research proposed

In making independent verification determinations, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, may retrospectively require such verification at the time of continuing review, review of amendments and/or unanticipated problems, or may require such verification at any time during the approval period in the light of new information.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

### ***Consent Monitoring***

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (a “consent monitor”) is required in order to ensure that the approved consent process is being followed and to ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

- high risk studies
- studies that involve particularly complicated procedures or interventions
- studies involving highly vulnerable populations (e.g., ICU patients, children)
- studies involving study staff with minimal experience in administering consent to potential study participants
- other situations when the IRB has concerns that consent process is not being conducted appropriately

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Chair or his or her designee will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The Principal Investigator will be notified of the IRB’s determination and the reasons for the determination. Arrangements will be made with the Principal Investigator for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor will determine whether the:

- informed consent process was appropriately completed and documented
- participant had sufficient time to consider study participation
- consent process involved coercion or undue influence
- information was accurate and conveyed in understandable language
- subjects appeared to understand the information and gave their voluntary consent

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

### ***Significant New Findings***

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The Principal Investigator must report any significant new findings to the IRB and the IRB will review them with regard to the impact on the subjects' rights and welfare. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the Principal Investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the Principal Investigator. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

### ***Reporting IRB Actions***

All IRB actions are communicated directly, in writing, to the Principal Investigator and designated protocol Principal contact person within five to seven (5-7) working days of the IRB's determination via a letter prepared and signed by the IRB Chair or his or her designee. When approving a protocol, the IRB will forward written notification of approval along with a copy of the approved consent form. The approval will contain date(s) of the protocol approval and the protocol expiration date. When deferring a protocol, the IRB notification will include the modifications required for approval along with the reasoning for requiring such modifications. When disapproving, terminating or suspending a protocol, the IRB notification will include the reasoning behind such decision.

All letters to investigators must be filed in the protocol files maintained by the IRB

The IRB reports its findings and actions to VHH in the form of its minutes, which are distributed to the VHH IO. Such findings are stored permanently and securely in the IRB Office.

## **7.6. Continuing Review of Active Protocols**

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur, even when the remaining research activities are limited to the analysis of private identifiable information.

### ***Approval Period***

At VHH IRB., determination of the approval period and the need for additional supervision and/ or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur, or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

For each initial or continuing protocol approval, the IRB will indicate an approval period with an approval expiration date specified. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB approved the research or the date the convened IRB deferred the research for non-substantive issues. For a study approved under expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

The approval date(s) and approval expiration date are clearly noted on all IRB notifications sent to the Principal Investigator and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse even if the investigator needs additional time beyond the date on which the preceding IRB approval would have expired to satisfy some or all of the IRB's conditions. However, conditions to secure approval must be satisfied within ten (10) business days of the expiration date for the research to proceed. Failure to satisfy conditions of approval within ten business days of the expiration date will result in suspension of the research study and is subject to reporting to the federal authorities as appropriate.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

No grace periods extending the conduct of research beyond the expiration date of IRB approval will be permitted. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires.

The IRB Office staff will send out expiration reminder notices to investigators in advance of the expiration date of protocols; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

### ***Continuing Review Process***

Investigators must submit the following for continuing review:

- the current consent document
- any newly proposed consent document
- the Application for Continuation
- protocol deviation log (if applicable)
- adverse event log (if applicable)
- signed Disclosures of Financial Interest Forms

In conducting continuing review of research ineligible for expedited review, all IRB members are provided with and review all of the above-referenced material. The Primary Reviewer and IRB Chair will also receive a copy of the most recent protocol version. At the convened IRB Board meeting, the Primary Reviewer will lead the IRB through the completion of the regulatory criteria for approval in the *Reviewer's Checklists*.

IRB staff will attend the convened meetings, and will retrieve any additional related materials the IRB Board members request.

In the case of expedited review, the IRB members may request the IRB office staff to provide them with any additional materials required for the review.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

A new protocol version that has not been previously approved by the IRB will not be accepted at the time of continuing review unless the protocol is also submitted through a *Request for Amendment* form with all accompanying materials for amendments.

### ***Expedited Review of Continuing Review***

In conducting continuing review under expedited review, the reviewers will receive all of the above-referenced materials. The reviewer(s) will complete the “*Reviewers Checklist*” to determine whether the research meets the criteria allowing continuing review using the expedited procedure and, if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it will not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 (see: [Categories of Research Eligible for Expedited Review](#)). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110 changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

### ***Lapse in Continuing Reviews***

The IRB and investigators must plan ahead in order to meet required continuing review dates. If the IRB has not reviewed and approved a research study by the end of the approval period specified by the IRB, all research activities must cease, including recruitment and enrollment of subjects, consent, interventions, interactions, data collection and data analysis, unless the IRB concludes that it is in the best interests of individual subjects to continue participation in the research interventions or interactions. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.

An expiration letter (or electronic mail) will be sent to investigators by the last date of the approval period. Once expired, all research activities must cease and IRB review and approval must occur prior to conducting the research again. If an investigator has not submitted a continuing review prior to the expiration date and the study is now expired, the IRB will still accept the continuing review application but only with-in 30 days of the study expiring (i.e. study expiration date is 9/30/2017, IRB will accept the continuing review application until 10/30/2017). After 30 days of the expiration date, the investigator will need to submit a new study if they plan to continue the research. If an investigator does not want to continue the research, the investigator will need to complete the Study Closure Form to close the study.

Failure to submit continuing review information on time is considered non-compliance and will be handled according to the non-compliance policy (see: [Non-Compliance](#)):

- if the study is FDA-regulated, the IRB and IRB Chair must follow FDA requirements set forth in 21 CFR 56.108(b)(3) in reaching their decision
- the sponsoring agency, private sponsor, or other federal agencies must be informed of any lapse in research via the Office of Clinical Trials or Sponsored Programs Administration as appropriate

The continuation of research after expiration of IRB approval is a violation of the regulations. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities must cease. No new subjects may be enrolled in the study. However, IRB may find that it is in the best interests of individual subjects to continue participating in



the research interventions or interactions. The procedure for obtaining approval to continue subject participation after expiration of IRB approval is as follows:

- the Principal Investigator will submit to the IRB Chair a written list of research subjects for whom stopping of the research would cause harm
- the IRB Chair will review written requests from investigators who wish to continue research with existing subjects in research procedures
- the IRB Chair will determine which subjects, if any, may continue with the study. The IRB Chair will further determine the specific procedures that may continue to be performed when ceasing such procedures will harm the subject
- the IRB Chair will either orally communicate the decision to the investigator(s) or communicate such decision via electronic mail. The IRB Chair will also provide a written response

## 7.7. Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. Investigators must seek IRB approval before making any changes in approved research—even though the changes are planned for the period for which IRB approval has already been given. A change may be implemented without IRB when the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

Modifications may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. Investigators must submit documentation to inform the IRB about the changes in the status of the study, including, but not necessarily limited to:

- completed *Change in Protocol Request* form
- revised Investigator's protocol application or sponsor's protocol (if applicable)
- revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study
- revised or additional recruitment materials
- any other relevant documents provided by the investigator
- the investigator's current curriculum vitae or other documentation evidencing qualifications if applicable

The Principal Investigator must electronically submit all revised materials in Microsoft Word format, noting changes via highlight or "Track Changes".

All changes must be accompanied by a detailed summary of the changes and a rationale (if applicable).

IRB office staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the protocol for full board review.

## ***Study Personnel Changes***

For efficiency purposes, additions and/or deletions of qualified study personnel can be submitted as a **Add/Remove Personnel Change Request** by the PI or study coordinator and are reviewed and approved by the IRB Staff. There is an exclusion to this process:

- Principal Investigator (PI) changes or changes in personnel that require a consent form change

Changes to study personnel that meet the exclusion criterion above must be submitted as an amendment using the *Change in Protocol Request* form.

### ***Expedited Review of Protocol Modifications***

The IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or designee(s) among the IRB Minor changes/modifications would not include the addition of procedures involving more than minimal risk to participants or changes that do not fall in categories (1)-(7) of research that could be reviewed using the expedited procedure. (see: [Categories of Research Eligible for Expedited Review](#))

The reviewer(s) complete the *Expedited Reviewer Checklist* to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications meets the regulatory criteria for approval.

### ***Full Board Review of Protocol Modifications***

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

Major changes/modifications would include the addition of procedures involving more than minimal risk to participants or changes that do not fall in categories (1)-(7) of research that could be reviewed using the expedited procedure (see: [Categories of Research Eligible for Expedited Review](#)).

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the modifications and leads the IRB through the completion of the regulatory criteria for approval.

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

### ***Closure of Protocols***

The completion or termination of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Investigators may submit closure applications to the IRB as a study closure of a protocol (in *Request for Final Study Closure*). The investigator must submit a final report with the closure application. IRB staff will review the closure application for completeness and will send to the Chair or Vice-chair for review.

Closure applications will be closed and the acceptance letter will be included on the next agenda as a *Notification of Completion of Research* item.

## 7.8. Unanticipated Problems

Federal regulations require organizations to have written policies and procedures to ensure the prompt reporting of unanticipated problems involving risks to subjects or others to the IRB, appropriate institutional officials, and regulatory agencies and departments.

*NOTE: For simplicity, unanticipated problems involving risks to subjects or others will be referred to as “unanticipated problems” in this policy.*

Not all unanticipated problems involve direct harm to subjects. Events can occur which are unexpected and result in new circumstances that increased the risk of harm to subjects without directly harming them. In addition, the event may have presented unanticipated risks to others (e.g., the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects. In each case, while the event may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported.

Events which direct harm to subjects are referred to as “Adverse Events”. Although adverse events occur most commonly in the context of biomedical research, adverse events can occur in the context of social and behavioral research. Only unanticipated adverse events that are related to the research need to be reported. If a research subject dies, the death is not reportable if it was not study-related.

### **Definitions**

#### **Unanticipated Problem Involving Risks to Participants or Others (Unanticipated Problem)**

Any event, any incident, experience, outcome, or new information that (1) was unforeseen and (2) indicates that the research procedures caused harm to participants or others or indicates that participants or others are at increased risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### **Adverse Event**

Any physical, psychological or social harm to subjects during the course of research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

#### **Unanticipated**

An event is “unanticipated” when its specificity and severity are not accurately reflected in the informed consent document, protocol and/or Investigator’s Brochure.

The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents; and the characteristics of the subject population being studied;

#### **Related to the Research**

An event is “related to the research procedures” if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely that not that the event affects the rights and welfare of current participants.

## Office of Human Research Protections Definition of UAP

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. 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;
2. related or possibly related to participation in the research (in this guidance document, *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); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## FDA Definition of UAP

The FDA defines a UAP as an event that is unexpected, serious, and has implications for the conduct of the study (e.g. requiring significant, and usually safety-related, changes in the protocol such as revisions to inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

## Reporting

Principal investigators must report to the IRB as soon as possible, but in all cases within 5 working days of any:

- adverse events which in the opinion of the principal investigator are both unexpected and related to the research
- an unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
- information that indicates a change to the risks or potential benefits of the research. For example:
  - an interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
  - a paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB
- a breach of confidentiality, including the loss of digital storage devices
- incarceration of a participant in a protocol not approved to enroll prisoners
- change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
- complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm
- event that requires prompt reporting to the sponsor
- sponsor imposed suspension for risk

The IRB will accept other reports when the investigator is unsure whether the event should be reported. The investigator should first contact the IRB Office by email or telephone to determine if the reporting is necessary.

Principal investigators should report the above events using the *Reportable Event Form*. Reports may be accepted by other means such as e-mail, or phone.

### ***IRB Review***

Upon receipt of an *Reportable Event Form* from a Principal Investigator, the IRB Office staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will contact the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the IRB staff making the correction.

The IRB Office staff submits the *Reportable Event Form* and all supporting documents provided by the investigator to the Chair for review. At the discretion of the Chair, if additional review is necessary, the Chair will forward the *Reportable Event Form* and all supporting documentation member(s) of the IRB who have appropriate expertise to review the event.

Based on the information received from the investigator and upon the advice of the reviewers, the IRB Chair or his or her designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or his or her designee must be reported to a meeting of the convened IRB.

Any IRB Member has authority to request submission of more detailed contextual information by the PI about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

If the Chair considers that either (1) the problem was foreseen OR (2) no participants or others were harmed AND participants or others are not at increased risk of harm, the Chair indicates on the form that the problem is not an unanticipated problem. The form is filed in the protocol record, the determination is communicated to the investigator and no further action is taken.

If the Chair considers that the problem is an unanticipated problem, but that the risk is no more than minimal, the Chair will review the:

- currently approved protocol
- currently approved consent document
- previous reports of unanticipated problems involving risks to participants or others
- investigator's brochure, if one exists

After reviewing all of the materials, the Chair will take appropriate action depending on the nature of the risk involved, including modification of the protocol or the consent form, if applicable. The results of the Chair's review will be recorded in the protocol record, communicated to the investigator, reported to the IRB, and referred to the IRB Office to be handled according the reporting procedures (see: [Reporting to Regulatory Agencies and Institutional Officials](#)).

All reported unanticipated problems where the risk is more than minimal will be reviewed at a convened IRB meeting. All IRB members are provided a copy of the *Reportable Event Form* and supporting documents.

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

- whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
- what action in response to the report is appropriate.
- whether suspension or termination of approval is warranted.

- whether further reporting to Institutional and/or federal officials is required.

If the IRB considers the event to not represent an unanticipated problem the results of the review are recorded in the protocol record, the IRB minutes and communicated to the investigator; the IRB may recommend any of the following actions:

- nothing further
- requiring modifications to the protocol
- revising the continuing review timetable
- modifying the consent process
- modifying the consent document
- providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
- providing additional information to past participants
- requiring additional training of the investigator and/or study staff
- other actions appropriate for the local context

If the IRB considers the event to represent an unanticipated problem, the IRB will consider the following actions:

- modification of the protocol
- modification of the information disclosed during the consent process
- providing additional information to current participants (This must be done whenever the information may relate to the participant's willingness to continue participation)
- providing additional information to past participants
- requiring current participants to re-consent to participation
- alteration of the frequency of continuing review
- observation of the research or the consent process
- requiring additional training of the investigator and/or study staff
- notification of investigators at other sites
- termination or suspension of the research
- obtaining additional information
- referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
- other actions appropriate for the local context

The results of the IRB review are recorded in the IRB minutes, protocol record, communicated to the investigator and referred to the IRB Office to be handled according the reporting procedures (see: [Reporting to Regulatory Agencies and Institutional Officials](#)).

## **7.9. Further Review/Approval of IRB Actions by Others within the Institution**

Research that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by officials of the institution; however, those officials may not approve research if it has been not been approved by the IRB. [45 CFR 46.112] There are no required institutional reviews after the IRB grants approval, but the institution reserves the right to subject research reviewed by the IRB to further review.

## **7.10. Sponsored Research Contracts**

All funded human subjects research must be reviewed and approved by VHH IRB.

Contracts will be reviewed for the following by the IRB:

- consistency between the contract and the consent form approved by the IRB
- that the contract indicates that VHH will follow the protocol, applicable regulations and its ethical standards
- that the contract defines who will be responsible for research related injuries.
- if the sponsor will monitor the conduct of the research, the contract states that if the study monitor uncovers information that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study, the sponsor will make sure that the information is communicated to the IRB
- that the contract indicates that, if the sponsor discovers results that could affect the safety or medical care, the sponsor will make sure the IRB is notified

## 7.11. IRB Fee Policy and Schedule

A fee may be required for all new, continuing review, and protocol amendment reviews of industry sponsored studies.

IRB fees are applied even if subjects are never enrolled, the study terminates before milestones are met, expenditures exceed revenue, or a contract is never finalized.

These fees should be included as a line item in the budget of the formal contract as an upfront and non-refundable item.

## 7.12. The Rights of Research Subjects

### *IRB Policy*

It is the policy of the IRB to provide information to the community regarding the rights of research volunteers.

- the IRB will require that a contact number be provided to each participant who has consented to participate in research. The number should appear on every informed consent document following a statement informing the participant of the right to contact the IRB regarding questions (i.e., need for additional information), concerns, or complaints regarding his/her rights as a research participant. This information is included in the VHH *Informed Consent template* in the section entitled Contact Person(s).
- the IRB maintains a mechanism to receive complaints from participants or others in a confidential manner.

### *Review Process*

#### **Investigator Responsibilities**

The Investigator is responsible for assuring the informed consent document contains the IRB phone number for participants to call if they have questions regarding their rights as a volunteer for research. If the IRB has waived the documentation of informed consent, it is the Investigator's responsibility to provide the IRB phone number to the participant by other means.

If the Investigator is requesting a waiver of documentation of informed consent, the IRB Chair or his or her designee will request information from the Investigator regarding the method of informing the participants of the IRB number for questions.

