Van Andel Research Institute

Human Research Protection Program
(HRPP)
Policies and Procedures
Manual

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ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
ASL	American Sign Language
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CoC	Certificate of Confidentiality
COI	Conflict of Interest
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
EC	Executive Committee
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
GC	General Counsel
GCP	Good Clinical Practices
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HSR	Human Subjects Research
ICH	International Conference on Harmonization
IO	Institutional Official
IRB	Institutional Review Board
IT	Information Technology
LAR	Legally Authorized Representative
LDS	Limited Data Set
MCL	Michigan Compiled Law
MTA	Material Transfer Agreement
NHS	Non-Human Subjects (research)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSR	Office of Sponsored Research/Grants and Contracts
PI	Principal Investigator
PHI	Protected Health Information
PHS	Public Health Service
PII	Personally Identifiable Information
PRIM&R	Public Responsibility in Medicine and Research
QA	Quality Assurance
QI	Quality Improvement
UAPs	Unanticipated Problems (Involving Risk to Subject or Others)
VAEI	Van Andel Education Institute
VAI	Van Andel Institute
VAIGS	Van Andel Institute Graduate School

VARI Van Andel Research Institute

1 Human Research Protection Program

The Van Andel Research Institute (VARI) fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In the review and conduct of research, actions by VARI will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (often referred to as the *Belmont Report*). The actions of VARI will also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this policy, VARI has established a Human Research Protection Program (HRPP). The VARI HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices. The research may be externally funded, funded from VARI sources, or conducted without direct funding.

The VARI Human Research Protection Program (VARI HRPP) operates under the authority of the VARI policy "*Human Research Protection Program (HRPP) and IRB Responsibilities*". 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 VARI." These operating procedures are reviewed at least annually by the Regulatory Programs Manager, updated as warranted, and are made available to the VARI research community on the VARI Intranet HRPP site. Changes to these policies and procedures are communicated to the VARI research community by way of email notifications and are updated and highlighted on the VARI Intranet HRPP site (https://vanandelinstitute.sharepoint.com/sites/compliance/Pages/HRPP.aspx).

Research that has been reviewed and approved by the VARI Institutional Review Board (IRB) may be subject to review and disapproval by officials of the institution. However, those officials may not approve human research that has not been approved by the IRB.

1.1 Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high-quality education, review and monitoring of human research projects; and
- To facilitate excellence in human subjects research.
- The HRPP includes mechanisms to:
    - Monitor, evaluate and continually improve the protection of human research subjects.
    - Dedicate resources sufficient to do so.
    - Exercise oversight of research protection.
    - Educate PIs and research staff about their ethical responsibility to protect research subjects.
    - When appropriate, intervene in research and respond directly to concerns of research subjects.

1.2 Definitions

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 including all Subparts. The Common Rule was updated in 2018. Throughout this manual, references to the "pre-2018 Common Rule" (or requirements) apply to studies approved or determined exempt prior to January 21, 2019, that have not been transitioned to comply with the 2018 Common Rule. References to the "2018 Common Rule" (or requirements) or the "revised Common Rule" apply to studies approved or determined exempt on or after January 21, 2019.

Human Subjects Research. – means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule or FDA regulations. At VARI this also includes use of specimens with keys or codes to identifiers that may be held by an external investigator.

Note: The terms "subject" and "participant" are used interchangeably in this document and have the same definition.

Pre-2018 Common Rule Definitions:

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

For the purposes of these policies and procedures, a **"systematic investigation"** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those 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.

Human subject. Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention. 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. Interaction includes communication or interpersonal contact between investigator and subject. *Please note that per OHRP interaction includes indirect means of communication such as via completion of a web-based survey.*

Private Information. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and

information that 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. Identifiable information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

2018 Common Rule Definitions:

Clinical Trial. Per the 2018 Common Rule and NIH Policy, clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. FDA regulations refer to "clinical investigations" (see definition of "research" in FDA section below).

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part [the Common Rule], the following activities are deemed not to be research: (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected. (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. [45 CFR 46.102(l)]

For the purposes of these policies and procedures, a **"systematic investigation"** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those 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 accordance with OHRP guidance, the establishment of a research repository is also considered a systematic investigation intended to develop generalizable knowledge.

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. [45 CFR 46.102(e)(1)]

Intervention means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(e)(2)]

Interaction means communication or interpersonal contact between investigator and subject. *Please note that per OHRP interaction includes indirect means of communication such as via completion of a web-based survey.*

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

Identifiable private information means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. [45 CFR 46.102(e)(5)]. *Note: This definition is within the 2018 Common Rule. For a discussion of identifiability under HIPAA, please see Section 19.*

Identifiable biospecimen means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen [45 CFR 46.102(e)(6)]

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Legal guardian. A person appointed by a court of appropriate jurisdiction.

Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

Food & Drug Administration (FDA) Definitions:

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

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

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

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

Human Subject. Human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject might be either a healthy individual or a patient. For research involving medical devices, a human subject is also an individual on whose specimen an investigational device is used or tested or used as a control (regardless of whether the specimens are identifiable). [21 CFR 50.3(g), 21 CFR 312.3(b), 21 CFR 812.3(p)]

Test Article. Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]

Test articles covered under the FDA regulations include, but are not limited to:

1. **Human drugs** – 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. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
2. **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."

   The 21st Century Cures Act amended the FD&C Act to specifically exclude certain software functions from the definition of medical device. Summarized, these include exclusions for software functions intended for administrative support of a health care facility; for maintaining or encouraging a healthy lifestyle; to serve as electronic patient records; for transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results and related information; and for displaying, analyzing, or printing medical information, for supporting or providing recommendations to a health care professional, and enabling the health care professional to independently review the basis for such recommendations. Additional information regarding the application of these exclusions is available on FDA's "Guidances with Digital Health Content" website.

3. **In Vitro Diagnostic Product (IVD).** In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory. [21 CFR 809.3(a)]

4. **Human Cells, Tissues, or Cellular or Tissue-based Products** (HCT/Ps) – HCT/Ps means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

   The following articles are not considered HCT/Ps: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/Ps; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

5. **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.