## 8. Criteria for IRB Approval of Research

In order for the IRB to approve human subjects' research it must determine that the following requirements are satisfied:

- Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by [45 CFR §46.116]
- Informed consent will be appropriately documented, in accordance with, and to the extent required by [45 CFR §46.117]
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects

### 8.1. Risk/Benefit Assessment

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

- judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks
- disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits

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

- identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research
- determine whether the risks will be minimized to the extent possible
- identify the probable benefits to be derived from the research
- determine whether the risks are reasonable in relation to the benefits to subjects, if any, and assess the importance of the knowledge to be gained
- ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits



Risks to subjects are minimized:

- by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk
- whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes

Risks to subjects are reasonable in relation to anticipated benefits, if any, and to the importance of the knowledge that may reasonably be expected to result.

- in evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research—as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research
- the IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility

### **Scientific Merit**

In order to assess the risks and benefits of the proposed research, the IRB must determine that the science is adequate to provide sufficient benefit to justify the risks, including:

- research uses procedures consistent with sound research design;
- research design is sound enough to reasonably expect the research to answer its proposed question; and
- knowledge expected to result from this research is sufficiently important to justify the risk.

Documentation is required by the IRB demonstrating the following:

- research utilizes procedures consistent with sound research design
- research design sound enough to reasonably expect the research to answer its proposed question;
- policies and procedures include the evaluation of the available nonclinical and clinical information on an investigational product adequately to support the proposed clinical trial
- clinical trials are scientifically sound and described in a clear, detailed protocol

### **Other Considerations**

In assessing the benefits of the research, the IRB must also review:

- the qualifications of the research team, including their technical and scientific expertise, as well as their knowledge and understanding of their obligation to protect the rights and welfare of research participants
- the adequacy of the resources necessary for human research protection, care of research participants, and safety during the conduct of the research

### **Equitable Selection of Subjects**

The IRB will review the inclusion/exclusion criteria for the research to ensure equitable selection of subjects. In making this assessment the IRB takes into account the purposes of the research and the setting in which the research will be conducted, and is particularly cognizant of the special considerations of research involving vulnerable populations, such as children, prisoners, fetuses, pregnant women, human in vitro fertilization, persons who are cognitively impaired, or persons who are economically or educationally disadvantaged (see: [Vulnerable Populations](#)).

### **Recruitment of Subjects**

The investigator will provide the IRB with all recruiting materials to be used in identifying participants including:

- information contained in the advertisement (including web-based sites)

- mode of communication
- final copy of printed advertisements
- final copy of audio/video taped advertisements

The IRB must approve any and all advertisements prior to posting and/or distribution. The IRB will review:

- information contained in the advertisement
- mode of communication
- final copy of printed advertisements
- final copy of audio/video taped advertisements

The IRB reviews advertising to ensure that advertisements do not:

- state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol
- make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation
- make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic or device
- use terms, such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational
- promise “free medical treatment,” when the intent is only to say subjects would not be charged for taking part in the investigation
- include exculpatory language
- emphasize the payment or the amount to be paid, by such means as larger or bold type

The IRB determines that advertisements are limited to the information prospective subjects need to determine their eligibility and interest, such as:

- name and address of the clinical investigator or research facility
- condition under study or the purpose of the research
- criteria that would be used to determine eligibility for the study in summary form
- brief list of participation benefits (if any)
- time or other commitment required of the subjects
- location of the research and the person or office to contact for further information
- clear statement that this is research and not treatment
- brief list of potential benefits (e.g. no cost of health exam)
- advertisements will not include reimbursement/compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing

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

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest.

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval.

## 8.2. Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the Committee will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by [45 CFR 46.117] and [21 CFR 50.27]. For detailed policies on informed consent (see: Informed Consent).

## 8.3. Data Safety Monitoring

The IRB will review the data safety-monitoring plan for protocols involving more than minimal risk during initial review and at continuing review. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB), if one exists, or an explanation why an independent data safety monitor is not necessary.

The IRB determines that the safety-monitoring plan makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study. The method and degree of monitoring needed is related to the degree of risk involved. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator in a small, low risk study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

The factors the IRB will consider in determining whether the safety-monitoring plan is adequate for the research are as follows:

- Monitoring is commensurate with the nature, complexity, size and risk involved
- Monitoring is timely. Frequency should commensurate with risk. Conclusions are reported to the IRB
- For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
- For an individual Safety- Monitor the plan must include:
  - Parameters to be assessed
  - Mechanism to assess the critical efficacy endpoints at intervals in order to determine when to continue, modify, or stop a study
  - Frequency of monitoring
  - Procedures for reporting to the IRB
- For a Data Safety Monitoring Board, the plan must include:
  - The name of the Data Safety Monitoring Board
  - Where appropriate, is an independent from the sponsor
  - Availability of written reports
  - Composition of the monitoring group (if a group is to be used): experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.
  - Frequency and content of meeting reports
  - The frequency and character of monitoring meetings (e.g., open or closed, public or private).

In general, it is desirable for a Data and Safety-Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies, the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

## 8.4. Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

### *Definitions*

#### **Privacy**

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

#### **Confidentiality**

Methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.

#### **Private Information**

Information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

#### **Identifiable Information**

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

### *Privacy*

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

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

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

### *Confidentiality*

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB

must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects is protected. The IRB assesses whether there are adequate provisions to protect subject privacy and maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information:

- about subjects
- about individuals who may be recruited to participate in studies
- the use of personally identifiable records
- the methods to protect the confidentiality of research data

The Principal Investigator will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the Principal Investigator and determine whether the privacy and confidentiality of research subjects is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data (see: [Certificate of Confidentiality](#)).

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

## 8.5. Vulnerable Populations

At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB determine if appropriate additional safeguards are in place to protect the rights and welfare of subjects if they are likely to be members of a vulnerable population (e.g., persons with diminished autonomy) (see: [Vulnerable Populations](#)).

## 8.6. Special Requirements for Research Funded by the Department of Defense

Research supported by the Department of Defense (DoD) must be reviewed and conducted in compliance with the Common Rule, adopted at part 219 of title 32 CFR, and FDA regulations on human subjects research, but also must comport with DoD Instruction (DoDI) 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," including all references included therein. These additional requirements apply to any human subjects research that is conducted, reviewed, approved, overseen, supported, managed or otherwise contractually subject to applicable regulations by DoD, or that uses DoD property, facility or assets ("DoD-Supported Research").

Excerpts and summaries of DoDI 3216.02 requirements are included below for ease of reference, but in the event of any conflict between provisions of this policy and any regulations or guidance provided by the DoD or its components, such regulations or guidance shall control. The complete DoDI 3216.02 is

available at [www.dtic.mil/whs/directives/corres/pdf/321602p.pdf] and is incorporated in full into this policy.

Following IRB review, non-exempt research protocols covered by these requirements must also be reviewed administratively by the DoD Human Research Protections Office (HRPO) before the activities that involve human subjects can begin (e.g., human subject recruitment and data collection). [DoDI 3216.02, enclosure 3, para 4c2.] No such research may begin until such approval by DoD has been received in writing.

### ***Minimal Risk – [DoDI 3216.02, enclosure 3, para 6b]***

The definition of minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

### ***Military Personnel as Subjects and Undue Influence – [DoDI 3216.02, enclosure 3, para 7e1]***

Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities. Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects. Superiors of service members in the chain of command shall not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. For research involving Service members as human subjects that has been determined to be greater than minimal risk and when recruitment occurs in a group setting, the IRB shall appoint an ombudsman who is not associated in any way with to the research. The ombudsman shall be present during the recruitment in order to monitor that the voluntary involvement or recruitment of Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. For any other research involving Service members, the IRB shall determine when it is appropriate to appoint an ombudsman.

### ***Education and Training – [DoDI 3216.02, enclosure 3, para 5]***

For initial and continuing research ethics education and training for all personnel who conduct, review, approve, oversee, support, or manage human subjects research, there may be specific DoD educational requirements or certification required. The IRB will assess, prior to issuance of IRB approval, whether all personnel have met any DoD training requirements that apply to the research. The DoD component may evaluate VHH IRB education and training policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

### ***Appointment of a Research Monitor – [DoDI 3216.02, enclosure 3, para 8]***

The IRB requires appointment of a research monitor for research involving human subjects that involve more than minimal risk and comparable DoD-Supported Research. The IRB or organizational official

can require a research monitor for a portion of the research or studies involving no more than minimal risk if appropriate. The research monitor is appointed by name. There may be more than one research monitor (e.g., if different skills or experience are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

The duties of the research monitor are determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and reports of unanticipated problems involving risks to participants or others, and oversee data matching, data collection and analysis) and report observations and findings to the IRB or a designated official.

The research monitor may discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study. The research monitor has the authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors must promptly report their observations and findings to the IRB or other designated official.

The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

The research monitors shall have expertise consonant with the nature of the risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

### ***Additional protections for pregnant women, prisoners, and children (Subparts B, C and D of 45 CFR 46) – [DoDI 3216.02, enclosure 3 para 7]***

DoD-Supported Research involving pregnant women, prisoners, and children are subject to additional protections set forth in the DHHS Common Rule at 45 CFR 46, Subparts B, C and D. DoD-Supported Research involving other vulnerable populations, such as research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of subjects in circumstances that may warrant provision of additional protections.

- Pregnant Women, Fetuses and Neonates as Subjects in DoD-Supported Research
  - For purposes of applying 45 CFR 46 Subpart B to DoD-Supported Research, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge."
  - The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
  - Fetal research must comply with the 42 USC sections 289g-289g-2.
- Children as Subjects in DoD-Supported Research
  - The exemption for research involving survey or interview procedures or observation of public behavior does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
- Treatment of Detainees

- Research involving a detainee as a human subject is prohibited, except for research activities covered by IND or IDE when for the purpose of diagnosis or treatment of a medical condition in a patient.
- Prisoners as Subjects in DoD-Supported Research
  - Research involving prisoners cannot be reviewed by the IRB through an expedited review procedure.
  - When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
  - In addition to allowable categories of research on prisoners in 45 CFR Part 46 Subpart C, epidemiological research is also allowable when:
    - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
    - The research presents no more than minimal risk.
    - The research presents no more than an inconvenience to the human subject.
    - Prisoners are not a particular focus of the research.
  - When a previously-enrolled human subject becomes a prisoner and the relevant protocol was not approved by IRB in accordance with these additional protections, the PI shall promptly notify IRB. If the PI asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the IO and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

### ***Limitation of Waivers and Exceptions from Informed Consent - [DoDI 3216.02, enclosure 3, paras 9 and 13]***

In accordance with 10 USC section 980, "research involving a human being as an experimental subject" is an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. This activity does not include activities that are not considered research involving human subjects, exempt categories of research, and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

For research involving a human being as an "experimental subject," informed consent must be obtained in advance from the experiment subject or the subject's legal representative if the subject cannot consent; if consent is obtained from the legal representative, the research must intend to benefit the individual subject, which shall be determined by the IRB.



The IRB may not waive these requirements, unless the requirement for informed consent is waived by the Assistant Secretary of Defense for Research and Engineering or such person's delegate when all of the following are met:

- The research is necessary to advance the development of a medical product for the Military Services.
- The research may directly benefit the individual experimental subject.
- The research is conducted in compliance with all other applicable laws and regulations.

If the research does not involve a human being as an experimental subject, IRB may waive the consent process in accordance with its policies and procedures.

For classified research, waivers of consent are prohibited.

### ***Limitations on Compensation for U.S. Military Personnel - [DoDI 3216.02, para 11; Dual Compensation Act and 24 U.S.C. 30]***

The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time and intermittent appointments. This law is not applicable to enlisted off-duty military personnel in relation to their military duty.

- When research involves U.S. military personnel, limitations on dual compensation include:
- Federal personnel (civil servants or Service members) participating as human subjects in DoD-Supported Research while on duty and non-Federal personnel may be compensated for blood draws for research up to \$50 for each blood draw.
- Federal personnel are prohibited from receiving pay or compensation for general research participation during duty hours, even if the research is not Federally funded or conducted.
- Non-Federal personnel participating as human subjects in DoD-Supported Research may be compensated for research participation other than blood draws in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research.
- Federal personnel may be compensated for general research participation only if the Federal personnel is involved in the research when not on duty in the same way as human subjects who are not Federal personnel (i.e., compensated for participating in a reasonable amount as approved by the IRB according to prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for general research participation may not come directly from a Federal source.

### ***Requirement for Reporting – [DoDI 3216.02, enclosure 3, para 4b4]***

The Institution shall promptly (no longer than within 30 days) notify the DoN Human Research Protection Program (HRPP) office and appropriate sponsor(s) of the following:

- When significant changes to the research protocol are approved by the IRB,
- The results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB,
- When the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and
- All unanticipated problems involving risks to participants or others, suspensions, terminations, and serious or continuing noncompliance of IRB approval regarding DoD-supported research involving human subjects.
- All suspensions or terminations of IRB approval of previously approved DoN-supported research protocols.
- The initiation and results of investigations of alleged non-compliance with human subjects protections.
- The initiation and results of investigations of alleged non-compliance with human subject protections.

### ***Recordkeeping Requirements - [DoDI 3216.02, para 15]***

Recordkeeping requirements for DOD-supported research with human subjects may be longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving.

Records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

### ***Classified research - [DoDI 3216.02, enclosure 3, para 13]***

The involvement of classified information in research involving human subjects may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. Secretary of Defense approval is required for all classified non-exempt research involving human subjects.

Waivers of informed consent are prohibited for this type of research.

Informed consent procedures shall include:

- Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.
- A statement that the research involving human subjects is classified and an explanation of the impact of the classification.
- The IRB approval process shall meet the following requirements:
- IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.
- At least one non-affiliated member shall be a non-Federal employee.
- Any IRB member who disagrees with a majority decision approved a project may appeal the decision to the Secretary of Defense.
- The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

Disclosure or use of classified information must comply with all applicable law.

### ***Additional Requirements for DoD Sponsored Research***

- For non-exempt research involving human subjects, the IRB must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of scientific merit. [DoDI 3216.02, enclosure 3, para 4b2.]
- When conducting research in a foreign country, the IRB shall consider the cultural sensitivities in the setting where the research will take place and shall require that the Principal Investigator has all necessary approvals and permissions to conduct research in that country in accordance with applicable law. [DoDI 3216.02, enclosure 3, para 4c2e.]
- Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component. [DoDI 3216.02, enclosure 3, para 10.]
- Surveys performed on Department of Defense personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.
- When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

## **Responsibilities**

The Principal Investigator must ensure compliance with all additional Department of Defense (DoD) requirements for human subject protection, including any necessary approvals from DoD following IRB approval prior to starting the research. It also is the responsibility of the IRB to ensure that all additional requirements by DoD Components for human subject protection have been met before IRB approval of the research project.

# **9. Informed Consent**

## **9.1. Informed Consent Process**

No investigator may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with 45CFR46.116 (c) and (d) and 45CFR46.117 (c) outlined in this policy. In general, the IRB considers individuals who are unable to consent for their own clinical care to be unable to consent for research participation. Tools or instruments such as the Mini Mental Exam can also be used to determine capability to consent.

Investigators must obtain consent prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

Consent must always be sought under circumstances that:

- provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate
- minimize the possibility of coercion or undue influence

The IRB will consider where the consent process will take place and the individual who will be obtaining consent (e.g. the investigator, collaborator, or qualified designee) in its determination regarding the appropriateness of the consent process. When the potential participant's understanding of the research may be impaired due to the timing, location, or individuals participating in the proposed consent process, the IRB will require an alternative process.

The information that is given to the subject or the representative must be in language understandable to the subject or the representative.

No informed consent, whether oral or written, may include exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights.

A person knowledgeable about the consenting process and the research (i.e.: a member of the project's research team) to be conducted must obtain the informed consent, and must be able to answer questions about the study.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity.

## **9.2. Definitions**

### **Legally Authorized Representative**

See [Section 10.6. Legally Authorized Representatives](#).

## Legal Guardian

A person appointed by a court of appropriate jurisdiction.

### 9.3. Basic Requirements

The requirement to obtain the legally effective informed consent of individuals before involving them in Research is one of the central protections provided for by the Federal regulations and the IRB. Investigators are required to obtain legally effective informed consent from a subject or the subject's Legally Authorized Representative. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features:

- disclosing to the prospective human subject information needed to make an informed decision
- facilitating the understanding of what has been disclosed
- promoting the voluntariness of the decision about whether or not to participate in the research

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading and signing the informed consent document. The informed consent process is the critical communication link between the prospective Human Subject and an Investigator, beginning with the initial approach of an Investigator and continuing through the completion of the research study. Investigators must have received the appropriate training and be knowledgeable about the study protocol in order that they may answer questions to help provide understanding to the study participant or potential study potential study participant.

The exchange of information between the Investigator and study participant can occur via one or more of the following modes of communication, among others; face to face contact, mail; telephone; or fax. When an online resource is used for recruitment, the queries incorporated must not go beyond screening to establish eligibility to participate.

Sample or draft consent documents may be developed by a Sponsor or cooperative study group. However, the IRB-of-record is the final authority on the content of the consent documents that is presented to the prospective study subjects.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

### 9.4. Basic Elements of Informed Consent

Informed consent must be sought from each potential subject or the subject's legally authorized representative, in accordance with, and to the extent required by [45 CFR 46.116] and [21 CFR 50.25].

The basic elements of informed consent are:

- 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; a description of any reasonably foreseeable risks or discomforts to the subject
- a description of any benefits to the subject or to others which may reasonably be expected from the research
- a statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained

- for research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of research-related injury, including who will pay for the treatment and whether other financial compensation is available
- an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
- 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
- for FDA-regulated studies, the possibility that the FDA may inspect the records needs to be included in the statement regarding subject confidentiality
- an explanation of whom to contact to voice concerns or complaints about the research
- contact information for the IRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff

Additional elements of informed consent to be applied, as appropriate:

- a statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
- a statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
- anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
- any additional costs to the subject that may result from participation in the research. (For example: Include when it is anticipated that subjects may have additional costs.)
- the consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.)
- procedures for orderly termination of participation by the subject. (For example: Include when the protocol describes such procedures.)
- 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. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
- the approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)

Additional elements of informed consent to be applied when research subject to ICH-GCP (E6):

- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject in addition to inclusion of any benefits or risks associated with alternatives
- a statement indicating that the monitor, the auditor, the IRBs, and the regulatory authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the subject or the subject's legally acceptable representative is authorizing such access. (ICH-GCP)

## 9.5. Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of

whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols/research plans and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.

When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review, of data and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

## 9.6. Waiver of Informed Consent

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement for informed consent provided the IRB finds and documents that all the following conditions are met:

- the research involves no more than minimal risk to the subjects
- the waiver or alteration will not adversely affect the rights and welfare of the subjects
- the research could not practicably be carried out without the waiver or alteration
- whenever appropriate, the subjects must be provided with additional pertinent information after participation

**OR**

- the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
  - public benefit or service programs;
  - procedures for obtaining benefits or services under those programs;
  - possible changes in or alternatives to those programs or procedures; or

- possible changes in methods or levels of payment for benefits or services under those programs;
- the research could not practicably be carried out without the waiver or alteration

*Note: Informed Consent cannot be waived under these criteria for FDA-regulated research. Note that some research involving FDA-regulated products is not FDA-regulated and that some research that does not involve FDA-related products is FDA-regulated. Exceptions from the FDA requirements for informed consent may be waived for emergency situations [21 CFR 50.23] or for emergency research [21 CFR 50.24].*

## 9.7. Documentation of Informed Consent (Signed Consent)

Informed consent must be appropriately documented, in accordance with, and to the extent required by [45 CFR 46.117] or [21 CFR 50.27]. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed and dated consent form must be given to the person signing the form.

The consent form may be either of the following:

- a written consent document that embodies the elements of informed consent may be read to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or
- a short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used:
  - there must be a witness to the oral presentation; and
  - the IRB must approve a written summary of what is to be signed by the subject or representative; and
  - the witness must sign both the short form and a copy of the summary; and
  - for subjects who do not speak English, the witness must be conversant in both English and the language of the subject.
  - the person actually obtaining consent must sign a copy of the summary; and
  - a copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

## 9.8. Waiver of Documentation of Informed Consent (Waiver of Signed Consent)

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

- 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, and the research is not FDA-regulated, or 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, or

*Note: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. Example: domestic violence research where the Principal risk is discovery by the abuser that the subject is talking to researchers.*

- research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive

surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.

In cases in which the documentation requirement is waived, the investigator will provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

## 9.9. Review and Approval of the Informed Consent Form

The IRB is responsible for the review and approval of the informed consent form prepared by the investigator. The wording on the informed consent form must contain all of the required elements and meet all other requirements as described in this section. If the wording of the informed consent has been initially prepared by an external entity (e.g., a pharmaceutical company or a cooperative study group, including National Cancer Institute (NCI) groups) other than by a VHHVHH Principal Investigator, the Investigator must prepare the consent using the VHH IRB Consent template.

IRB approval of the wording of the consent must be documented through the use of a certification stamp on the first page that indicates the date of the most recent IRB approval of the document and the expiration date. If the consent form is amended during the protocol approval period, the consent form must bear the approval date of the amendment rather than the date of the approved protocol.

## 9.10. Parental Permission and Assent

For policies on parental permission and assent in research involving children, see: [Parental Permission and Assent](#).

## 9.11. Surrogate Consent

Any use of surrogate consent requires prior approval by the IRB. See [Section 10.6 Persons who Lack Capacity to Provide Informed Consent for Research and Surrogate Consent](#).

## 9.12. Consent and Language Barriers

Researchers should prepare both English language and translated consent forms for proposals that include non-English-speaking subjects. An explanation of the translations and evidence of the comparability of the English and non-English consent forms is requested. The IRB may consult with language experts or require a "back-translation" into English. The translation should provide documentation to verify the accuracy of the translation and back-translation. When non-English speaking subjects enroll, they and the witness sign the translated document. The subjects are given a copy of the signed translated consent document.

If a non-English-speaking subject is enrolled unexpectedly, researchers may rely on an oral translation of the English language consent form, but should take extra care in the informed consent process to ensure that the subject has understood the project. A statement in the research records (and on the English language consent form) should indicate that the translation took place, identify the translator, and document the translator's belief that the subject understands the study and the consent process. If the subject is a patient, a note about the translation should be made in the patient's research records as well. Researchers should try to provide a written translation of the vital emergency contact information.



If the subject does not clearly understand the information presented at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If a Principal Investigator decides to enroll a subject into a protocol for which there is not an existing IRB-approved informed consent document in the prospective subject's language, the Principal Investigator must receive IRB approval to follow the procedures for a "short form" written consent (see: [Documentation of Informed Consent \(Signed Consent\)](#)).

### ***Use of Interpreters in the Consent Process***

Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to deliver information in the IRB-approved script and to facilitate the consent conversation. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the short form and the IRB-approved consent script well before (24 to 48 hours if possible) the consent conversation with the subject. If the interpreter also serves as the witness, she/he may sign the short form consent document and script as the witness and should note "Interpreter" under the signature line. The person obtaining consent must document that the "short form" process was used in the progress notes of the subject's medical record, including the name of the interpreter.

### ***Braille Consent***

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise verbal consent will be obtained, witnessed and documented as described below.

### ***Oral Consent***

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in [Waiver of Documentation of Informed Consent \(Waiver of Signed Consent\)](#).

For more than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide verbal consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject gave verbal consent. The consent process will also be documented in the medical record or in accord with the Institution's policy. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video tape.

Sometimes a subject understands English but does not read or write English. Again, an impartial witness should document that the subject understands the research and the consent process and consented to participate.

## 10. Vulnerable Populations

When some or all of the participants in a protocol are likely to be vulnerable to coercion or undue influence, the IRB should include additional safeguards to protect the rights and welfare of these participants. Some of the vulnerable populations that might be involved in research include children, pregnant women, fetuses, neonates, prisoners, or adults who lack the ability to consent, students, employees, or homeless persons.

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. For example, the IRB will include one or more individuals who are knowledgeable about or experienced in working with children, prisoners, or adults with limited decision-making capacity, when reviewing research that involves individuals from these populations.

[45 CFR 46] has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs:

### **Subpart B**

Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

### **Subpart C**

Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

### **Subpart D**

Additional Protections for Children Involved as Subjects in Research

The subparts apply to all research regardless of funding source.

Researchers conducting human subject research must check with the IRB to determine applicability of and how to apply the subparts.

### 10.1. PI Responsibilities

The Principal Investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The Principal Investigator is responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness, and who are being asked to participate in a research study with greater than minimal risk.

### 10.2. IRB Responsibilities

- IRB shall include representation, either as members or ad hoc consultants, individual(s) interested in or who have experience with the vulnerable populations involved in a research proposal.
- IRB reviews the PI's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.
- IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects as needed at the time of initial review of the research proposal.
- information reviewed as part of the continuing review process should include the number of participants considered as members of specific vulnerable populations.
- studies that do not have or are not required to have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable subjects, the IRB needs to carefully review the safety monitoring plan.

- IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

### ***Initial Review of Research Proposal***

- Principal Investigator should identify the potential to enroll vulnerable subjects in the proposed research at initial review and provide the justification for their inclusion in the study.
- Principal Investigator should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
- IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
- IRB evaluates and approves the proposed plan for the assent of participants.
- IRB evaluates the research to determine the need for additional protections and consider the use of a data and safety monitoring board or data monitoring committee as appropriate.
- IRB assesses the adequacy of additional protections for vulnerable populations provided by the Principal Investigator.
- NOTE: Studies that warrant independent monitoring include those involving schizophrenic patients who will be exposed to placebo, and/or drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations requiring independent monitoring would include individuals with schizophrenia, other psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders.

### ***Continuing Review and Monitoring***

At continuing review the Principal Investigator should identify the number of vulnerable subjects enrolled and any that needed an independent monitor in the progress report.

## **10.3. Research Involving Children**

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with [Subpart D of 45 CFR 46], which applies to DHHS-funded research and [Subpart D of 21 CFR 50], which applies to FDA-regulated research involving children.

### ***Definitions***

#### **Child**

Under DHHS and FDA regulations "children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

#### **Guardian**

Under DHHS and FDA regulations "guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

#### **Assent**

A child's affirmative agreement to participate in research. Mere failure to object, absent affirmative agreement, should not be construed as assent.

#### **Permission**

The agreement of parent(s) or legal guardian to the participation of their child or ward in research.

## Parent

A child's biological or adoptive parent.

### *Allowable Categories*

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk). [45 CFR 46.404]
  - requires assent of the child
  - permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child
  - The IRB may determine that the permission of one parent is sufficient, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. [45 CFR 46.405]
  - the risk is justified by the anticipated benefit to the subjects
  - requires assent of the child
  - permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child.
  - The IRB may determine that the permission of one parent is sufficient, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. [45 CFR 46.406]
  - the risk represents a minor increase over minimal risk
  - 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
  - permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child
  - requires assent of the child
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. [45 CFR 46.407]
  - Federally-funded research in this category must be approved by the Secretary of Health and Human Services, and requires consent of either both parents, or legal guardian.
  - FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs.
  - For non-federally-funded research, non-FDA research, IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
    - That the research in fact satisfies the conditions of the previous categories, as applicable; or
    - The following:

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- the research will be conducted in accord with sound ethical Principles; and
- informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual

## ***Parental Permission and Assent***

### **Parental Permission**

In accordance with [45 CFR 46.408(b)] and [21 CFR 50.55(e)], the IRB must determine that adequate provisions have been made for soliciting the permission of each child's parents or guardians.

Permission from both parents is required for all research to be conducted with children unless: one parent is deceased, unknown, incompetent, or not reasonably available; or when only one parent has legal responsibility for the care and custody of the child; or the research falls under 1 and 2 above and the IRB has determined that the permission of one parent is sufficient.

Parents or guardians must be provided with the basic elements of consent as stated in [45 CFR 46.116(a)(1-8)] and [21 CFR 50.25(a)(1-8)] and any additional elements the IRB deems necessary.

The IRB may find that the permission of one parent is sufficient for research to be conducted under [45 CFR 46.404] (21 CFR 50.51) or [45 CFR 46.405] (21 CFR 50.52). The IRB's determination of whether consent must be obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under [45 CFR 46.406] (21 CFR 50.53) and [45 CFR 46.407] (21 CFR 50.54) unless:

- one parent is deceased, unknown, incompetent, or not reasonably available; or
- when only one parent has legal responsibility for the care and custody of the child

The IRB may waive the requirement for obtaining consent from a parent or legal guardian for research that is not FDA-regulated if both of the following are true: the research meets the provisions for waiver in [45 CFR 46.116(d)(1-4)]; or the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), and an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal State, or local law.

The IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

- the research meets the provisions for waiver in [45 CFR 46.116(d)(1-4)] and if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirements to protect the subjects (for example, neglected or abused children)
- an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by [Parental Permission and Assent](#).

## **Assent from Children**

Because “assent” means a child’s affirmative agreement to participate in research, [45 CFR 46.402(b)], the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved. The VHH IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7-11 years of age. The proposed script should be included in the packet/consent form. Written assent using a written document for the children to sign may be sought for older children. If the child’s assent is not obtained the Principal Investigator, may either re-approach the child at a later time or not enroll the child.

At times there may be inconsistency between parent permission and child assent. Usually a “no” from the child overrides a “yes” from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that 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 and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the [Waiver of Informed Consent](#).

## ***The Assent Form***

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

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

- tell why the research is being conducted

- describe what will happen and for how long or how often
- say it's up to the child to participate and that it's okay to say no
- explain if it will hurt and if so for how long and how often
- say what the child's other choices are
- describe any good things that might happen
- say whether there is any compensation for participating
- ask for questions

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

### ***Children who are Wards***

Children who are wards of the State or any other agency, institution, or entity can be included in research involving 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, only if such 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 the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

The advocate must be an individual who has 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 who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

## **10.4. Research Involving Pregnant Women, Human Fetuses and Neonates**

### ***Definitions***

#### **Dead Fetus**

a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord

#### **Delivery**

complete separation of the fetus from the woman by expulsion or extraction or any other means

#### **Fetus**

the product of conception from implantation until delivery

#### **Neonate**

a newborn

#### **Nonviable neonate**

a neonate after delivery that, although living, is not viable

## **Pregnancy**

encompasses the period of time from implantation until delivery. A woman is assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery

## **Viable**

as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration

## **Research Involving Pregnant Women or Fetuses**

For DHHS-funded research in addition to non-funded DHHS research, [45 CFR Subpart B] applies to all research involving pregnant women. Under [45 CFR Subpart B], pregnant women or fetuses may be involved in research funded by DHHS if all of the following conditions are met:

- where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses
- 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 any other means
- 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 a 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, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent
- 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 in accord with the provisions for informed consent, 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
- each individual providing consent under previous two elements of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate
- for children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent under [Parental Permission and Assent](#)
- no inducements, monetary or otherwise, will be offered to terminate a pregnancy
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy
- individuals engaged in the research will have no part in determining the viability of a neonate

DHHS-funded research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review

## **Research Involving Neonates**

The following policies and procedures apply to all research involving neonates, regardless of funding source.

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:



- where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates
- each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate
- individuals engaged in the research will have no part in determining the viability of a neonate
- the requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable

### **Neonates of Uncertain Viability**

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met.

The IRB determines that:

- the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
- the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
- the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest

### **Nonviable Neonates**

After delivery, nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- vital functions of the neonate will not be artificially maintained
- the research will not terminate the heartbeat or respiration of the neonate
- there will be no added risk to the neonate resulting from the research
- the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means
- the legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply

However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

### **Viable Neonates**

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of [IRB Review Process](#) and [Research Involving Children](#).

### ***Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material***

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of this manual are applicable.

### **Research Not Otherwise Approvable**

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

- that the research in fact satisfies the conditions of *Research Involving Pregnant Women or Fetuses*, as applicable
- the following:
  - the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates
  - the research will be conducted in accord with sound ethical Principles, and
  - informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual

## **10.5. Research Involving Prisoners**

The VHH IRB is not constituted to serve as an IRB that reviews prisoner research.

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### **Waiver for Epidemiology Research**

The Secretary of DHHS has waived the applicability of [45 CFR 46.305(a)(1)] and [46.306(a)(2)] for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

- in which the sole purposes are:
  - to describe the prevalence or incidence of a disease by identifying all cases, or
  - to study potential risk factor associations for a disease, and
  - where the IRB has approved the research and fulfilled its duties under [45 CFR 46.305(a)(2)–(7)] and determined and documented that:
    - the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
    - prisoners are not a particular focus of the research

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in [45 CFR 46.306(a)(2)].

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.

In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

## 10.6. Persons who Lack Capacity to Provide Informed Consent for Research and Surrogate Consent

Individuals with reduced or impaired decision-making capacity may not be able to understand or appreciate information necessary to make a voluntary and informed decision about participating in research. Such individuals may be vulnerable to coercion and undue influence. This policy is designed to protect the rights and welfare of these individuals, while also facilitating research into the very conditions and disorders that affect them.

This policy applies to all research involving individuals 18 years of age or older who lack or who may lack the capacity to make a voluntary and informed decision to participate in research. This policy applies to all such research regardless of funding source. Any research involving individuals who lack or who may lack capacity also must comply with applicable law, including those relating to assessment of capacity, authority to make health care decisions on behalf of another individual, and research involving persons living in an institution.

### *General Requirements for Surrogate Consent*

Obtaining research informed consent from a representative of a subject who is 18 years of age or older rather than directly from the subject (“surrogate consent”) requires prior approval of the IRB. Surrogate consent may be used only for individuals who lack capacity to provide their own consent. Surrogate consent may be provided only by the subject’s legally authorized representative (as defined in Section 10.6. *Legally Authorized Representatives*).