6. **Dietary Supplements** – A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.

7. **Medical Foods** – A medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)), is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

8. **Mobile Medical Apps** - Mobile apps are software applications that can be executed on a mobile platform or a web-based software application that is tailored to a mobile platform but is executed on a server. Mobile medical apps are a subset of mobile apps that medical devices that meet the definition of a medical device and either are intended to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device.
9. **Radioactive Drugs** – The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes "radioactive biological product".
10. **Radiation-Emitting Electronic Products** - a radiation-emitting electronic product as any electrically-powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).
11. **Food Additives** – A food additive is defined in Section 201(s) of the Food Drug and Cosmetic Act as 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 characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food *additives.* *http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm*
12. **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. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time. *http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm*
13. **Foods** – Foods include dietary supplements that bear a nutrient content claim or a health claim.
14. **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother's milk.

Other Definitions:

Institutional Review Board (IRB). An IRB is a board designated by VARI to review, to approve the initiation of, and to conduct periodic review of research involving human subjects in research as defined above. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The IRB may be assigned other review functions as deemed appropriate by VARI.

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

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

Engagement. The following is based on the Office of Human Research Protection (OHRP) guidance on engagement in research. VAI is considered *engaged* in a research project when VAI is the prime awardee of a federal support for the research activity and 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 PIs.

1.3 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and VARI policies (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe). As applicable, human subjects research at VARI is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of VARI will also conform to all other applicable federal, state, and local laws and regulations.

When human subjects research is not subject to the Common Rule or FDA regulations, VARI ensures that human research subjects benefit from equivalent protections by applying the Common Rule standards, with purposeful deviations that do not meaningfully diminish protections as noted within this manual.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR 160, 162, and 164.

VARI investigators involved in the conduct of clinical trials adhere to the Investigator Responsibility guidelines outlined in the International Conference on Harmonization (“ICH”) Good Clinical Practices

("GCP") Guidelines (sometimes referred to as "ICH-GCP" or "E6") when applicable (i.e., for clinical trials involving drugs when the sponsor or collaborative has committed to adherence with the guidelines).

1.3.1 Management of pre-existing studies subject to the Common Rule

For research subject to the Common Rule (whether due to support or organization policy) the following outlines when the pre-2018 rule or the revised rule will apply to research conducted at VARI.

A. **Research subject to the pre-2018 Common Rule requirements.** The pre-2018 requirements will apply to all studies initially approved, waived under .101(i), or determined exempt before January 21, 2019, through the close of the study, unless a study is transitioned to comply with the revised rule.

B. **Research subject to the revised Common Rule (2018 requirements).** The 2018 requirements will apply to all studies initially approved, waived under .101(i), or determined exempt on or after January 21, 2019, will be subject to the 2018 requirements as well as any pre-existing studies that VARI chooses to voluntarily transition to comply.

1.4 Federalwide Assurance (FWA) & IRB Registration

The federal regulations require that federally funded human subjects research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an institution's assurance to the federal government that human subject research conducted at that site is in compliance with federal regulations pertaining to the protection of human subjects. The FWA designates the Institutional Review Board (IRB) that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research.

VARI has an OHRP-approved Federalwide Assurance FWA00004131 and has designated one IRB (registered as IORG0002610) to review all human research protocols.

In its FWA, VARI has opted to limit the application of the FWA to research funded by DHHS or federal agencies that have adopted the Common Rule.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations. VARI's HRPP/IRB office maintains its FWA and IRB registration(s) in accordance with applicable regulations and guidance provided by OHRP and FDA.

The HHS registration system database can be used to verify the status of VARI's FWA, IORG, and IRB registration.

VAI's Federal Registration Numbers	
FWA	FWA00004131 - VARI FWA00015162 - VAEI
IORG	IORG0002610
IRB Registration	IRB00003176

1.5 VARI HRPP Structure

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It consists of various individuals and committees such as: the Institutional Official, the Regulatory Programs Manager, Compliance Staff, the IRB, other committees or subcommittees addressing human subjects protection (e.g., the Institutional Biosafety Committee, Radiation Safety Committee, Conflict of Interest Committees), PIs, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer, Environment, Health and Safety Manager). The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for human subjects protections:

1.5.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent VARI. The IO is the signatory of the FWA and assumes the obligations of the FWA. The IO is responsible for ensuring that the VARI HRPP and IRB have the resources and support necessary to fulfill their responsibilities and to comply with the regulations and requirements that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, meeting space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of noncompliance;
- Access to general counsel;
- Access to consulting reviewers as needed to ensure that the IRB has the appropriate expertise for the research it reviews, and
- Training in human research protections and other relevant subject matter for researchers, IRB members, and staff to support the review and conduct of human research in accordance with ethical standards and applicable regulations and requirements.

With the assistance of the Regulatory Programs Manager, the IO performs an annual review of the HRPP and makes adjustments as needed. In addition to the above, the review includes evaluation of:

- Whether IRB membership remains appropriate or whether changes are needed (e.g., for expertise, due to attendance or performance issues, etc.);
- Whether there are any institutional or IRB member conflicts of interest that require management;
- The adequacy of the education provided to the IRB, HRPP/IRB staff, and the research community;
- The outcomes of the HRPP Quality Improvement activities and the plan for the upcoming year; and
- The adequacy of community outreach activities.

The IO is also responsible for:

- Fostering, supporting and maintaining an institutional culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and institutional policies;
- Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair and members if they experience undue influence or if they have concerns about the function of the IRB;
- Oversight of the Institutional Review Board (IRB);
- Determining when reliance upon an external IRB is acceptable and appropriate;
- Oversight over the conduct of research conducted by all VARI PIs; and
- Taking action as necessary to ensure the protection of human subjects and compliance with regulatory and other requirements.