### *Approval Criteria for Research Involving Surrogate Consent*

The IRB may approve use of surrogate consent only for studies that have the prospect of direct benefit to participants directly or will answer a scientific question that will further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of the studied population, thereby benefitting those similarly situated in the future. Within this framework, the IRB may approve use of surrogate consent for research only if the research belongs to one of the following categories.

1. **Research involving interventions or procedures that are considered minimal risk and present the prospect of direct benefit to the individual subject.** The IRB may approve such studies if the risks are reasonable in relation to the prospective benefits. For new protocols, this is the only category of research involving surrogate consent that may be eligible for expedited review, subject to all other requirements as described in [Section 7.3. Expedited Review of Research](#).
2. **Research involving interventions or procedures that are considered minimal risk and have no prospect of direct benefit to the individual subject, but are likely to yield generalizable knowledge about the subject’s disorder or condition.** The IRB may approve such studies if important to advance to the scientific knowledge of a medical condition that affects the research population, and if the risks are reasonable in relation to such importance. For research in this category, the disorder, condition or factor

that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.

3. **Research involving interventions or procedures that are considered a minor increase over minimal risk but present the prospect of direct benefit to the individual subject.** The IRB may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants.
4. **Research involving interventions or procedures that are considered a minor increase over minimal risk and have no prospect of direct benefit to the individual subject, but are likely to yield generalizable knowledge about the subject's disorder or condition.** The IRB may approve such studies if vitally important to advance to the scientific knowledge of a medical condition that affects the research population, and if the risks are reasonable in relation to such vital importance. For research in this category, the disorder, condition or factor that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.
5. **Research involving interventions or procedures that are considered a more than a minor increase over minimal risk but present the prospect of direct benefit to the individual subject.** The IRB may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants. Such ratios are less favorable when the risk is substantially more than a minor increase over minimal risk. Such ratios are more favorable when the prospect of direct benefit is more certain, or the benefit is expected to be more frequent or more significant.

In order to determine whether an intervention or procedure is a “minor increase over minimal risk” or if research is “vitally important,” the IRB will apply, as appropriate, principles for reviewing research-involving children under federal regulations and applicable IRB policies. A “minor increase over minimal risk” means that the increase in the probability and magnitude of harm is only slightly more than minimal risk, any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm, and there is no or an extremely small probability that subjects will experience significant pain, discomfort, stress or harm. Research is “vitally important” if there is clear and significant evidence that the use of such a procedure or intervention presents a reasonable opportunity to further the understanding of the etiologist, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder.

The Principal Investigator must provide sufficient safety and efficacy data to the IRB in order for the IRB to determine whether the research interventions or procedures present only a minor increase over minimal risk. Such data is especially critical for research in which there is no prospect of direct benefit.

The IRB shall have discretion to determine whether such procedures are appropriately classified for a given research population, since the serious medical, neurological and psychiatric illnesses that give rise to impaired consent capacity may also place these individuals at an increased risk of harm and discomfort from research participation as compared to a healthy population.

The IRB will especially scrutinize any research protocols that are designed to provoke symptoms, to withdraw subjects rapidly from therapies (“wash-out”), or to use placebo controls.

## ***Additional Safeguards***

The IRB will assess the level of risk and likelihood of direct benefit that the research offers to the research participant to assess the amount and scope of any additional safeguards for this population. The higher the risk or the less prospect of direct benefit, the more protections will be required.

Protective measures include, but are not limited to, independent consent monitors (“ICMs”) and medically responsible clinicians (“MRCs”).

An ICM is an individual not affiliated with the research who is designated by the IRB to monitor the informed consent process. The IRB may determine the role and responsibilities of the ICM, from monitoring the informed consent process to advocating on behalf of potential and current research participants. A MRC is a licensed medical doctor who is skilled, is experienced in working with the research population, and is not affiliated with the research, who acts as an active advocate for cognitively impaired research participants.

The IRB will require researchers employing surrogate consent to use of ICMs and MRCs for (1) any study involving more than a minor increase over minimal risk or (2) any study involving a minor increase over minimal risk with no prospect of direct benefit. The IRB will usually require use of ICMs and MRCs for any study involving a minor increase over minimal risk with the prospect of direct benefit. In all other cases, the IRB shall consider whether the use of ICMs and MRCs is necessary or appropriate to safeguard the interests of the research population.

## ***IRB Composition***

An IRB that reviews research that is expected to enroll individuals who lack or who may lack capacity must include at least one individual who is an expert in the area of research and at least one individual who is knowledgeable about or experienced in working with the relevant population. The IRB may also consider consulting with a member of the population, a family member of such person or a representative of an advocacy group for the research population.

## ***Required Submissions to IRB***

The Principal Investigator must describe in submission to IRB whether the research is expected to enroll individuals who lack or who may lack capacity. If so, the Principal Investigator must specify:

- The research population and the justification for the use of these individuals as the least burdened population and for specific institutional settings, if any.
- The process by which capacity would be assessed and by whom, which may include involvement of ICMs, or a justification for why assessment may not be required for a given research population. See [Section 10.6. Determination of Decision-Making Capacity](#).
- The process by which legal authority of surrogates will be verified. See [Section 10.6. Legally Authorized Representatives](#).
- The process by which prospective subjects and, if necessary, the legally authorized representative, will be informed about any capacity assessment, determination, consequence of such determination (including whether it will be documented in the individual’s medical record), the identity of a surrogate, the nature of the research, and the opportunity to assent, to the extent compatible with the subject’s understanding, prior to enrollment. See [Section 10.6. Notification and Assent of Subjects Who Lack Capacity](#).
- An appropriate monitoring plan that
  - Describes how capacity will be monitored throughout the duration of the study, including a plan for obtaining re-consent by the subject (if any subject is reasonably expected to regain capacity) or by an LAR (if any subject is reasonably expected to lose capacity), or why such processes may not be required for a given research population;

- Minimizes risks and negative impact on the subject's well-being, which may include involvement of MRC and must require regular communication with the legally authorized representative; and
- Requires that subjects who appear to be unduly distressed must be withdrawn from the research in a manner consistent with good clinical practice.

### ***Determination of Decision-Making Capacity***

The method used to assess capacity should be tailored to the research population, the level of study risk, and the likelihood of the involvement of participants with impaired consent capacity, and in accordance with law. In general, the IRB considers individuals who are unable to consent for their own clinical care to be unable to consent to participate in research.

The IRB will require investigators to consult with a licensed physician(s) who shall perform the capacity assessment in accordance with applicable law. In general, the individual performing the assessment should be a clinician familiar with the relevant population and qualified to assess and monitor capacity of such subjects on an ongoing basis. Ideally, the individual performing the assessment should not be otherwise involved in the research. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team. Where the reason for lack of capacity is mental illness, a psychiatrist or licensed psychologist must document this determination in the individual's medical record in a signed and dated progress note.

For research in which recruitment of individuals with impaired consent capacity is not expected at the time of IRB submission, judgment that prospective participants have the capacity to consent to the research can ordinarily be made informally during routine interactions with the individual during the consent process. An investigator who questions a prospective subject's capacity to consent may not enroll the individual and should consult with the IRB.

### ***Legally Authorized Representatives***

Surrogate consent may only be provided by a subject's "legally authorized representative." A legally authorized representative is an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research.

The following persons are considered legally authorized representatives who may act as a surrogate under this policy, in order of priority:

- A court-appointed legally authorized representative/guardian or a guardian authorized to decide about health care pursuant to Article 81 of the Mental Hygiene Law.
- An individual who is designated as a representative/agent through a health care proxy signed by both the subject and the appointed representative/agent. For a health care proxy to be effective, it must have been signed at a time when the subject had decision-making capacity. In addition, the health care proxy must not specifically prohibit research.
- The spouse, if not legally separated from the subject, or domestic partner.
- A son or daughter 18 years of age or older.
- A parent.
- A sibling 18 years of age or older.
- A step-child, step-sibling, step-parent, grandparent or grandchild 18 years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health or beliefs.

The IRB shall have discretion to limit the classes of persons who may act as the legally authorized representative for a given study, given that each class of persons may have varying degrees of understanding of the wishes of the impaired individual regarding research participation. In general, the

riskier the research protocol and more remote the prospect of direct benefit, the closer (by kinship or intimacy level) the legally authorized representative should be to an impaired individual in order to consent to the impaired individual's participation in research.

The person highest on the priority list who is willing, competent and available shall be the surrogate, unless that person designates another person from the list and no one higher on the priority list than the newly designated person objects.

The Principal Investigator shall describe how he or she will verify the legal authority of any surrogate. The relationship of the surrogate to the individual must be documented on the signed informed consent form.

For research conducted outside of Colorado State, the categories of persons who may act as legally authorized representatives will be considered by the IRB in accordance applicable state or local law.

### ***Notification and Assent of Subjects Who Lack Capacity***

The Principal Investigator must describe in its submission to the IRB the process by which prospective subjects and, if necessary, the legally authorized representative, will be informed about any capacity assessment to be performed, the results of the assessment, and any consequences of a determination of incapacity. Such notice to the prospective subject shall include the identity of a surrogate should the assessment determine lack of capacity, the nature of the research, and the opportunity to assent. The IRB shall require assent to the extent and in a manner compatible with the prospective subject understands.

If the prospective subject objects to the capacity determination, proposed surrogate, or decision to participate in research, such person may not be enrolled in the research unless otherwise required by law.

Once enrolled, no subject shall be required to continue to take part in research over his/her objection at any point, unless specifically authorized by a court of competent jurisdiction. Any early withdrawal of a subject shall be done in a manner consistent with good clinical practice.

### ***Additional Considerations***

#### **Subjects Whose Capacity May Change After Enrollment**

Individuals who lack capacity to consent should be included in the process of consent to the extent possible. The IRB shall require assent to the extent and in a manner compatible with the prospective subject understands.

The Principal Investigator is always responsible for assessing the decision-making capacity of subjects enrolled in any research study.

If a subject unexpectedly loses capacity after enrollment, and the IRB has not prospectively approved a monitoring plan to address this circumstance, the Principal Investigator must notify the IRB. See [Section 14.5 Required Reports to the IRB](#). In most cases, the IRB will require re-consent by a legally authorized representative in order for the subject to continue to participate in the research.

For some research populations, decision-making capacity may be reasonably expected to change during the course of the research study.

- For research involving subjects who have capacity to provide informed consent at the time of enrollment but who may be reasonably expected to lose such capacity during the course of the research study, the Principal Investigator must submit to IRB a plan that addresses how capacity will be monitored and establishes safeguards to protect the welfare of the subject should he or she lose capacity. As part of this

plan, the IRB may require that investigators establish and maintain ongoing communication with involved caregivers who could act as legally authorized representatives. The IRB may require re-consent by a legally authorized representative in order for the subject who has lost capacity to continue to participate in the research; especially when circumstances significantly change the potential benefits or risks or when new, scientific information becomes available. When re-consent by a legally authorized representative is required but not obtained, the subject must be withdrawn from the study in a manner consistent with good clinical practice.

- For research involving subjects who may be reasonably expected to regain capacity during the course of the research study, the Principal Investigator must submit to IRB a plan that addresses how capacity will be monitored and establishes how re-consent by the subject will be sought if he or she regains capacity. A subject who regains capacity must re-consent in order to remain in the study. Such re-consent process must disclose all research procedures performed to date and all research procedures that remain to be performed, and allow the subject the opportunity to continue in or withdraw from the study. The subject must sign the informed consent document. If not, the subject must be withdrawn from the study in a manner consistent with good clinical practice.

### **Subjects with Decisional Impairment who are Determined to Have Sufficient Capacity to Consent**

The IRB recognizes that decisional capacity varies along a continuum, and that the ability to provide voluntary and informed consent to participate in research may depend on factors that are specific to each protocol, such as protocol design, risks, anticipated benefits and safeguards. If appropriate, the IRB may require a Principal Investigator to include steps in the informed consent process in order to enable persons with some decisional impairment to make voluntary and informed decisions to consent to (or to refuse participation in) research, such as:

- Involvement of a trusted individual in the decision-making process
- Allocation of additional time for the consent process
- Waiting periods after initial discussion before enrollment
- Repetitive teaching
- Oral or written recall tests to assess subject understanding
- Audiovisual presentations
- Group sessions
- Videotaping or audio-taping of consent interviews
- Use of independent consent monitors to observe the consent process

## **11. Complaints, Non-Compliance and Suspension or Termination of IRB Approval of Research**

### **11.1. Complaints**

As part of its commitment to protecting the rights and welfare of human subjects in research, the IRB reviews all complaints and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

Complaints reported to the IRB will be evaluated as possible unanticipated problems involving risks to participants or others under [Unanticipated Problems](#).

The Chair of the IRB or his or her designee will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from investigators, research participants and others.



All complaints, written or verbal (including telephone complaints), and regardless of point of origin, are recorded and forwarded to the IRB Chair or his or her designee.

Upon receipt of the complaint, the Chair will make a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in [Suspension](#) will be followed.

If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to [Non-Compliance](#).

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to [Unanticipated Problems](#).

Within three business days of receipt of the complaint, the IRB Chair or his or her designee shall generate a letter to acknowledge that the complaint has been received and is being investigated, providing a follow-up contact name.

## 11.2. Non-Compliance

All members of the VHH community involved in human subject research are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and institutional and IRB policies governing the conduct of research involving human subjects.

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

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

Reports of non-compliance must be submitted to the IRB Office within 10 working days of discovery of this noncompliance via the *Reportable Event Form*. The report must include a complete description of the noncompliance, the personnel involved and a description of the non-compliance.

Complainants may choose to remain anonymous.

\*Study personnel include the principal Investigator and any staff member directly involved with participants or the informed consent process.

### Definitions

#### Non-Compliance

Failure to comply with any of the regulations, state and/or local laws, or VHHHRPP policies described in this document and failure to follow the determinations of the IRB. Non-compliance may be minor, serious, or continuing.

#### Serious Non-Compliance

Failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the human

research protection program. Research being conducted without prior IRB approval or participation of subjects in research activities without their prior consent (in studies where consent was not specifically waived by the IRB) is considered serious noncompliance.

### **Continuing Non-Compliance**

A pattern of non-compliance that continues after initial discovery or, in the judgment of the IRB Chair or convened IRB, suggests likelihood those instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

### **Allegation of Non-Compliance**

An unproved assertion of non-compliance.

### **Finding of Non-Compliance**

An allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator of that the protocol was willfully not followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance.) Once a finding of non-compliance is proven, it must be categorized as serious, non-serious, or continuing.

## ***IRB Review of Allegations of Non-Compliance***

All allegations of non-compliance will be reviewed by the IRB Chair and a second member of the IRB designated by the IRB Chair. They will review:

- all documents relevant to the allegation
- the last approval letter from the IRB
- the last approved IRB application and protocol
- the last approved consent document
- the last approved Investigator's Brochure, if applicable
- the grant (if applicable)
- Any other pertinent information (e.g., questionnaires, DSMB reports, etc.)

The IRB Chair and his or her designee will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question.

When the Chair and his or her designee determine that noncompliance did not occur because the incident was within the limits of an approved protocol for the research involved, the determination is reported in writing to the Principal Investigator and, if applicable, the reporting party. The determination letter will be copied to the Institutional Official in cases where the Institutional Official and any other parties had been notified at the outset.

If, in the judgment of the IRB Chair and his or her designee, the reported allegation of non-compliance is not true, no further action will be taken. If, in the judgment of the IRB Chair and his or her designee, the reported allegation of non-compliance is true, the non-compliance will be processed according to [Review of Findings of Non-Compliance](#).

If, in the judgment of the IRB Chair and his or her designee, any allegation or findings of noncompliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB Chair may suspend the research as described in below in [Suspension or Termination](#) with subsequent review by the IRB.

The Chair may determine that additional expertise or assistance is required to make these determinations and may form an ad hoc committee to assist with the review and fact gathering process. When an ad hoc committee assists in the review process, the Chair is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the ad hoc committee.

### ***Review of Findings of Non-Compliance***

If, in the judgment of the IRB Chair and his or her designee, the reported finding of non-compliance is not serious, not continuing, and the proposed corrective action plan seems adequate, no further action is required and the IRB is informed at the next convened meeting. Otherwise, the matter will be presented to the IRB at a convened meeting with a recommendation that a formal inquiry (described below) will be held.