The IO must complete training about institutional oversight of human subjects research which may include OHRP's Human Research Protection Training Lesson 5, CITI Program's Institutional/Signatory Official: Human Subjects Research training, or equivalent and any other appropriate training on human research protections. The HRPP Office will provide on-going continuing education for the IO concerning human research protections. The IRB Executive Committee meets with the IO, as needed to discuss issues or updates to the HRPP. In addition, the IO is invited to attend IRB in-services that are provided by external consultants, webinars, as well as presentations by IRB members.

The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chair and HRPP Director have access to the IO for any concerns or issues related to the HRPP.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about all human subjects protections responsibilities at the organization.

1.5.2 Regulatory Programs Manager

The Regulatory Programs Manager is selected by and reports to the IO and is responsible for:

- 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 the administration of the IRB.
- Advising the IO on key matters regarding research at VARI.
- Implementing the institution's HRPP policies and procedures.
- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP).
- Managing the finances of VARI IRB.
- Assisting PIs in their efforts to carry out VARI'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 PIs, subcommittee members and research staff, and ensuring that training is completed on a timely basis.
- Serving as the primary contact at VARI for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies.
- Day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP and IRB staff.
- Responding to questions regarding the protection of human subjects.
- Working closely with the Chair of the IRB on the development of policy and procedures, as well as organizing and documenting the review process.

1.5.3 HRPP Staff

In addition to the leadership structure described above, other support staff members for the HRPP and IRB include the Compliance Department Administrative Assistant. The HRPP and IRB staff for VARI must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis.

1.5.4 Institutional Review Board (IRB)

VARI has one IRB, appointed by the IO. The IRB prospectively reviews and makes decisions concerning all human research conducted at VARI facilities, by its employees or agents, or under its auspices unless another IRB has been designated to do so (See *Section 2* IRB Reliance). The IRB is responsible for the protection of rights and welfare of human research subjects at VARI. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and institutional policies. (See Section 3 for a detailed discussion of the IRB.)

The IRB functions independently of, but in coordination with, other institutional committees and officials. The IRB, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected.

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

1.5.5 General Counsel's Office

The VARI HRPP relies on the General Counsel for the interpretations and applications of Michigan state law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research.

1.5.6 Department Chairs and Institutional Leaders

Department Chairs and institutional leaders are responsible for ensuring that the Principal Investigator (PI) is qualified by training and experience to conduct the proposed research.

Department chairs are responsible for assuring that PIs have the resources required to conduct the research in a way that will protect the rights and welfare of subjects. Such resources include but are not necessarily limited to personnel, space, equipment and time.

1.5.7 The Principal Investigator (PI)

The PI is the ultimate protector of the human subjects who participate in research. The PI is expected to abide by the highest ethical standards and for developing a research protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing training and supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent unless the requirement has specifically been waived by the IRB. The PI 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 PI must comply with institutional and administrative requirements for conducting research. The PI is responsible for ensuring that all research staff complete appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the PI is responsible for providing for their storage, security, dispensing, accounting, and disposal.

For more information on Investigator Responsibilities, see *Section 17.*

1.5.8 Other Related Units

1.5.8.1 Office of Grants and Contracts

The Office of Sponsored Research (OSR) staff review all research agreements with federal, foundation, or non-profit sponsors. This review ensures that all terms of the award are in compliance with VARI policies. Only designated senior individuals within the OSR have the authority to approve research proposals and to execute research agreements on behalf of VAI.

When the grant or contract agreement includes human research activities that will be conducted by PIs who are not employees or agents of VARI, a subcontract is executed between VARI and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval by submission of an executed Form 310 (as applicable). The collaborating institution must also ensure that key personnel involved in human subjects research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to VARI.

1.5.8.2 Business Development/Tech Transfer (protecting proprietary information)

The Business Development Department supports all research involving industry or external funds, including forging new relationships/collaborations, review and preparation of legal agreements, etc.

The Business Development (BD) Department assists PIs in the process of identifying funding from for-profit entities and works with the Office of Sponsored Research (OSR) in procuring research funding from industry sources. BD staff facilitates this by developing new relationships and building partnerships with potential for-profit collaborators that foster scientific exchange, as well as preparation and review of legal agreements, etc. During the preparation and review of research agreements, the OSR staff is charged with confirmation that the appropriate IRB and IACUC protocol approvals are in

place for any proposed research performed by VARI PIs prior to the commencement of work on the project.

Oversight of externally sponsored research activities is accomplished through the efforts of the OSR. The OSR supports PIs with applications for, and administration of, extramurally funded research projects. OSR provides oversight in the application and funding process, and assist PIs in fulfilling their scheduled deliverables, reporting, and overall programmatic compliance requirements to funding agencies.

Technology transfer refers to the activities of professional staff to develop and commercialize marketable technologies for the public good. Technology is typically transferred through an agreement in which VARI grants a license to a third party. The license allows the third party to use VARI's intellectual property rights in the defined technology, sometimes for a particular field of use and/or region of the world. Licenses include terms that require the licensee to meet development milestones and to make financial payments to VARI. These payments are shared with the inventors, labs, and re-invested in VARI's budget to provide support for further research, education and participation in the technology transfer process.

1.5.8.3 Environment, Health and Safety

The Environment Health and Safety (EHS) Office provides guidance and education to promote health, safety, protection of the environment, and assure regulatory compliance.

Research involving biological, chemical, or radioactive materials require additional approval from VARI committees/boards, in accordance with related VARI policies, including:

- VAI Radiation Safety Manual
- VARI Chemical Hygiene Plan
- VARI Bloodborne Pathogens Exposure Control Plan

1.5.9 Protocol-specific Coordination

In addition to IRB approval, the PI must obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Permission to enter classrooms or hospital units
- Permission from external research locations, including associated IRB(s), if required (e.g., Corewell Health, Saint Mary's/Mercy Health, Hudsonville School District)
- Departmental approvals
- Institutional Biosafety Committee
- Radiation Safety Committee
- Safety Committee
- Conflict of Interest Committee

For any that are indicated, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Protocol Application to the IRB. The application

will be reviewed in the IRB Office to ensure that all necessary letters are included. The IRB may request review or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not technically required by policy.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB.

1.6 HRPP Emergency Preparedness, Continuity and Recovery

In the event of an emergency or disaster (e.g., public health or weather-related), the procedures in these SOPs may be modified as appropriate for the situation. Such modifications may include alternative meeting procedures, alternative procedures for the submission and review of modifications, alternative procedures for prompt reporting, and any other changes necessary to ensure appropriate ongoing oversight and conduct of research. Because procedural modifications may vary based on the nature of the event, these cannot be anticipated and described in these SOPs. Instead, such procedural modifications will be recorded in an addendum to the SOPs, note-to-file, or other appropriate means of documentation and communicated to the research community. This documentation will be maintained in accordance with applicable record retention requirements.

Additionally, the Van Andel Emergency Action Plan will be implemented when an emergency occurs that falls within the scope of the plan.

2 IRB Reliance

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, VAI acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. VAI may choose to review the research in its entirety, only those components of the research VAI is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When VAI is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety.

When relying upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between VAI and the outside organization or investigator through an IRB Authorization Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before the VARI HRPP will accept any human research proposals from the outside organization or investigator or rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement, in SOPs, or other written materials. The Regulatory Programs Manager collaborates with Legal Counsel in the review and development of reliance agreements and utilizes a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with VARI's standards. To support compliance, VARI will make every effort to ensure as much consistency as possible across reliance agreements.

Requests for VARI to either rely upon an external IRB or for the VARI IRB to serve as the IRB of record for an external organization or investigator should be initiated as early as possible in the grant/contract process by contacting the Regulatory Programs Manager. Generally:

- VARI will not serve as the reviewing IRB for another organization unless the VARI IRB is familiar with the organization, has sufficient knowledge of local context, and has the appropriate expertise, itself or through the use of consultants, to review the research. When the VARI IRB serves as the reviewing IRB for another organization, the requirements and procedures outlined throughout this manual apply unless an alternative procedure has been agreed to in the reliance agreement or outlined in a companion document.
- VARI will only agree to rely upon other accredited IRBs but may consider reliance on non-accredited IRBs when the VARI components of the research are minimal risk and the reviewing IRB provides written assurance that its review of research will be in accordance with applicable regulations and ethical standards and that it will report to VARI any regulatory violations or investigations of the reviewing IRB by agencies such as OHRP or FDA.

The external IRBs that serve as the IRB of record for VARI research have the same authority as the VARI IRB and all determinations and requirements of the external IRBs are equally binding. Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). VARI will support compliance with the terms of reliance agreements by providing investigators with information relevant to their responsibilities, such as a copy or summary of the agreement, an information sheet, or reliance SOPs.

Regardless of which IRB is designated to review a research project, VARI is responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, and oversight by VARI and must adhere to all applicable policies, procedures, and requirements, including those of the VARI HRPP.

VARI has signed the SMART IRB joinder agreement. When the organizations participating in the research are signatories to the joinder agreement, IRB reliance may be requested and documented utilizing the SMART IRB online reliance platform. In collaboration with the other participating organizations, VARI will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be utilized to implement the reliance.

2.1 VARI/Corewell Health Joint Appointees:

Corewell Health's IRB reviews clinical studies conducted by joint appointees (clinicians who hold appointments at both Corewell and VARI). Because a reliance agreement and procedures are already in place for such studies, investigators do not need to contact the Regulatory Programs Manager in advance. Corewell Health IRB Analysts contact the VARI IRB staff when a new study, modification, continuing review is submitted. VARI IRB staff have access to Corewell Health's electronic protocol submissions system and can access the documents electronically. Because Corewell has provided the VARI HRPP with access to their electronic IRB system for joint appointee studies and inform VARI of all submissions, the study registration and post-approval requirements described in *Sections 2.4 and 2.5* do not apply to these studies.

Corewell Health IRB Analysts also inform VARI IRB staff immediately when investigators report any of the following:

- Any negative actions by a government oversight office, including, but not limited to, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), and any FDA Restrictions Placed on IRBs or Investigators;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the HRPP (including the research or the investigators).

2.2 VARI – Stand Up to Cancer (VARI-SU2C) Studies:

VARI provides leadership, funding, laboratory, analytical, and other support for VARI-SU2C studies. A clinical site lead or coordinating center is identified for each study who takes primary responsibility for leading the implementation of the protocol at participating clinical sites, for ensuring that the research is conducted in compliance with applicable regulations, and for ensuring that all necessary approvals, including IRB, are obtained. Generally, the VARI IRB will review the components of the research in which VARI is engaged (e.g., laboratory and data) while the IRB of one or more of the collaborating organizations reviews the clinical activities (including any FDA aspects) and the investigational plan as a whole. VARI may also choose to rely upon a collaborative-designated IRB and provide input on the VARI components through administrative review processes.

When the VARI IRB will conduct component review of VARI-SU2C studies, the investigator submits to the IRB using the appropriate Initial Application form and provides all relative materials including the study-wide protocol, the available consent forms, and other relevant materials. The VARI IRB reviews the VARI components of the research in accordance with applicable regulations and the procedures for

IRB review and ongoing oversight outlined in this manual. When reviewing the protocol and consent form(s), the VARI IRB will focus its review on the aspects of the research that VARI is engaged in. When the VARI IRB identifies a need for changes to documents such as the consent form that are approved by the IRB of a clinical site, or has recommendations, the investigator will be informed on the IRB determination letter and will be responsible for ensuring that the necessary changes are submitted, or recommendation communicated, to the IRB(s) with jurisdiction over the relevant activities (e.g., consent). The investigator is responsible for providing the VARI IRB with documentation confirming IRB approval (e.g., the IRB approval letter and a copy of the approved consent form). If consent forms from participating sites are not available at the time of the VARI IRB initial approval, or if sites are added after initial approval, the consent form(s) and participating site information are submitted to the VARI IRB as modifications. Such modifications typically qualify as a minor change (see *Section 4.1*) and are eligible for expedited review.