All findings of non-compliance referred to the IRB will be reviewed at a convened meeting. All IRB members will receive:

- all documents relevant to the allegation
- the last approval letter from the IRB
- the last approved IRB application
- the last approved consent document

At this stage, the IRB may:

- find that there is no issue of non-compliance
- find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place
- find that there may be serious or continuing non-compliance and direct that a formal inquiry (described below) be held
- request additional information

### ***Inquiry Procedures***

A determination may be made by the IRB that an inquiry is necessary based on several issues that may include but are not limited to:

- subjects' complaint(s) that rights were violated
- report(s) that investigator is not following the protocol as approved by the IRB;
- unusual and/or unexplained adverse events in a study
- FDA audit report of an investigator
- repeated failure of investigator to report required information to the IRB

A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

- review of protocol(s) in question
- review of FDA or sponsor audit report of the investigator, if appropriate
- review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human subjects
- interview of appropriate personnel if necessary
- preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting
- recommend actions if appropriate

## **Final Review**

The results of the inquiry will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the inquiry substantiate the finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

- request a correction action plan from the investigator
- verification that participant selection is appropriate and observation of the actual informed consent
- an increase in data and safety monitoring of the research activity
- request a directed audit of targeted areas of concern
- request a status report after each participant receives intervention
- modify the continuing review cycle
- request additional Investigator and staff education
- notify current subjects, if the information about the non-compliance might affect their willingness to continue participation
- modification of the protocol
- modification of the information disclosed during the consent process
- requiring current participants to re-consent to participation
- suspend the study (see below)
- terminate the study (see below)

In cases where the IRB determines that the event of noncompliance also meets the definition of unanticipated problem involving risks to subjects or others, the policy and procedure for review of such events will also be followed.

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

## **Additional Actions**

A finding of serious or continuing non-compliance may also result in the following sanctions, among others:

- suspension or termination of IRB approval of specific research protocols or of all research involving human subjects in which the investigator participates
- sponsor actions: in making decisions about supporting or approving applications or proposals covered by this policy, the DHHS or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension as described above, and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the DHHS or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects
- Institutional or individual action by the OHRP and/or the FDA. The OHRP and/or the FDA may:
  - withhold approval of all new studies by the IRB
  - direct that no new subjects be added to any ongoing studies
  - terminate all ongoing studies, except when doing so would endanger the subjects
  - notify relevant state, federal and other interested parties of the violations
- Individual disciplinary action of the investigator or other personnel involved in a study.

Failure to secure necessary IRB approval before commencing human subject research must be reported to the IO and the IRB Chair for disciplinary action.

### 11.3. Suspension or Termination

An IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Suspensions of IRB approval is a directive of the convened IRB, the IRB Chair or the Chair's designee temporarily or permanently, stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB Chair or his or her designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or his or her designee must be reported to a meeting of the convened IRB.

Research may only be terminated by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

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

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

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

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

*Note: Suspension or termination of protocols approved by the IRB can also be issued by Organization officials acting outside of, and unrelated to, the IRB (i.e., not necessarily related to protecting the rights and welfare of study participants). Such Organization actions can be made by the VHH President. Such Organization actions may be made for any reason in furtherance of VHH's interest. The Principal Investigator must report any suspension or termination of the conduct of research by organization officials to the IRB. The IRB will then determine if suspension or termination of IRB approval is warranted.*

## ***Investigator Hold***

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

### **Procedures**

Investigators must notify the IRB in writing that:

- they are voluntarily placing a study on administrative hold
- a description of the research activities that will be stopped
- proposed actions to be taken to protect current participants
- actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate harm

Upon receipt of written notification of the investigator, the IRB Chair or his or her designee places the research on the agenda for review.

The IRB Chair and/or his or her designee, in consultation with the investigators, determine whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in “Protection of currently enrolled participants” below.

The IRB Chair or his or her designee, in consultation with the investigators, determines how and when currently enrolled participants will be notified of the administrative hold.

Investigators may request a modification of the administrative hold by submitting a request for a modification to previously approved research.

## ***Protection of Currently Enrolled Participants***

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

- transferring participants to another investigator
- making arrangements for clinical care outside the research
- allowing continuation of some research activities under the supervision of an independent monitor
- requiring or permitting follow-up of participants for safety reasons
- requiring adverse events or outcomes to be reported to the IRB and the sponsor
- notification of current participants
- notification of former participants

## **11.4. Reporting**

Serious or continuing noncompliance with regulations or the requirements or determinations of the IRB; and suspensions or terminations of IRB approval will be reported to the appropriate regulatory agencies and institutional officials according to the procedures in [Reporting to Regulatory Agencies and Institutional Officials](#).

## 12. Reporting to Regulatory Agencies and Institutional Officials

Federal regulations require prompt reporting to appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. The IRB will comply with this requirement and the following procedures describe how these reports are handled.

The IRB office will initiate these procedures as soon as the IRB takes any of the following actions:

- determines that an event may be considered an unanticipated problem involving risks to participants or others
- determines that non-compliance was serious or continuing
- suspends or terminates approval of research

The IRB Chair or designee prepares a letter that contains the following information:

- the nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of approval of research)
- name of the institution conducting the research
- title of the research project and/or grant proposal in which the problem occurred
- name of the principal investigator on the protocol
- number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
- a detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
- 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, etc.)
- plans, if any, to send a follow-up or final report by the earlier of
  - a specific date
  - when an investigation has been completed or a corrective action plan has been implemented
- the IRB Chair and the Institutional Official review the letter and modify the letter as needed
- the Institutional Official signs the letter and returns it to the IRB Chair or designee
- the IRB Chair or designee sends a copy of the report to:
  - the IRB by including the letter in the next agenda packet as an information item
  - the Institutional Official
  - OHRP, if the study is subject to DHHS regulations or subject to a DHHS federal wide assurance
  - FDA, if the study is subject to FDA regulations.
  - if the study is conducted or funded by any Federal Agency other than DHHS that is subject to "The Common Rule", the report is sent to OHRP or the head of the agency as required by the agency
    - Reporting to a regulatory agency is not required 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.
  - principal investigator
  - sponsor, if the study is sponsored
  - contract research organization, if the study is overseen by a contract research organization
  - chairman or supervisor of the principal investigator
  - the Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity

- the Information Security Officer of an organization if the event involved violations of information security requirements of that organization
  - office of Risk Management
  - others as deemed appropriate by the Institutional Official
- The IRB Chair or his or her designee ensures that all steps of this policy are completed within 10 days of the initiating action. For more serious actions, the IRB Chair or his or her designee will expedite reporting.

## 13. Investigational Drugs & Devices in Research

The following procedures describe the use of investigational drugs and devices in research under the auspices of VHH. Use of investigational drugs must be conducted according to FDA IND regulations, [21 CFR Part 312], and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, [21 CFR Part 812], and other applicable FDA regulations.

The IRB will provide written documentation of approval to the investigator with a determination of whether the device presents a significant or non-significant risk Investigational Drugs & Devices in Research

### 13.1. Definitions

#### **Investigational Drug**

An investigational drug for clinical research use is one for which the Principal Investigator or a sponsor has filed an IND application [21 CFR Part 312] or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

#### **Investigational Device**

Is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its Principal intended purpose by chemical action or by being metabolized. The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describes two types of device studies; "significant risk" (SR) and "non-significant risk" (NSR).

#### **Investigational New Drug (IND)**

IND means an Investigational New Drug application in accordance with [21 CFR Part 312].

#### **Investigational Drug Exemption (IDE)**

IDE means an Investigational Device Exemption in accordance with [21 CFR 812].

#### **Emergency Use**

Emergency use is defined as the use of a test article with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].

#### **Test Article**

A test article is defined as any drug, biological product, or medical device for human use [21 CFR 56.102(1)].

#### **Significant Risk Device (SR)**

Significant risk device is defined [21 CFR 812.3(m)] as a device that presents a potential for serious risk to health, safety, or welfare of a subject and;



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

### **Non-Significant Risk Device (NSR)**

A non-significant risk device is an investigational device that does not meet the definition for a significant risk study.

### **Humanitarian Use Device (HUD)**

Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year.

## **13.2. FDA Exemptions**

The following categories of clinical investigations are not regulated by DHHS or another federal agency and are exempt from the requirements of FDA regulations for IRB review:

### **Emergency Use of a Test Article**

Emergency use of a test article is exempt from prior IRB review and approval, if such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]

### **Taste and Food Quality Evaluations and Consumer Acceptance Studies**

if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

## **13.3. IND/IDE Requirements**

When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an Investigational New Drug (IND) or Investigational Device Exemption (IDE) may be required.

Investigators will be asked on the IRB application to indicate whether the research involves drugs or devices. If so, they will be asked if there is an IND/IDE for the research. If there is, they will be asked for evidence of the IND/IDE, which could be a:

- industry sponsored protocol with IND/IDE
- letter from FDA
- letter from industry sponsor
- Other document and/or communication verifying the IND/IDE

An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):

- (i) Labels the device in accordance with 812.5;
- (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
- (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
- (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
- (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
- (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the Principal Investigator must provide a rationale why it is not required.

The IRB Chair or his or her designee will confirm validity of IND/IDE by contacting appropriate representatives at FDA. When research is conducted to determine the safety or effectiveness of a drug or device, the IRB Research Analyst will confirm: (1) that the drug or device has an IND or IDE (as applicable) issued by the FDA. Additionally for devices: the Research Analyst will confirm (1) the device fulfilled the requirements for an abbreviated IDE or (3) the device fulfilled one of the exemption categories. The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

## 13.4. Investigator-Sponsors

In reviewing research involving FDA regulated articles, the IRB determines if the study involves an investigator-sponsor. If so, the IRB informs the investigator that there are sponsor responsibilities, including reporting requirements to the FDA, (as well as the investigator responsibilities) and all these requirements are his/her responsibility.

The IRB's Chair or his or her designee will visit the investigator-sponsor before initiation of the research to determine compliance with these FDA regulatory requirements. If compliance has been

demonstrated, the investigator-sponsor may begin the research. The QA&I Specialist will evaluate whether the investigator is knowledgeable about the regulatory requirements of sponsors and will follow them. An audit will take place at the time of and prior to the renewal, of the protocol by the IRB.

If the research involves drugs or devices and there is no IND/IDE, the investigator will be asked for a rationale as to why it is not required.

For drugs, an IND may not be necessary if all seven of the following conditions are met:

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

For devices, an IDE may not be necessary if any of the eight following conditions are met:

- there is a claim that it is a Non-significant risk device (NSR)
- the research involves a device other than a transitional device, in commercial distribution immediately before May 28, 1976 when used or investigated in accordance with the indications in labeling in effect at that time
- the research involves a device other than a transitional device, in commercial distribution immediately before May 28, 1976 that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of [21 CFR 807] in determining substantial equivalence
- the research involves 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 subject
  - is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
- the research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- the research involves a device intended solely for veterinary use

- the research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with [21 CFR 812.5(c)]
- the research involves a custom device as defined in [21 CFR 812.3(b)], unless the device is being used to determine safety or effectiveness for commercial distribution

The IRB will review the application and determine:

- whether there is an IND/IDE and if so, whether there is appropriate supporting documentation
- if there are drugs or devices involved, but no IND/IDE, whether the research meets the above criteria

## 13.5. Responsibilities

### *Investigator*

The investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines and IRB policies and procedures and must obtain approval from the IRB.

The investigator proposing the drug/device research will be required to provide a plan, that will be evaluated by the IRB and that will include:

- storage
- security
- dispensing

The investigator is responsible for the accountability of investigational drug/device including storage, security, dispensing, administration, return, disposition and records of accountability. The investigator will delegate the responsibility for drugs/biologic accountability to the Pharmacy.

If because of special circumstances, an investigational drug/device is not stored in the pharmacy, the investigator is responsible for the storage, security and dispensing of the device. The investigator must complete and submit an investigational control sheet containing information on the plan for storage, security and dispensing of the device to the IRB prior to its approval of the study. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of investigator's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

The investigator is responsible for reporting all unexpected adverse events associated with the use of an investigational drug/device to the FDA within 10 working days. All adverse events that require prompt reporting to the IRB are to be reported according to IRB policies and procedures on Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. The investigator is responsible for notifying the sponsor as specified in the protocol.

For research involving investigational new drugs:

- the Principal Investigator is responsible for informing the Pharmacy that IRB approval has been obtained. In addition a signed copy, of the consent form must be sent to the Pharmacy to document each subject's consent to participate in the study
- the Principal Investigator must inform the IRB and the Pharmacy when a study involving investigational drugs has been terminated.
- Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.
- The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subjects, and the return to the sponsor or

alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects. Investigators should maintain records that document adequately that the subjects are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor

The Principal Investigator will maintain the following:

- current curriculum vitae (CV)
- protocol
- records of receipt and disposition of drugs
- list of any co-investigators with their curriculum vitae
- certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
- case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to Pharmacy Service and the IRB in the manner defined by the protocol.
- IRB letters of approval

For research involving investigational devices:

- if a device considered NSR by the investigator or sponsor, is determined to have significant risk upon IRB review, the investigator is responsible for notifying the sponsor of the IRB's determination upon receipt of written notice. The Principal Investigator should provide the IRB with confirmation of this action
- a copy of the protocol approval by the FDA and the IRB and the consent must be provided to the pharmacist if the device will be stored in the pharmacy. A request for the IDE and a copy of the signed consent from the research subject must be provided to the pharmacist when the device is required for use. If the investigator is storing the devices, a log must be maintained to indicate name of subject, date dispensed, by whom it was dispensed, amount remaining, and who received the device (see below for detailed requirements related to management of research involving investigational devices)
- following completion of the study the termination procedure for investigational drugs must be applied if pharmacy control, or if the devices are kept by the investigator the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation

The Principal Investigator will maintain the following:

- current curriculum vitae (CV)
- protocol of the study
- records of animal study reports
- records of receipt and disposition of devices
- list of any co investigators with their curriculum vitae
- certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation
- case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable (see item
- IRB letters of approval and the EOC Committee approval letter if applicable
- device training

When an Investigator files an IND or IDE, the Investigator is considered the Sponsor and as such carries all of the FDA regulatory responsibilities and reporting obligations of both the Investigator and the Sponsor as described in the FDA regulations. The *Application for New Protocol Review* asks the investigator if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that they have reviewed the Guidance on Requirements of the Sponsor and the Investigator as a Sponsor are

aware of the regulatory responsibilities of a sponsor and confirm that they will comply. The IRB will periodically conduct random audits of investigators holding an IND or IDE.

The Principal Investigator is responsible for protecting the rights, safety and welfare of research participants under the investigator's care by ensuring that:

- the device is not used on a research participant until FDA and/or IRB approval has been obtained and the research participant has signed an informed consent document
- the investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines
- the device is used only in accordance with the IRB-approved protocol
- investigator is thoroughly familiar with the appropriate use of the investigational device, as described in the protocol and product brochure, and in other informational sources provided by the sponsor
- all persons assisting in the trial are adequately informed about the protocol and the investigational device
- research participants receive adequate instructions about the investigational device to assure their safe participation in the research study

The investigator is responsible for maintaining security of the investigational devices by ensuring that:

- all investigational devices used in conjunction with an investigational protocol must be kept in a locked and secured area
- access to investigational devices must be limited to personnel designated by the Principal Investigator
- accountability logs must be maintained for all investigational devices. Documentation of the following elements (as applicable) are required for each device used:
  - the type of device
  - model number
  - serial number
  - lot number
  - date received
  - research participant name and Medical Record Number (for internal tracking purposes)
  - research participant study Identification number
  - date implanted or used
  - disposition (If device is returned to the sponsor or destroyed, documentation of why, when and persons involved.)
  - names of all persons who received, used, or disposed of each device.
  - date of expiration of the device

The full names, title/positions, and signatures of all personnel responsible for maintaining or documenting in the logs must be indicated on a separate sheet or on the log itself.

Device accountability logs must be maintained in the project files or in the Principal Investigator's project regulatory binder for the period of time required by the federal regulations or the agreement/contract term, whichever is longer.

Prior to commencement of research involving investigational devices, the IRB QA Specialist will conduct a review to evaluate compliance with aforementioned in order to affirm compliance.

## **IRB**

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

For research involving investigational devices where there is a claim of a non-significant risk device:

- the IRB is responsible for reviewing the protocol and determining whether it is adequate. If the Chair determines that the IRB does not have the necessary expertise to evaluate the plan, outside consultation will be used (e.g., Biomechanical Engineering).
- unless the FDA has already made a risk determination for the study, the IRB will review NSR studies, determine if the device represents significant or non-significant risk, and report the findings to the investigator in writing.
- the IRB must consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as NSR is considered SR, the IRB must recommend that an IDE be obtained
- protocols involving Significant Risk devices do not qualify for expedited review. Protocols involving non-significant risk devices do not automatically qualify for expedited review.
- the IRB must document in the Minutes the rationale for the determination of a device that is classified as NSR/SR
- the IRB will provide written documentation of approval to the investigator with a determination of whether the device presents a significant or non-significant risk of whether the device presents a significant or non-significant risk.

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

## 13.6. Emergency Use

HHS regulations do not permit human subjects' research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under [45 CFR Part 46]. However, nothing in the HHS regulations at [45 CFR Part 46] is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, state or local law.

### *Emergency Exemption from Prospective IRB Approval*

FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. If all conditions described in [21 CFR 56.102(d)] exist then the emergency exemption from prospective IRB approval found at [21 CFR 56.104(c)] may be utilized. Informed consent is required, should be obtained, and documented as per FDA regulations unless the conditions for exemption are met.