VARI-SU2C Investigators are responsible for reporting any issues or events related to the VARI components of the research, submitting any proposed modifications to the research, including to the VARI personnel, and submitting for continuing review to the VARI IRB, and adhering to all other responsibilities as outlined in this manual. In addition, investigators must submit the following items from other participating sites:

- Consent form modifications and corresponding IRB approvals (so that the VARI IRB can confirm the accuracy of any information involving the VARI components of the research);
- Unanticipated Problems Involving Subjects or Others (and any associated federal reports);
- Serious or Continuing Noncompliance (and any associated federal reports);
- Suspensions or Terminations of IRB Approval (and any associated federal reports);
- Any study-wide issues or holds;
- Any DSMB, medical monitor, or similar safety-monitoring reports that indicate any issues or concerns with the study; and
- Any other information that could impact the VARI components of the research

2.3 Single IRB (sIRB) Mandates for Multi-Site or Cooperative Research:

Non-exempt, federally funded multi-site or cooperative research requires review by a Single IRB (sIRB) as described below.

NIH considers research to be **multi-site** when the same protocol is conducted at more than one location.

As per the revised Common Rule, research is **cooperative** when a single project involves more than one institution.

NIH Single IRB Requirement

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a single IRB (sIRB) for review of non-exempt human subject research unless there is justification for an exception. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The NIH policy **does not** apply to career development,

research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (e.g., sites providing statistical support or laboratory analysis only) or to foreign sites.

Generally, when VARI is engaged in research subject to the NIH policy, VARI is not implementing the same protocol as the other participating sites (e.g., the VARI components of the research may be limited to laboratory analyses/interpretation) and thus VARI is not subject to the NIH's sIRB requirement.

However, sIRB may still be required for domestic sites under the Cooperative Research provisions of the revised Common Rule (see below).

Exceptions to the NIH policy are rare. Information regarding exception requests is available on NIH's Single IRB website.

Common Rule sIRB Requirement

The January 21, 2020 Common Rule Cooperative Research regulation requires single IRB review for domestic sites engaged in cooperative, non-exempt human subjects research that involves multiple institutions and is sponsored by signatories of the revised Common Rule. All sites in the US that are engaged in a federally funded cooperative research project subject to the revised Common Rule must rely upon approval by a sIRB for that portion of the research that is conducted in the US.

Exceptions to the Common Rule Cooperative Research provision include:

- Participating sites located outside of the United States.
- Research that requires individual IRB review by law (e.g., American Indian or Alaskan Native tribal law).
- Research for which a federal agency determines and documents that the sIRB model is not appropriate. Information regarding federal agency exception requests for HHS-supported research is available on OHRP's Single IRB Exception Determinations website.
- Research funded by the Department of Justice (DOJ) since DOJ is not currently a signatory of the revised Common Rule.

sIRB is Not Required for Exempt Research

Common Rule and NIH requirements for single IRB review **do not** apply to exempt research, including exempt research for which limited IRB review takes place. When an organization opts to rely upon another IRB for the review of exempt research with limited IRB review, the agreement to do so must be documented.

2.4 Registration of Studies Reviewed by External IRBs:

Once reliance has been established (e.g., via execution of an IRB Reliance Agreement), investigators must register studies that will be reviewed by an external IRB by submitting basic information about the research to the HRPP/IRB office by completing and submitting the *External IRB Registration Form* and a copy of the proposed protocol and consent document(s), when applicable, to researchprotections@vai.org. The HRPP/IRB office staff will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed, and determine the need for relaying local context information to the reviewing IRB in accordance with the reliance agreement. When applicable, and when the external IRB is not responsible for reviews of requests for waivers or alterations of HIPAA authorization, the HRPP/IRB staff will forward requests for waiver or alteration of HIPAA authorization and any relevant materials to the VARI IRB Chair or a

designated expedited reviewer for review. The HRPP/IRB office staff will notify the investigators once the proposed research has been cleared for submission to the external IRB via an email. Once approved by the external IRB, investigators must submit a copy of the approval notice and any approved consent document(s) to the HRPP/IRB office via researchprotections@vai.org. If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well.

2.5 Post-Approval Requirements:

Other than as described in *Section 2.1* above (Corewell-VARI joint appointees), investigators approved through external IRB review must still report local unanticipated problems, complaints, and any noncompliance to the VARI HRPP/IRB office via researchprotections@vai.org in addition to reporting to the external IRB in accordance with the external IRB's policies and procedures. Copies of the report submitted to the external IRB are generally acceptable, but additional information may be requested on an as-needed basis. Investigators must also submit copies of continuing review reports, updated protocols, updated consent forms, study closures, and the corresponding IRB approval or acknowledgment. Based upon the terms of the IRB Reliance Agreement, modified or additional reporting requirements may apply. Investigators will be informed of any such requirements at the time the research is approved for submission to the external IRB.

Changes in PI and the addition of other research team members must be submitted to the HRPP/IRB office via researchprotections@vai.org prior to the new PI or research team member assuming any study responsibilities. The HRPP/IRB office must verify CITI training, COI review, and any other applicable requirements.

Notices about and reports from external monitors, auditors, or inspectors must be provided to the HRPP/IRB Office as described in *Section 5.4* of this manual.

Any of the following issues must be reported immediately (asap once aware) to the VARI HRPP/IRB office by phone or email:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding VARI's HRPP.

See *Section 16* for more information.

3 Institutional Review Board

The Van Andel Research Institute (VARI) has established an Institutional Review Board (IRB) to ensure the protection of human subjects in human subjects research conducted under the auspices of the Organization. All non-exempt human subjects research conducted under the auspices of VARI must be reviewed and approved by VARI IRB or another institutionally designated IRB prior to the initiation of the research.

3.1 IRB Authority

The IRB derives its authority from VARI policy. Under the Federal Regulations, the IRBs authority includes:

- To approve, require modifications to secure approval, or disapprove all human subjects research activities overseen and conducted under the auspices of VARI, including exempt research activities under 45 CFR 46.104 of the revised Common Rule for which limited IRB review is a condition of exemption (under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8));
- To require that informed consent be obtained and documented in accordance with regulatory requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects;
- **For research subject to the revised Common Rule (2018 requirements):** To conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year, except as described in *Section 4.10*;

  When research is subject to other regulations (e.g., pre-2018 Common Rule, FDA) or requirements (e.g., grant or contract terms) that require continuing review, the IRB will conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year;
- To suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects;
- To observe, or have a third party observe, the consent process;
- To observe, or have a third party observe, the conduct of the research;
- To determine whether data or specimens gathered without IRB approval or in association with serious or continuing noncompliance may be published or used for research purposes; and
- To oversee the conduct of human subjects research that qualifies for exempt status and to take action as needed to ensure the protection of human subjects and the integrity of the research.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy. Likewise, the IRB must remain free from the influence of financial and other organizational interests.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. VARI officials may strengthen requirements and/or

conditions, or add other modifications to secure VARI approval or approval by another VARI committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications.

3.2 Roles and Responsibilities

3.2.1 Chair of the IRB

VARI IO, in consultation with the Regulatory Programs Manager, appoints a Chair and Vice Chair of the IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual, from within VARI, fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the VARI community will fall primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by VARI's administration, the PIs whose protocols are brought before it, and other professional and nonprofessional sources.

The IRB Chair is responsible for conducting the meetings and is a signatory for correspondence generated by the IRB.

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 and Regulatory Programs Manager.

The IRB Chair advises the IO and the Regulatory Programs Manager about IRB member performance and competence.

The performance of IRB Chair will be reviewed on an annual basis by the Regulatory Programs Manager in consultation with the IO. Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB's mission, following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.

3.2.2 Vice Chair of the IRB

When the IRB Chair is absent or is required to be recused, i.e. the Chair has a conflict of interest, the Vice Chair, or designee, will serve as the Acting Chair. The Vice Chair, or designee, has the same authority and duties as the Chair.

3.2.3 IRB Executive Committee (EC)

The IRB EC constitutes the senior leadership of the IRB with responsibility to review issues and make recommendations to the full IRB for their consideration and vote. The IRB EC is led by the IRB Chair and its members include the IRB Vice Chair, and Regulatory Programs Manager. The IRB EC facilitates IRB review and decision-making but does not have decision-making responsibility itself. Matters that will be considered by the IRB EC include policies related to new mandates from OHRP, the FDA, the NIH, the NCI, etc. The IRB EC will also review matters of major concern, such as reports of suspected noncompliance, deviations from approved protocols, major safety issues, and other matters related to human subjects research which require fact finding to facilitate review and decision making by the full IRB. The IRB EC meets on an ad hoc basis, when determined necessary at the request of the IRB members, the IRB Chair or any member of the IRB EC. (The IRB EC Charter can be found on the IRB SharePoint site.)

3.2.4 Subcommittees of the IRB

The IRB Chair, in consultation with the Regulatory Programs Manager, may designate one or more IRB members to a subcommittee of the IRB to perform duties, as appropriate, to review and undertake other IRB functions, and to make recommendations to the IRB. The IRB Chair, in consultation with the Regulatory Programs Manager, will appoint IRB members to serve on each IRB subcommittee created under this Section. The number and composition of the IRB subcommittee members shall depend on the authority delegated by the IRB Chair to such IRB subcommittee (e.g., merely making recommendations versus decision-making authority).

If the IRB Chair creates one or more IRB subcommittees, he/she shall also indicate whether it is a standing or *ad hoc* IRB subcommittee.

3.3 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, 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 reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at VARI. VARI has procedures (See *Section 4*) that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

In addition, the IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in VARI research.

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. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals from VARI's Offices of Sponsored Research/Grants and Contracts, Business Development or Technology Transfer may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

3.4 Composition of the IRB

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

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, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

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

In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of organizational

commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas

The IRB will therefore include persons knowledgeable in the following areas:

- If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects.
- Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including VARI's consideration of qualified persons of both sexes, so long as 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 primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The IRB includes at least one member who is not otherwise affiliated with VARI and who is not part of the immediate family of a person who is affiliated with VARI.
- The IRB includes at least one member who represents the general perspective of participants.
- One member may satisfy more than one membership category.
- The IRB Chair and Vice-Chair are voting members of the IRB.
- Staff of VARI'S IRB Office may be voting members of the IRB.

On an annual basis, the IRB Chair, IRB Vice Chair and the Regulatory Programs Manager shall review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements. Changes in IRB membership will be reported to the OHRP within 90 days of the change.

3.5 Appointment of Members to the IRB

The IRB Chair, Vice Chair and/or the Regulatory Programs Manager, identifies a need for a new, replacement, or alternate member. The IRB nominates candidates and sends the names of the nominees to the IRB Office. Department Chairs and others may forward nominations to the IO, or to the IRB Office, or to an IRB Chair.

The final decision in selecting a new member is made by the IO, in consultation with, the IRB Chair and the Regulatory Programs Manager.

Appointments are made for a renewable three-year period of service. Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written or verbal notification to the IRB Chair or Regulatory Programs Manager.

On an annual basis, the IRB Chair and the Regulatory Programs Manager review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

3.6 Alternate members

The appointment and function of alternate members is the same as that for primary IRB members, and the alternate's expertise and perspective are comparable to those of the primary member. The role of

the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) or class of members (e.g. physician scientist) for whom each alternate member may substitute. The alternate member will not be counted as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

3.7 IRB Member Conflict of Interest

No IRB member or alternate may participate in the review (initial, continuing, or modification) of any research project in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB member to disclose any COI in a study submitted for review and recuse him/herself, by leaving the room, prior to the final deliberations and vote.

All members and alternate members of the IRB complete a VARI Conflict of Interest Disclosure Form when first appointed and annually thereafter. If a member responds affirmatively to the existence of a potential conflict, the Regulatory Programs Manager is notified. Potential COIs of IRB members are reviewed by the COI Committee to determine if an actual conflict exists. A listing of COI's of IRB members and/or alternate members are provided to the Regulatory Programs Manager, IRB Chair and Vice Chair. This listing is used to ensure that IRB members and alternates are not assigned to conduct reviews of studies for which they have a conflict and to ensure appropriate recusal during convened meetings.