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

[21 CFR 56.102(d)] states the following three specific conditions:

- the subject is confronted by a life-threatening situation necessitating the use of the test article
- no standard acceptable alternative treatment is available
- because of the immediate need for the use of the test article, there is not sufficient time to obtain IRB approval

If use is initiated without prior IRB review approval, the patient data may not be included in DHHS-regulated research in a prior or subsequent IRB approved project. If use is initiated without prior IRB

review and approval, FDA will require the data to be included in the research results submitted to the FDA.

### ***Emergency Waiver of Informed Consent***

The Principal Investigator is required to obtain informed consent from the patient or the patient's legally authorized representative unless an exception is met as follows.

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

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

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

### ***Expanded Access of Investigational Drugs***

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

#### **Compassionate Use**

The term "compassionate use" is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.

#### **Group C Treatment Investigational New Drug (IND)**

A means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, VHH requires prospective IRB review and approval.

#### **Open-Label Protocol**

A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.



### **Parallel Track**

A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that “parallel” the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a protocol-by-protocol basis, waive the provisions of [45 CFR Part 46] where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the IRB.

### **Single-Patient Use**

The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required.

### **Emergency IND**

The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics.

### ***Treatment IND***

FDA regulations [21 CFR 312.34 and 312.35] address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements.

### **Treatment IND or Biologics**

A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.

There are four requirements that must be met before a treatment IND can be issued:

- the drug is intended to treat a serious or immediately life-threatening disease
- there is no satisfactory alternative treatment available
- the drug is already under investigation or trials have been completed
- the trial sponsor is actively pursuing marketing approval

The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:

### **Informed Consent**

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications that have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their

ability to make an informed assessment of the risk involved. Therefore, the IRB should ensure that potential subjects are fully aware of the risks involved in participation.

### **Charging for Treatment INDs**

The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee should pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

### ***Emergency Waiver of IND***

FDA regulations at [21 CFR 312.34, 312.35, and 312.36] address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at [21 CFR Parts 50 and 56], and [21 CFR 312.34 and 312.35].

### ***Waiver of Informed Consent for Planned Emergency Research***

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived is covered by [21 CFR §50.24]. The research plan must be approved in advance by the FDA or DHHS and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are not allowed under the regulations covering the emergency use of a test article in a life-threatening situation [21 CFR §56.104(c)].

**VHH does not permit emergency research that entails Waivers of Informed Consent**

### ***Expanded Access of Investigational Devices***

#### **Compassionate Use (or Single Patient/Small Group Access)**

The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group. It must be a serious disease or condition and no alternative treatment available. Prior FDA approval is needed before compassionate use occurs.

#### **Treatment Use**

An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. The criteria include:

- life-threatening or serious disease
- no alternative
- controlled clinical trial
- sponsor pursuing marketing approval

## Continued Access

FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA. There must be a public health need or preliminary evidence that the device will be effective and there are no significant safety concerns.

## 13.7. Humanitarian Use Devices (HUD)

In accordance with [21 CFR 814.124], treatment with a HUD is subject to full board initial and continuing review by the IRB. At the time of review, the IRB will determine if written consent from participants for use of the HUD is necessary. If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, approval must be obtained from the IRB Chair or his or her designee and the investigator is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use. It is the responsibility of the investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval. Investigators are reminded that Humanitarian Device Exemptions are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application. Required medical device reports submitted to the FDA must be copied to the IRB. Post-approval requirements are detailed in [21 CFR 814.126].

## 14. Investigator Responsibilities

Principal Investigators are ultimately responsible for the conduct of research. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

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

- develop and conduct research that is in accordance with the ethical principals in the *Belmont Report*
- develop a research plan that is scientifically sound and minimizes risk to the subjects
- have sufficient resources necessary to protect human subjects, including:
  - access to a population that would allow recruitment of the required number of subjects
  - sufficient time to conduct and complete the research
  - adequate numbers of qualified staff
  - adequate facilities
  - a process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions
  - availability of medical or psychological resources that subjects might require as a consequence of the research
- assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Colorado and the policies of VHH
- assure that all personnel involved with the research are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based
- protect the rights and welfare of prospective subjects

- ensure that risks to subjects are minimized:
  - by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
  - whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes
- recruit subjects in a fair and equitable manner
- have plans to monitor the data collected for the safety of research subjects
- protect the privacy of subjects and maintain the confidentiality of data

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, include additional safeguards in the study to protect the rights and welfare of these subjects.

- have a procedure to receive complaints or requests for additional information from subjects and respond appropriately
- ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating medical and research staff
- obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent
- ensure that all research involving human subjects receives IRB review and approval in writing before commencement of the research
- comply with all IRB decisions, conditions, and requirements
- ensure that protocols receive timely continuing IRB review and approval
- report problems that require prompt reporting to the IRB (see: )
- obtain IRB review and approval in writing before changes (i.e. amendments) are made to approved protocols or consent forms
- seeking IRB assistance when in doubt about whether proposed research requires IRB review

## 14.1. Investigator Classifications

### Principal Investigators

The IRB recognizes one Principal Investigator (PI) for each study. The Principal Investigator has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet the investigator's skills or have one or more additional qualified faculty as Co-investigator(s).

### Student Investigators

Students (including Fellows, Residents, medical students, nursing students, etc.) may not serve as Principal Investigators. They must have a sponsor who fulfills the Principal Investigator eligibility criteria and who will serve as Principal Investigator and faculty advisor on the study.

### Research Team

The Principal Investigator and other individuals (also known as key personnel) who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol. The research team also consists of individuals who intervene or interact directly with human subjects (including the recruitment or consenting thereof), or who analyze data and/or tissue derived from humans for the purposes of the activity in question.

## 14.2. Protocol Development

When developing a protocol, the Principal Investigator or a member of the protocol research team may contact the IRB Office for a determination whether the proposed project constitutes human subjects research, and if so, what level of review would be required. Contact with the IRB Office may be in the form of a phone call, by letter, or by email and must include a brief description of the proposed research. The IRB Office will respond to the Principal Investigator or member of the research team by phone, letter, or email.

Investigators must provide complete answers to all questions on the *Health Biological Medical Research Application* and make certain that consent information is in agreement with the research plan.

Proposed consent/assent form (if applicable) must include or address:

- the general Principals and basic elements of informed consent
- translated consent documents, as necessary, considering likely subject population(s)
- VHH IRB -approved formats for consent forms and assent forms
- waiver of consent conditions

The investigator must submit the *Health Biological Medical Research Application* and all attachments to appropriate institutional regulatory committee offices (e.g., Scientific Review, etc.) for review and sign-off (if applicable).

Following institutional regulatory committee review and sign-off, the investigator must submit protocol and all attachments to departmental IRB reviewer, if applicable.

If research is DHHS-sponsored, materials delivered to the IRB reviewer must include the entire sponsoring application; if there is a significant variation between the DHHS application and the IRB protocol, the investigator must identify and justify the discordance.

If research is FDA-regulated and industry-sponsored, materials delivered to the IRB must include the entire sponsor's protocol as well as, for drug studies, the investigator's brochure [21 CFR 312.23(a)(5) and 312.55], FDA form 1572, and the sponsor Financial Disclosure form.

Review by Approved Departmental Reviewer (ADR) (if applicable). The investigator must make any changes recommended by the department reviewer. The intent is to address problems prior to review by the full IRB, thus avoiding delays in receiving approval for the research study.

Following departmental review and sign-off by Department Chairs or other appropriate institutional official, the investigator must submit the original and required copies of all materials to VHH IRB Office.

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*Note: Investigators who have other individuals write their protocols and responses to the IRB must recognize that the ultimate responsibility of any study lies with the Principal Investigator (PI). It is incumbent upon the PI to check all material that is submitted to the IRB for review.*

## 14.3. Changes to Approved Research

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

Minor changes (i.e., changes that do not involve increased risk or discomfort) may be authorized by the IRB Chair or his/her designee. A completed Application for Approval of an Amendment with information

specifying the changes requested, a revised consent form (if applicable), and a copy of the approved protocol with the proposed changes highlighted, should be sent directly to IRB Office. The IRB Chair or his or her designee must sign and return a letter to indicate approval. For further information regarding amendments, see: [Modification of an Approved Protocol](#).

*Note: IRB approved amendments to ongoing research do NOT extend the original approval expiration date.*

## 14.4. Continuing Review after Protocol Approval

Ongoing research studies must be reviewed by the IRB at least annually, or more often, if the IRB finds that the degree of risk to subjects warrants more frequent review. This renewal must take place prior to the end of the approval period noted on the approved protocol; otherwise, subject recruitment/enrollment must be suspended and, if the research is DHHS-sponsored, the Agency must be notified.

It is the responsibility of the Principal Investigator (PI) to submit a timely continuing review application. As a courtesy, the VHH IRB Office will send out renewal notices to investigators two months prior to the expiration of each approved protocol. The investigator should allow sufficient time for development and review of renewal submissions. Note: The "approval date" and the "approval expiration date" are listed on all IRB approval letters. By federal regulation, no extension to that date can be granted.

Investigators must provide complete answers to all questions on the *Continuing Review Application*, the current consent document and newly proposed consent document. Note: additional information may be required as specified in your original protocol review. For further information regarding continuing review, see [Continuing Review of Active Protocols](#).

## 14.5. Required Reports to the IRB

### *Unanticipated Problems*

Principal investigators must report to the IRB as soon as possible, but in all cases within 5 working days of any:

- adverse events involving direct harm to participants which in the opinion of the principal investigator are both unexpected and related
- an unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk but that does not involve direct harm to participants
- IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
- new information that indicates a change to the risks, conduct of the trial or potential benefits of the research. For example:
  - an interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
  - a paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB
  - a breach of confidentiality
  - incarceration of a participant in a protocol not approved to enroll prisoners
  - Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial
  - change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant

- complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm
- event that requires prompt reporting to the sponsor
- sponsor imposed suspension for risk
- any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research

The IRB will accept other reports when the investigator is unsure whether the event should be reported. The investigator should first contact the IRB Office by email or telephone to determine if the reporting is necessary.

Principal investigators should report the above events using the *Reportable Event Form*. Reports may be accepted by other means such as e-mail, or phone.

### **Submission of Reports**

Investigators must report possible unanticipated problems to the IRB promptly.

If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.

Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

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

Investigators or the study team must report possible unanticipated problems to the IRB Office in writing using the Reportable Event Form. The reportable event should contain the following:

- detailed information about the possible unanticipated problems, including relevant dates
- any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again
- an assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences
- any other relevant information
- any other information requested by the IRB Office

A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded to the IRB Chair or his or her designee if immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a reportable event of a possible unanticipated problem from someone other than the investigator or study staff, the IRB Chair or his or her designee will notify the Principal Investigator on the study when appropriate.

### **Complaints, Non-Compliance and Protocol Deviations**

Investigators must report all complaints and concerns from subjects and reports of non-compliance to the IRB within ten (10) working days.

The following procedures describe how protocol exceptions and deviations are reported to the IRB.

## 14.6. Exceptions

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

These exceptions must be approved by the sponsor and IRB before being implemented.

Exceptions may not increase risk or decrease benefit, affect the participant's rights, safety, welfare, or affects the integrity of the resultant data.

## 14.7. Deviations

A **protocol deviation** is defined as a departure or inadvertent action in study activity from the currently-approved protocol. Deviations can result from actions of the research team or the study subjects and can be the result of deliberate changes to the protocol or from circumstances out of the control of the study team. Examples of deviations that may be considered non-serious include failure to complete a Quality of Life survey, failure of subjects to return unused study drug, or study visits/procedures conducted outside of protocol-defined window.

**Serious protocol deviation:** a departure or inadvertent action in study activity from the currently approved protocol that affects the rights, safety and welfare of the research subject, or adversely affects the scientific integrity of the study. (I.e. missed study treatments or safety labs, etc.).

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

Deviations that increase risk have potential to recur or undertaken to eliminate an immediate hazard would be considered an [Unanticipated Problem](#).

Serious protocol deviations must be reported to the IRB within five (5) business days of the study team's knowledge of the deviation. All other protocol deviations can be submitted at the time of Continuing Review.

When a sponsor requests that the IRB be notified of a deviation, the study team will complete the Reportable Event form; this completed form will be forwarded to the IRB chair or designate for review.

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

## 14.8. Reporting & Review

*Reportable Event Forms* are to be completed for protocol deviations, non-compliance, serious adverse events, UAPs, or protocol exceptions. These reports should be filed with the IRB Office. The IRB Office will forward the report to the IRB Chair or designee for review and signature. A signed acceptance/determination letter will be sent back to the investigator for the study file. The Chair may choose to place any reportable event on the agenda at the next convened IRB meeting for discussion. The investigator may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.



## **Progress Reports**

Investigators must report the progress of the research to the IRB in the manner and frequency prescribed by the IRB, but no less than once a year.

When an approved research project is completed, the investigator must promptly notify the IRB and file with the IRB a final progress report, which includes the information listed above for continuing review of protocols for the last research project period.

Once data collection has been completed and the research is closed at the Institution or other sites, a final closure submission must be forwarded to the IRB. Once this final submission is complete, the Principal Investigator is not required to submit any further reports of the research to the IRB.

## **14.9. Investigator-Required Record Keeping**

Investigators must retain copies of approved IRB documents, and implement a system to comply with approval expiration dates.

In addition to providing a copy of the signed and dated consent form to each subject, a copy must be stored securely by the Principal Investigator (PI) and placed in the subject's medical record (if the subject is a patient and this requirement has not been waived by the IRB), and a copy must be retained by the Principal Investigator for a minimum of 5 years after completion of the research.

## **14.10. Training & Ongoing Education of Principal Investigator and Research Team**

As stated above, one component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. VHH IRB is committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

### **Orientation**

All Principal Investigators and members of their research team (also known as "key personnel") must review core training documentation including the *VHH IRB Policies & Procedures for Human subjects' research Protection*, and the "*Belmont Report: Ethical Principals and Guidelines for the Protection of Human Subjects of Research*"

### **Initial Education**

Education in human subject protections is required for all researchers directly involved in the conduct of research. This includes individuals who collect or enter data, individuals who conduct study procedures (including informed consent) or interventions with human subjects, and individuals who use or have access to private information that can be linked to research subjects. The policy applies to all research involving the use of human participants, regardless of funding.

The Principal Investigator and key investigators must complete VHHthe VHH IRB required Biomedical Researcher Core Modules in the CITI Program Courses in the Protection of Human Research Subjects. In addition to the Biomedical Researcher core modules, researchers are also required to complete the Information Privacy Security (IPS) module.

New research protocols and applications for continuing review will not be accepted from principal investigators who have not completed the initial education requirement.

While research protocols and applications for continuing review will be accepted and reviewed if the Principal Investigator holds a current certification of training, final approval will not be granted until all co-investigators and members of the research team have completed the initial education requirement (or the continuing education requirement once the initial education requirement has been satisfied).

### **Waiver of Initial Education**

If investigators or members of their research team can verify that they have successfully completed human subjects' research training equivalent to that required by VHH IRB, they may request a waiver of the requirement for initial education. However, all investigators or members of their research team must complete the requirements of continuing education.

### **Continuing Education and Recertification**

All investigators and members of their research teams must meet VHH IRB continuing education requirement every three (3) years after certification of Initial Education for as long as they are involved in human subject research. There is no exception to this requirement. Acceptable training includes attendance at PRIM&R or OHRP seminars and conferences, attendance at an IRB office Human subjects' research Presentation, or review of appropriate refresher modules at the CITI web-based training site. Other training may be acceptable. In these cases the researcher should check with the IRB Office for a determination. Investigators must submit evidence of continuing education prior to the expiration of their training certification. New research protocols and applications for continuing review will not be accepted from principal investigators who have not submitted satisfactory evidence of continuing education.

Investigators who are also IRB Chair, IRB members, or IRB Office staff will satisfy the training requirements for IRB members and staff described in this policy.

### **Additional Resources**

Human research protection information will be made available on the IRB website on an ongoing basis to ensure that the VHH research community is apprised of current regulatory and policy requirements and training opportunities.

## **14.11. Investigator Conflict of Interest**

Under *VHH's Policy on Conflicts of Interest*, VHH and all investigators participating in research at VHH have a primary obligation to conduct the research free of the appearance of conflict. To participate in research that might be perceived to be compromised due to a personal or institutional interest is contrary to this commitment unless the conflict of interest is managed or eliminated. Under certain circumstances, an investigator's personal interest (or VHH's institutional interest) might be too significant to permit participation in the research.

The *Conflicts of Interest Policy* accommodate current federal regulations designed to protect the integrity of federally funded research and all other applicable laws and regulations and are consistent, to the extent appropriate for the VHH community with the latest best practices recommendations of the Association of American Medical Colleges.