An IRB member, alternate, or consultant may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

- Substantive involvement in the design, conduct, and reporting of the research.
- Significant financial interests (See *COM-POL-001.01 Financial Conflict of Interest Policy* for a definition of significant financial interests) related to the research being reviewed.
- Any other situation where an IRB member or alternate member believes that another interest conflicts with his or her ability to deliberate objectively on a protocol.

The IRB Chair will poll IRB members at each convened meeting to determine if a COI exists regarding any protocol to be considered during the meeting and reminds them that they should recuse themselves by leaving the room during the discussion and vote of the specific protocol. If a conflicted member is participating by conference call, videoconference or web meeting the member's participation is terminated for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. All recusals by members with COI are recorded in the minutes.

If the COI status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair and Regulatory Programs Manager.

3.8 Use of Consultants

When necessary, the IRB Chair or the Regulatory Programs Manager may solicit individuals from the organization or the community with competence in special areas to assist in the review of issues or

protocols, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB. The IRB Office will ensure that all relevant materials are provided to the consultant prior to the convened meeting.

Key information provided by consultants at meetings will be documented in the minutes. Written reviews and/or written statements provided by the consultants will be filed with the IRB protocol file.

The Regulatory Programs Manager reviews the VAI COI policies (LEG-POL-001.01 Conflict of Interest Policy, COI-POL-002.01 Conflict of Commitments Policy, COI-POL-003 Institutional Conflict of Interest Policy) with consultants to the IRB. Consultants must verbally confirm to the Regulatory Programs Manager that they do not have a COI prior to reviewing the project. Individuals who have a conflicting interest or whose spouse or immediate family members have a COI in the sponsor of the research cannot provide consultation.

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

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the VAI COI policies (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

3.9 Duties of IRB Members

The agenda, submission materials, protocols, proposed consent forms and other appropriate documents are distributed to members prior to the convened meetings at which the research is scheduled to be discussed. Members review the materials at least three working days before each meeting, in order to participate fully in the review of each proposed project. IRB members will treat the research proposals, protocols, and supporting data confidentially. Copies of the protocols and supporting data are returned to the IRB staff at the conclusion of the review for professional document destruction.

IRB members reviewing research under expedited review or limited IRB review under the 2018 requirements should respond within one week of receipt.

3.10 Attendance Requirements

Members should attend at minimum seven meetings per year. If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or IRB Office staff. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the IRB Chair or the Regulatory Programs Manager.

If an IRB member is to be absent for an extended period of time, such as for a sabbatical, 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, the alternate can serve during the primary member's absence, provided the IRB has been notified in advance.

3.11 Training/Ongoing Education of the Regulatory Programs Manager, and IRB Chair, Members, and Staff

A vital component of a comprehensive human research protection program is an education program for the Regulatory Programs Manager, IRB Chair, Vice Chair and members. VARI is committed to providing training and an on-going educational process for IRB members and the staff of the HRPP Office, related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

3.11.1 Orientation

New IRB members, including alternate members will meet with the IRB Chair and/or Regulatory Programs Manager for an informal orientation session. At the session, the new member will be given a copy of the text, *Institutional Review Board—Management and Function* that includes the:

- Belmont Report,
- Federal regulations relevant to the IRB,
- Web address of the VARI Policies and Procedures for the Protection of Human Subjects.

New members are required to complete the Initial Education requirement for IRB members before they may serve as Primary Reviewer.

3.11.2 Initial Education

The Regulatory Programs Manager, IRB Chair, Vice Chair, Members, and Staff are required to complete the following courses in the CITI online Training Program or request the HRPP Director consideration of applicable training that can be substituted for the training listed below:

- Human Subjects Research Training – IRB Chair and Vice Chair Course (IRB Chair and Vice Chair only)
- Human Subjects Research Training – IRB Member Basic Course
- Good Clinical Practice (GCP) Training – IRB Members Basic Course
- Responsible Conduct of Research (RCR) – IRB Members Basic Course
- Conflict of Interest Course

3.11.3 Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB is consistent with current regulatory and VARI policy requirements, training is continuous for IRB members throughout their service on the IRB.

In addition to initial training requirements, the Regulatory Programs Manager, IRB Chair, Vice Chair, Members, and Staff must also satisfy continuing education requirements on an annual basis. VARI uses the following activities as a means for offering continuing education to IRB members, Regulatory Programs Manager, and IRB staff:

- In-service training at IRB meetings that include current hot topics;
- Local and regional training workshops and conferences;

- *Institutional Review Board—Management and Function*, Bankert & Amdur, eds.
- Identification and dissemination by the Regulatory Programs Manager or IRB Office staff of new information that might have affected the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings.

The Regulatory Programs Manager, IRB Chair, Vice Chair, Members, and Staff are also required to complete additional CITI training every 3 years, except for Conflict of Interest Training, as part of the VARI continuing education requirements.

- Human Subjects Research Training – IRB Chair and Vice Chair Course (IRB Chair and Vice Chair only)
- Human Subjects Research Training – IRB Member Refresher Course
- Responsible Conduct of Research (RCR) – IRB Members Refresher Course
- Conflict of Interest Course (Every 4 years)

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the Regulatory Programs Manager. The Regulatory Programs Manager and the IRB Chair determine which continuing education activities are mandatory for IRB members and staff in a given year and tracks whether each individual has satisfied the requirements. Training is tracked by the Compliance Staff through use of an electronic tracking database. Continuing noncompliance will result in the individual not being renewed as an IRB member. Completion of training requirements is included as part of the evaluation of the performance of HRPP staff.

The IO will provide support to send as many members of the IRB as possible to attend regional conferences and when possible, the annual PRIM&R conference on human research protections.

3.12 Liability Coverage for IRB Members

VARI's insurance coverage applies to employees and any other person authorized to act on behalf of VARI IRB or acts of omission within the scope of their employment for authorized activity.