All Investigators and key research personnel must follow *VHH Conflict of Interest Policy*.

It is IRB policy to preserve public trust in the integrity and quality of research at the Organization by minimizing actual or perceived conflict of interest in the conduct of research.

The following describe the procedures by which this responsibility is carried out.

## **Definitions**

### **Conflict of Interest**

A conflict of interest (COI) occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings.

### **Ownership Interest**

Ownership interest means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly traded corporation during the time the investigator is carrying out the study and for 1 year following completion of the study.

### **Compensation**

Compensation means payments made by an organization to the investigator or the institution exclusive of the costs of conducting the research during the time the investigator is carrying out the study and for 1 year following the completion of the study. This includes, but is not limited to:

- Income from seminars, lectures or teaching engagements
- Income from service on advisory committees or review panels
- Grants to fund ongoing research
- Compensation in the form of equipment
- Retainers for ongoing consultation

### **Patent**

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

### **Royalty**

A royalty is compensation for an invention.

### **Immediate Family Member**

Immediate family member: having a relationship to a person (whether by blood, law, or marriage) as a spouse (including domestic partner, partner through civil union), parent, child, grandparent, grandchild, stepchild, or sibling.

### **Financial Interest Related to the Research**

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

### **Significant Financial Interest**

Significant Financial Interest includes:

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

- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement
- Board or executive relationship related to the research, regardless of compensation

### **Non-Financial Conflict of Interest**

Non-financial conflict of interest may exist when an individual serves dual roles, such as health care provider and investigator. Other interests such as publication, promotion or tenure, can also become conflicts of interest that may affect an individual's judgment. Membership in oversight committees such as the IRB as well as positions of authority may pose potential conflicts of interest. Any position that includes responsibilities for the review and approval of research projects or contracts other than his/her own may potentially affect the design of, decisions made and/or action taken surrounding a specific study.

### **Key Personnel**

Key research personnel are those individuals who:

- obtain consent from human subjects
- recruit human subjects; or
- evaluate the response of human subjects

## **14.12. Individual Conflicts of Interest**

These procedures apply to both financial and non-financial conflicts of interest and are guided by Code of Federal Regulations [Title 42 of the Code of Federal Regulations (CFR) Part 50 Subpart F] that promotes objectivity in research to ensure conflict of interests do not adversely affect the protection of participants or the credibility of the VHH Human Research Protection Program (IRB).

For clinical studies involving the use of new human drugs and biological products or medical devices, certifications and disclosure requirements are defined in Food and Drug Administration (FDA) regulations, Title [21 CFR Part 54].

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively disclosed and managed when they cannot be eliminated.

The research section of the Conflicts of Interest Policy identifies procedures for disclosure, evaluation and either management or elimination of potential conflicts of interest in research. Under the Conflicts of Interest Policy, a conflict of interest may exist whenever an investigator has a financial interest in a research project, including any interest in entities sponsoring or otherwise affected by the research and any interests in products being used in the research. When the interest is considered minor, the investigator's participation in the research will normally be permitted, subject to a conflict of management plan issued by VHH. When an interest is significant, an investigator will not normally be permitted to participate in the research, unless compelling circumstances exist to merit an exception to the policy and a conflict management plan is adopted to maintain research integrity and serve the best interests of subjects enrolled in the research.

Under the Conflict of Interest Policy, all investigators and other key research personnel must make protocol-specific financial interest disclosures for every research project, regardless of subject matter or funding. Investigators and other key research personnel include all of those individuals who do any of the following things in connection with VHH research:

- design, conduct or direct the research

- apply for grants or awards to perform research
- serve as a principal investigator, co-investigator or sub-investigator
- enroll subjects
- obtain consent from human subjects
- make decisions related to eligibility of human subjects
- analyze, report, present or publish research data

In addition, all such individuals must complete and return an annual disclosure form under which they disclose any outside interests related to their responsibilities at VHH and its affiliates.

For an individual research project, in the event a completed Investigator Financial Interest Disclosure Form indicates that an investigator or other key personnel (or any of their immediate family members) has a financial interest in the protocol, the investigator is required to submit additional information as requested by the IRB. The IRB will review the disclosures, together with the protocol and any proposed conflict management plan, and will determine if the disclosed financial interest is a significant financial interest which needs to be reviewed by a qualified independent person(s) appointed by the IO. For any matter submitted to it, a qualified independent person(s) appointed by the IO will review and evaluate the matter to determine whether compelling circumstances exist to justify participation in the research notwithstanding the disclosed financial interest. If yes, the qualified independent person(s) appointed by the IO will issue a conflict management plan to be reviewed and approved upon by the investigator with the conflict and the principal investigator for the project. At a convened meeting, the IRB committee will review the management plan and provide further recommendations to the plan or accept the plan.

Based on the significance of the interest and the conflict and the potential for adverse effects on the protection of subjects, conflict management plans issued by the qualified independent person(s) appointed by the IO can include:

- reduction, divestiture or elimination of the disclosed financial interest
- disclosure to subjects through the consent process
- disclosure to the research sponsor, to public officers and to other investigators
- modifications in the research plan
- restrictions on the investigator's participation in the research
- monitoring by independent reviewers
- appointment of a non-conflicted Principal Investigator

Where the qualified independent person(s) appointed by the IO determines that compelling circumstances do not exist to justify participation in the research, the investigator with a disclosed financial interest will not be permitted to participate in the conduct of the research at VHH.

For all human subjects research projects where an investigator discloses a financial interest, the IRB will not issue its final approval of any project before the IRB and/or the qualified independent person(s) appointed by the IO has completed its review and evaluation of the potential conflict as required under the Conflicts of Interest Policy.

A qualified independent person(s) appointed by the IO will submit to the IRB Chair the conflict management plan issued by the Counsel and approved by the applicable investigators.

Upon receipt, the IRB Chair (or designee) will review the conflict management plan issued by the qualified independent person(s) appointed by the IO and report the results of the evaluation of the management plan to the convened IRB prior to issuing the IRB's final approval of the project. The IRB may modify the plan to impose more stringent restrictions than those imposed by the qualified independent person(s) appointed by the IO in order to protect research subjects or accept the plan as written. The completion of the review required under the Conflicts of Interest Policy will be documented

in the IRB's protocol file. A copy of the final, approved conflict management plan will also be filed in IRB Office.

If an investigator's financial interests in a research protocol changes during the course of a study, the investigator is required to submit a revised Investigator Financial Interest Disclosure Form to the IRB prior to acquiring such new financial interests. The IRB and, for material changes to prior disclosures, the qualified independent person(s) appointed by the IO will review the change to determine if the conflict management plan on file is adequate and appropriate for the changed circumstances.

In addition, an investigator is required to update their disclosure form at each annual continuation of a research project if a conflict has changed or a new conflict exists. The IRB will review material changes to the financial interest disclosures as part of its continuing review (as applicable).

### **14.13. Institutional Conflict of Interest**

An institutional conflict of interest (ICOI) arising in human subjects research when a financial interest of VHH may affect or appear to affect the design, conduct, reporting, review, or oversight of human subjects research. ICOI are of significant concern when VHH's interests create the potential for inappropriate influence over the research project, particularly to the integrity of the research and the safety and care of patients enrolled in the research. All potential ICOI require disclosure, evaluation and either management or elimination under this Institutional Conflicts Policy.

An ICOI is deemed to arise under this Policy whenever VHH either (a) receives or might reasonably be expect to receive royalty income from the sale of a product covered by an VHH intellectual property right being used in human subjects research or (b) holds equity interests acquired in VHH's technology licensing activities (or investments related to such activities) in the research sponsor.

As a matter of this policy, VHH will not participate in a human subjects research project when an ICOI is deemed to arise due to such institutional interests. An exception may only be made if the VHH IO determines that compelling circumstances exist to merit an exception and a conflict management plan is adopted. The conflict management plan can include the restrictions contemplated for individual conflict management plans as outlined above and additional restrictions on VHH institutional participation in the research.

For all human subjects research projects where an ICOI exists, the IRB will defer review and approval to an external Institutional Review Board.

### **14.14. Subject Recruitment**

Investigators are responsible for recruiting research subjects in a manner that is fair, ethical and equitable. IRB approval is required for all recruitment procedures and materials. Recruitment materials must be consistent with the approved IRB protocol, accurate, and not coercive. For specific information regarding recruitment materials, review and creation guidance, please see the Informational Sheet regarding Advertisements and Recruitment Materials.

#### ***Recruitment Incentives***

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from researchers (physicians) ("finder's

fees”) is not permitted. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.

### **Payment to Subjects**

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment. Such justification should:

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

The IRB must review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive.

The IRB prohibits:

- the entire payment to be contingent upon completion of the entire study. Payment in exchange for referrals of prospective participants from researchers (physicians) (“finder’s fees”) is not permitted. •
- compensation for participation in a trial offered by a sponsor from including a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
- payments to the organization or research staff designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”).

The consent form must describe the terms of payment and the conditions under which subjects would receive partial payment or no payment (e.g., if they withdraw from the study before their participation is completed).

Unless the study is confidential, the VHH Office of Business and Financial Services requires identifying information to issue checks, cash, or gift certificates to subjects. The consent form must inform subjects that they will be asked to provide their social security number and verification of U.S citizenship or permanent resident status to receive payment. For confidential studies only name and address are required by OBFS, but the Principal Investigator must keep an identity key in a secure place.

## **14.15. Investigator Concerns**

Investigators who have concerns or suggestions regarding VHH’s human research protection program should convey them to the Institutional Official or other responsible parties regarding the issue, when appropriate. The Institutional Official will research the issue, and when deemed necessary, convene the parties involved to form a response for the investigator or make necessary procedural or policy

modifications, as warranted. In addition, the Chair of the IRB or his or her designee will be available to address investigators' questions, concerns and suggestions.

## 15. Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. While the main affect of the Privacy Rule will be on the routine provision of and billing for health care, the Rule will affect the conduct and oversight of research. Researchers, IRB staff and members as well as research administration must be aware of these changes.

Protected Health Information (PHI) obtained by VHH may not be used internally or disclosed to any outside person or organization for research purposes without prior approval of the IRB. VHH researchers must also abide by all corporate HIPAA policies regarding HIPAA privacy and security.

The following describe the procedures for conducting research at VHH in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

### 15.1. Definitions

#### **Access**

Access is the mechanism of obtaining or using information electronically, on paper, or other medium for performing an official function.

#### **Authorization**

An authorization is a detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

#### **Covered Entity**

Covered entity is the term applied to institutions that must comply with the Privacy Rule. These include:

- health plans
- health care clearinghouses
- health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.

#### **Common Rule**

Common Rule is a federal Policy on human subject protection that provides for the primary source of regulation of research.

#### **De-Identified Information**

De-Identified Information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. If information is de-identified, it no longer is subject to the Privacy Rule and exempt from HIPAA.

#### **Deletion**

Deletion is the removal, erasing, or expunging information or data from a record.



## Disclosure

Disclosure is the release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity.

## Health Information

Health Information is any information created or received by a health care provider or health plan that 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 payment for the provision of health care to an individual.

## Identifiable Health Information

Identifiable Health Information is a subset of health information including demographic information collected from an individual.

## Limited Data Set

Limited Data Set is protected health information that excludes specific direct identifiers of the individual or of relatives, employees or household members of an individual. A limited data set can only be used for the purposes of research, public health, or healthcare operations, and disclosed for the purpose of research.

## Minimum Necessary

Minimum Necessary refers to the principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

## Privacy Board

Privacy Board is the term used to describe a board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's private rights. It is only an alternative to an IRB for privacy issues. It cannot replace the IRB for Common Rule purposes.

## Privacy Act

Privacy Act is an act that provides for the confidentiality of individually identified and retrieved information about living individuals that is maintained in a system of records and permits the disclosure of records only when specifically authorized by the statute. The Act provides that the collection of information about individuals is limited to that which is legally authorized, relevant, and necessary.

## Privacy Rule

Privacy Rule provides guidance on the use of protected health information in the conduct of research. It imposes requirements on those involved in research, both individuals and institutions. Privacy refers to a person's desire to control the access of others to themselves. The evaluation of privacy involves consideration of how the investigator will access information from or about participants. The IRB members should know strategies to protect privacy interests relating to contact with potential participants, and access to private information.

## Protected Health Information (PHI)

Protected Health Information is individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule.

## Preparatory Research

Preparatory Research is the method applied to developing or designing a research study.

## Waiver of Authorization

Waiver of Authorization is a means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.

## 15.2. Historical Background

HIPAA is an expansive federal law, only part of which is intended to protect the privacy of health care information. HIPAA required Congress to enact a health information privacy law by August 1999 and stated that if it did not act by then, which it did not, the U. S. DHHS must develop privacy regulations. The final Privacy Rule was published on August 14, 2002.

The objective of the rule is to protect the privacy of an individual's health care information. It creates a federal "floor" of protection so that every person in this country has at least the same basic rights and protections, though some may have additional rights depending on state law.

## 15.3. Effects of HIPAA on Research

The final Privacy Rule published on August 14, 2002 included a number of changes in how the Rule applies to research. See the NIH HIPAA Privacy Rule Booklet for Research and the NIH fact sheet on Institutional Review Boards and HIPAA for more information on how HIPAA applies to research. See also Impact of the Privacy Rule on Academic Research, a white paper published by the American Council on Education.

VHH is a covered entity under HIPAA. Researchers who are working with "Protected Health Information" (PHI) will be required to comply with the rules on HIPAA. The VHH IRB acts as the Institution's Privacy Board.

The Privacy Rule permits covered entities to use or disclose protected health information for research purposes when the individual who is the subject of the information authorizes the use or disclosure. For clinical trials, authorization must be sought in addition to informed consent. Authorization must also be sought for other research uses or disclosures of protected health information that do not qualify for an IRB waiver of authorization (discussed below).

The Privacy Rule has several special provisions that apply to research authorizations for uses and disclosures of PHI for research purposes. These requirements are as follows:

- an authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the end of the research study; and
- an authorization for the use or disclosure of protected health information for research may be combined with a consent to participate in the research, or with any other legal permission related to the research study (except for research involving the use or disclosure of psychotherapy notes, which must be authorized separately); and
- research authorization forms must be filled out completely and accurately by the investigator, to ensure that all parties who require access to protected health information for the research (including sponsors, CROs, DSMBs, IRBs, etc.) are identified in the form and may receive the information. The IRB combined authorization/consent form should be completed by the investigator and submitted to the VHH IRB for review and approval.

## 15.4. Research under HIPAA

HIPAA defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." This definition is identical with the one used in the "Common Rule", separate federal legislation designed to protect human subjects involved in research. HIPAA describes privacy standards for protecting PHI and so only applies to research that involves humans' (not animals') health information.

## ***Waiver of Authorization for Use or Disclosure of Protected Health Information in Research***

Under the Privacy Rule, covered entities [are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances. A covered entity may use or disclose protected health information for research when presented with documentation that an IRB has granted a waiver of authorization [see 45 CFR 164.512(i)(1)(i)]. This provision of the Privacy Rule might be used, for example, to conduct records research, epidemiological studies, or other research where de-identified data is unavailable or not suited to the research purpose.

The waiver documentation presented to the covered entity must include the following:

- identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved
- a statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule
- a brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board
- a statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
- the signature of the chair or other member, as designated by the chair, of the IRB or the Privacy Board, as applicable

The following criteria must be satisfied for the IRB to approve a waiver of authorization under the Privacy Rule. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

- an adequate plan to protect the identifiers from improper use and disclosure
- an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law
- adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart
- the research could not practicably be conducted without the waiver or alteration; and
- the research could not practicably be conducted without access to and use of the protected health information

## ***Review Preparatory to Research***

The Privacy Rule permits a covered entity to use or disclose protected health information to a researcher without authorization or waiver for the limited purpose of a “review preparatory to research.” Such reviews may be used to prepare a research protocol, or to determine whether a research site has a sufficient population of potential research subjects. Prior to permitting the researcher to access the protected health information, the covered entity must obtain representations from the researcher that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and that protected health information for which access is sought is necessary for the research purpose. Researchers should consult the covered entity regarding any forms or applications necessary to conduct a review preparatory to research.

Researchers conducting a review preparatory to research may not record information in identifiable form, nor may they use the information that they receive to contact potential subjects, unless the investigator is also the subject's treating physician. Because the Privacy Rule permits a covered entity to disclose protected health information to the individual who is the subject of the information, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization. Even when permitted by the Privacy Rule, however, any use of patient information for recruitment must comply with IRB recruitment policies (see discussion below):

- all human subjects' research requires IRB review to determine either a) exempt status or b) need for further review.
- reviews preparatory to research that are permitted under HIPAA may or may not be human subjects' research depending on the investigation being conducted.
  - only those reviews of a database by an individual entitled to access that database intended to enumerate an available data set without reviewing PHI and for which no PHI is recorded do not require review. For example: medical records may be queried for information such as: In the year XXXX how many patients had a discharge diagnosis of [indicate disease/diagnosis]. IRB Privacy Board Review is required for all other uses of PHI as indicated.
  - if the research involves a de-identified data set, defined as removing the following identifiers, then a de-identified data set certification form must be completed submitted for administrative review and certified prior to accessing the data set. This activity also requires an IRB determined exemption from review:
    - names
    - geographic info. (city, state, and zip)
    - elements of dates (except years)
    - telephone #s
    - fax #s
    - e-mail address
    - social Security#
    - medical Record, prescription #s
    - health Plan Beneficiary #s
    - account #s
    - certificate /License #s
    - VIN and Serial #s, license plate #s.
    - device identifiers, serial #s
    - web URLs
    - IP address #s
    - biometric identifiers (finger prints)
    - full face, comparable photo images
    - unique identifying #s

IRB Privacy Board review and approval is required prior to initiating this research. Investigators are not authorized to contact potential research subjects identified in reviews preparatory to research unless they are directly responsible for care of the potential subject and entitled to PHI as a result of that duty.

Investigators who have previously obtained full consent and authorization to contact a research subject as a result of a previously approved research project may contact his or her former research subjects provided that the subject agreed to be contacted for information on future research conducted by the same principal investigator or co-investigator (s).

### ***Research on Protected Health Information of Decedents***

The protections of the Common Rule apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons ("decedents"). The Privacy Rule contains an exception to the authorization requirement for research that involves the protected health

information of decedents. A covered entity may use or disclose decedents' protected health information for research if the entity obtains representations from the researcher that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought. Researchers should submit the applicable IRB form for IRB approval when they intend to conduct research involving decedents' protected health information.

### ***Limited Data Sets with a Data Use Agreement***

When a researcher does not need direct identifiers for a study but does require certain data elements that are not permitted in de-identified data, the Privacy Rule permits a covered entity to disclose a "limited data set" to the researcher without authorization or waiver, provided that the researcher has signed a data use agreement. The limited data set is still considered protected health information, but it must exclude only specified direct identifiers of the individual or of relatives, employers, or household members of the individual.

If the research involves a limited data set, defined as removing the following 16 identifiers:

1. Names
2. Postal address info. (if other than city, state and zip)
3. Telephone and fax #s
4. Email addresses
5. Social Security #s
6. Medical record
7. Prescription numbers
8. Health plan beneficiary #s
9. Account #s
10. Certificate/license #s
11. Vin and serial #s, license plate #s
12. Device identifiers, serial #s
13. Web URLs
14. IP address #s
15. Biometric identifiers (finger prints)
16. Full face, comparable photo images

The Privacy Rule requires that the data use agreement used in conjunction with the limited data set contain provisions that:

- establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or disclosure that would violate the Rule if done by the covered entity
- limit who can use or receive the data
- require the recipient to agree to the following:
  - not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
  - use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
  - report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware; Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
  - not to identify the information or contact the individual.

- researchers who will be receiving limited data sets must submit a signed copy of the covered entity's data use agreement to the VHH IRB for approval, prior to initiating the research.

### **Transition Provisions**

The Privacy Rule contains certain grandfathering provisions that permit a covered entity to use and disclose protected health information for research after the Rule's compliance date of April 14, 2003, if the researcher obtained any one of the following prior to the compliance date:

- An authorization or other express legal permission from an individual to use or disclose protected health information for the research
- The informed consent of the individual to participate in the research
- An IRB waiver of informed consent for the research

Even if informed consent or other express legal permission was obtained prior to the compliance date, if new subjects are enrolled or existing subjects are re-consented after the compliance date, the covered entity must obtain the individual's authorization. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization must be sought at the same time.

The transition provisions apply to both uses and disclosures of protected health information for specific research protocols and uses or disclosures to databases or repositories maintained for future research.

## **15.5. HIPAA and Document Requirements**

HIPAA documents include an authorization form, a waiver of authorization form, limited data set form, and a de-identification form. One of these documents must be used whenever PHI is utilized in the research.

## **15.6. Patient Rights and Research**

Under HIPAA, patients have certain rights. Those that may affect research include the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain disclosures of PHI that occur outside the scope of treatment, payment and health care operations that have not been authorized.

## **15.7. HIPAA and Existing Studies**

Any research subject enrolled in a study that uses PHI from a covered entity must sign a HIPAA-compliant authorization form. This form is in addition to the existing Informed Consent document, and is federally required. In a few cases, the Informed Consent document may be combined with a HIPAA authorization.

## **15.8. Waivers to HIPAA Consent Form**

In some cases the VHH IRB may approve a waiver to use of the HIPAA authorization form. This may occur when the IRB finds that the research could not be practically done without the waiver, and not without access to and use of the PHI, and that disclosure poses minimal risk to privacy.

## 16. Special Topics

### 16.1. Certificate of Confidentiality

#### *Statutory Basis for Protection*

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.

*Certificates of Confidentiality* constitute an important tool to protect the privacy of research study subjects. Certificates are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

*Certificates of Confidentiality* may be granted for studies collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, *Certificates of Confidentiality* help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Certificates are granted sparingly. The study's funding source, if any, is not relevant to the decision.

The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the subjects).

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a *Certificate of Confidentiality*. Research can be considered "sensitive" if it involves the collection of:

- information about sexual attitudes, orientation, practices
- information about personal use of alcohol, drugs, or other addictive products
- information about illegal conduct
- information that could damage an individual's financial standing, employability, or reputation within the community
- information in a subject's medical record that could lead to social stigmatization or discrimination
- information about a subject's psychological well-being or mental health

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB Office for help in applying for a certificate.

The IRB may require investigators to apply for a *Certificate of Confidentiality*.

### **Limitations**

The protection offered by a *Certificate of Confidentiality* is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does not restrict voluntary disclosures.

For example, a Certificate does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if researchers intend to make such disclosures, this should be clearly stated in the informed consent form which research subjects are asked to sign.

In addition, a Certificate of Confidentiality does not authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if:

- the subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information
- authorized personnel of the DHHS request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees
- release of such information is required by the Federal Food, Drug, and Cosmetic Act or regulations implementing that Act

### **Application Procedures**

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. For most research, Certificates are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a Certificate through the NIH Institute or Center (IC) funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the AHRQ confidentiality statute [42 U.S.C. section 299a-1(c)] entitled "limitation on use of certain information" or the Department of Justice confidentiality statute [42 USC section 3789g], then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

## **16.2. Mandatory Reporting**

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Colorado law mandates that certain persons who suspect child or elder abuse or neglect report this to the Colorado Department of Children and Family Services or the Colorado Department on Aging, as appropriate.

VHH policy requires the solicitation of informed consent from all adult research subjects and assent from children involved as research subjects, in addition to the consent of their parents/legal guardians. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of elder abuse or neglect.



### 16.3. VHH Students and Employees as Subjects

When VHH and employees of the PI or related entities are being recruited as potential subjects, researchers must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be principal and without undue influence on their decision. Researchers must emphasize to subjects that their employment will not be affected by their participation decision. Record of the participation cannot be linked to an employment record. The IRB also ensures when necessary a certificate of confidentiality is sought in sensitive research topics such as Mental Health, drug/alcohol abuse, sexual behavior, or others that fall into this category.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures that are neither therapeutic nor diagnostic.

### Recruitment of Research Team and/or Family Members to participate in Research

The enrollment of spouses, dependents, or research team members presents the perception, whether real or not, of research bias and coercion and is not allowed by the VHH IRB. These individuals can participate in research but not in a study in which they are on the study team or are the spouse or dependent of a study team member.

### 16.4. Oral History

The following is based on guidance received from OHRP:

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution's FWA and HHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under HHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

- The activity involves a prospective research plan which incorporates data collection, including qualitative data, and data analysis to answer a research question; and
- The activity is designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

In order to be subject to the VHH's human research protections policies, the activity must meet both of the above standards. This determination will be made according to the procedures described in Section 7.1.

General Principals for evaluating Oral History type activities:

- Oral history activities, such as open-ended interviews, that only document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings would not constitute "research" as defined by HHS regulations 45 CFR part 46.

Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the videotape does NOT intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

- Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by HHS regulations at 45 CFR parts 46.

Example: An open-ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

- Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Since the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR part 46, the creation of such an archive would constitute research under 45 CFR part 46.

Example: Open ended interviews are conducted with surviving Negro League Baseball players in order to create an archive for future research. The creation of such an archive would constitute research under 45 CFR part 46 since the intent is to collect data for future research.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.

## 16.5. Genetic Studies

Since human genes are the sequence instructions to make all human proteins, genetic studies can lead to a molecular description of normal physiological function. Likewise, defects (mutations) in individual genes can lead to pathology. This is a major current area of health research, although the potential power of genetic research is also the inherent risk. In particular patients and family members can learn of ominous mutations prior to disease symptoms. Thus genetic information, not specifically solicited by the subject, could be the first warning sign of a troubled future. Furthermore, such mutations can be carried through subsequent generations, affecting as yet unborn descendants; and potential illness can be predicted even for family members, un-enrolled and unaffiliated with the research protocol. Although of high predictive value when proven, un-validated results of genetic experiments can still cause actual psycho-social hardship even leading to financial loss.

### *Privacy and Confidentiality*

In human subject research using genetic testing, the actual physical interventions involved are usually minor, and would ordinarily be reviewed under the minimal risks categories of the Federal Regulations as just a blood draw. However the IRB board, when reviewing any studies with genetic testing, must also consider the various psychosocial and financial risks. This includes examining the procedures in place to preserve confidentiality of study information, and subject identity. It also includes assessing the potential consequences of inadvertent disclosure.

The procedures that could be used include: keeping the test results in the research records and out of the clinical patient charts, doing the testing in research laboratories where results could not be relied on for clinical decision-making or provided to insurance companies as validated health records.

Encoding data such that individual identity is separate from medical/genetic information (de-identification) is a key element in dealing with all research data that could suggest among other things that:

- a subject may eventually suffer a serious loss of abilities related to his/her career
- they might incur higher than usual health care costs
- they have a statistically lower life expectancy
- that their ability to procreate and perform socially may become impaired

### ***Diagnostic Status and Types of Tests***

In assessing these risks, aside from considering the predictive confidence of the information and its health implications, one should also consider the current diagnostic status of the patient. For example genetic test studies that are confirmatory of an established diagnosis (testing the test), have much lower risk than when they are predictive in the absence of any symptoms. In addition, gene expression studies that are mechanistic in nature may not directly relate to a genetic mutation that could be inherited.

Pharmacogenomic studies, for example, could help choose the most effective therapy, or inform the patient that the available therapies would or would not be effective—thus conferring a range of risks and benefits that must be considered.

### ***Federal vs. State Law***

Thus, Federal Human Subjects Regulations treat genetic testing to the extent that risks associated with breach of confidentiality, financial harm and psychosocial consequence must all be analyzed along with the potential benefits of the study. However, Colorado State law may have some specific provisions that must be applied whenever human subjects participate in a genetic testing trial located in Colorado.

The definition of “genetic test” is less important for Federal law because there is no “genetic testing article”. Both sets of laws apply to all subjects in VHH clinical trials.

The presence of these affirmative requirements for informing the subjects of the purpose and procedures of the genetic tests do not preclude more open-ended use of de-identified genetic material at a later time, providing certain provisions are followed and that the subject did not specifically disallow this.

The Federal law requires full board review for any study that poses a greater than minimal risk and the reviewers have the latitude to invoke that risk categorization for instances when the only risks are confidentiality related or psychosocial in nature.

Furthermore, HHS, in an advisory publication, has listed a variety of specific issues that must be dealt with in the consent form (and the review process), including:

- what data (including its reliability and significance) will be provided to the subject and when;
- that subjects may obtain information about themselves or family members which may make them uncomfortable, and likewise family members may be privy to the same information;
- that actions taken may compromise their privacy, insurability and result in financial loss;
- a list of assurances about safeguards to prevent loss of privacy;
- the rights subjects retain over tissue samples and medical information, including the consequences of withdrawing from the study; and
- any potential costs associated with participation.

## Recruitment for Individual or Pedigree Studies

During genetic studies, confidentiality (the obligation of institutions to appropriately use restricted information once disclosed to them) and respect for privacy (the right to be left alone) begin with the recruitment process.

Contacting an individual to solicit participation in a genetic study can produce stress in the individual and should be done by the physician treating the patient for the related illness. However, this is often not possible for pedigree studies, where it is desired to recruit family members. In such cases, the current subject under treatment or enrolled in the **study (proband)** should be used to contact the family members and assess their interest in being contacted. Nonetheless instances may develop where unsolicited disclosure is necessary, and the need to violate confidentiality must be considered. The conditions under which this is acceptable require all of the following:

- Subjects are at risk of serious harm;
- Harm can be ameliorated; and
- Only information necessary for amelioration is communicated.

There is additional legal basis for protecting the privacy of third parties in NYS law, which acts decisively in this regard. Thus:

3.(b) No person who lawfully possesses information derived from a genetic test on a biological sample from an individual shall incorporate such information into the records of a non-consenting individual who may be genetically related to the tested individual; nor shall any inferences be drawn, used, or communicated regarding the possible genetic status of the non-consenting individual.

## Summary

The following questions are useful when reviewing genetic studies. In studies involving genetic testing, several questions need to be addressed, including:

- Will test results be given?
- Will disease risk be quantified, including the limits on certainty of the testing?
- Will a change in a family relationship be disclosed, such as mistaken paternity?
- Does the subject or family member have the option not to know the results? How will this decision be recorded?
- Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
- Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
- Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

- Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
- Will the subject be contacted in the future by the investigator to obtain updated clinical information?
- How can the subject opt out of any distribution or subsequent use of his/her genetic material?

## Research Involving Coded Private Information or Biological Specimens

This policy is based on the OHRP guidance document entitled *Guidance on Research Involving Coded Private Information or Biological Specimens* (August 10, 2004

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects [45 CFR part 46].
- Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subjects' research.
- Provides guidance on who should determine whether human subjects are involved in research.

For purposes of this policy, *coded* means that:

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

Under the definition of human subject in this document, obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research.

### **Obtaining**

means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving only coded private information or specimens do not involve human subjects if the following conditions are **both** met:

5. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals;

and

6. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
  - the key to decipher the code is destroyed before the research begins;
  - the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); data use agreement
  - there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
  - there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(d) above may:

- unexpectedly learn the identity of one or more living individuals, or
- for previously unforeseen reasons now believe that it is important to identify the individual(s).

If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects' research is determined to be exempt (See [Exempt Research](#)), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent (See [Waiver of Informed Consent](#)).

### ***Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research***

The investigator in consultation with the IRB Chair or his or her designee will determine if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

## **16.6. Case Studies Requiring IRB Review**

In general, an anecdotal report on a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and would not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore would be considered research and would require IRB approval.

### ***Definitions***

#### **Single Case Report/Study**

The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

#### **Case Series**

The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

## **16.7. International Research**

The IRB will review all international research utilizing human participants to assure adequate provisions are in place to protect the rights and welfare of the participants.

Approval of research is permitted if "the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in [45 CFR 46]."

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

The IRB must receive and review the foreign institution or site's IRB review and approval of each study prior to the commencement of the research at the foreign institution or site.

For Federally funded research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the Investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials are permitting the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/IEC determination, or letter of cooperation, as applicable.
- It is the responsibility of the VHH Investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
- It is the responsibility of the VHH Investigator and the foreign institution or site to confirm the qualifications of the Researchers and Research Staff for conducting research in that country(ies).
- It is the responsibility of the VHH Investigator and the foreign institution or site to ensure that the following activities will occur.
  - Initial review, continuing review, and review of modification
  - Post-approval monitoring
  - Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.

The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

- It is the responsibility of the VHH Investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research participants, etc.).
- The IRB will consider local research context when reviewing international studies to assure protections are in place that are appropriate to the setting in which the research will be conducted, including knowledge of local laws and cultural context.
- In the case where there is no local IRB review the IRB may require an expert consultant, either from the local country where the research is conducted or from an international organization, with the expertise or knowledge required to adequately evaluate the research in light of local context.
- The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document that must be provided by the Investigator, with the credentials of the translator detailed in the IRB application or amendment form. Verification of the back translation should be made available for the IRB file.

### ***Monitoring of Approved International Research***

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. When the

IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local ECs

The IRB will require documentation of regular correspondence between the IRB Investigator and the foreign institution or site and may require verification from sources other than the IRB Investigator that there have been no substantial changes in the research since its last review.

## **16.8. Embryonic Stem Cell Research**

VHH regulates the use in research and the derivation for research, of human embryonic stem cells and other human stem cells to assure compliance with all applicable laws, rules and regulations and to ensure that all such research is performed ethically. Certain activities relating to human stem cells, such as human reproductive cloning and research requiring the breeding of animals into which human embryonic stem cells have been introduced are subject to the oversight and approval of the VHH Ethics Committee.

The composition, duties and responsibilities of the Ethics Committee are distinct and separate from the IRB.