3.13 Review of IRB Member Performance

The performance of IRB members will be reviewed on an annual basis by the HRPP Director, IRB Chair and Vice Chair. IRB members will receive formal feedback on the results of this review. Members who are not performing in accordance with the IRB's mission or policies and procedures or who have an undue number of absences may be removed.

3.14 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, they shall make a confidential report to the Regulatory Programs Manager or IO, depending on the circumstances. The IO will ensure that a thorough investigation is conducted. If the allegation is determined valid, a corrective action is put in place by the IO or delegated authority to prevent additional occurrences.

4 IRB Review Process

All human subjects research conducted under the auspices of VARI must meet the criteria for one of the following methods for review:

- Exempt
- Exempt with Limited IRB Review
- Expedited Review
- Full Committee Review

The IRB will ensure that the research meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research.

VARI currently has Reliance Agreements with Michigan State University (MSU) and Corewell Health to provide IRB oversight for defined studies. The IO, at his/her discretion, may choose to enter into an agreement, to cede review to another external IRB for a specific study or groups of studies. However, this is uncommon, unless required as a condition of an award or agreement. Generally, VARI will only rely upon another IRB when that IRB is part of an HRPP-accredited program.

All IRB applications, forms, templates, and checklists are available at https://vanandelinstitute.sharepoint.com/sites/Research-Protections

4.1 Definitions

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

Minor Change. A minor change is one which makes no substantial alteration in:

- The level of risks to subjects,
- The research design or methodology (adding procedures that are not eligible for expedited review (See *Section 3.4*) would not be considered a minor change),
- For studies that are more than minimal risk, the number of subjects enrolled in the research (no greater than 10% of the total requested),
- The qualifications of the research team,
- The facilities available to support safe conduct of the research,
- Any other factor which would warrant review of the proposed changes by the convened IRB.

For Studies currently closed to accrual, all study procedures completed, now in long-term follow-up would also be considered a minor change or minor alteration in a currently approved protocol.

Minor changes also include: (1) the addition of investigators/sites with another IRB of record responsible for review of their activities; and (2) the addition of investigators/sites when VARI IRB serves as the IRB of record for their activities so long as the investigator(s)/site(s) do not have a conflict of interest, potential compliance concerns (e.g., a 483 that has not been adequately resolved), or any

other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

Quorum. A quorum of the IRB consists of a simple majority of the voting membership, 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.

Suspension of IRB approval. A suspension is a directive of the convened IRB or other authorized individual (See *Section 6*) to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing review.

Termination of IRB approval. A 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.

4.2 Human Subjects Research Determination

PIs are required to complete the *Specimens and Data Use Application Form* for activities they believe constitute non-human subjects research. The application form solicits pertinent information in order to make the non-human subjects determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Section1.2. Determinations regarding activities that are either clearly or clearly not human subjects research, may be made by the Regulatory Programs Manager. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

Documentation of all determinations made through the IRB Office will be recorded and maintained in the IRB Office. Email and other written requests will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept in the study file.

Note: With the implementation of the revised Common Rule, the requirement of the Newborn Screening Saves Lives Reauthorization Act of 2014 that federally-funded "research on newborn dried blood spots shall be considered research carried out on human subjects" is eliminated. Whether such research involves human subjects shall now be considered using the same standards as are used for other research involving human biospecimens (e.g., whether the identity of subjects may be readily ascertained, whether the specimens are coded and who has access to the key, whether the research involves the evaluation of the safety or effectiveness of an FDA-regulated device, etc.).

4.3 Exempt Studies

All research using human subjects must be approved by VARI. Certain categories of research (i.e., “exempt research”) do not require IRB oversight. Exempt research is subject to VARI review and must be approved by the IRB Chair or his/her designee.

The designee may be a voting member of the IRB or Regulatory Programs Manager. Individuals involved in making the determination of IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers cannot have any apparent conflict of interest. Identification of individuals designated to conduct exempt determinations will be made in writing. Voting members who are designated to conduct exempt determinations will be noted on the IRB roster, which is maintained in the IRB office.

Studies that are determined to be exempt from the Common Rule (45 CFR 46), are not exempt from VARI review and approval. Although exempt research is not covered by the federal regulations, this research is not exempt from ethical considerations, such as the principles described in the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles.

Unless otherwise required by law or by Federal department or agency heads, exempt studies are exempt from the requirements of the Common Rule (i.e., IRB approval and full research consent are not required) other than as specified within the regulations (e.g., the conditions that permit exemption, and when limited IRB review is required). Exempt research is not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual/s making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

4.3.1 Limitations on Exemptions

For research subject to the pre-2018 requirements:

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the PI does not participate in the activities being observed.

Prisoners: Exemptions DO NOT apply to prisoners and IRB review is required**.**

For research subject to the revised Common Rule (2018 requirements):

Children: Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed. Exemption #2(iii), where identifiable information is obtained and the IRB conducts a limited IRB review, is NOT applicable to research in children. Exemption #3 does NOT apply to research involving children. [45 CFR 46.104(b)(3)]

Prisoners: Exemptions do not apply except for research aimed at involving a broader subject population that only incidentally includes prisoners. [45 CFR 46.104(b)(2)]

4.3.2 Categories of Exempt Research

With the above exceptions and any other limitations or restrictions due to applicable law, regulation, or agency policy, research activities not regulated by the FDA (see *Section 4.3.3* for FDA Exemptions) in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review, but require institutional review at VARI:

For research subject to the pre-2018 Common Rule requirements:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
    a. Research on regular and special education instructional strategies, or
    b. Research on the effectiveness of, or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and
    b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's 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:
    a. The human subjects are elected or appointed public officials or candidates for public office, or
    b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the PI in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

    NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
5. Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs,
    b. Procedures for obtaining benefits or services under those programs,
    c. Possible changes in or alternatives to those programs or procedures, or
    d. Possible changes in methods or levels of payment for benefits or services under those programs.
    e. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older American Act).
    f. The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of 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,
    a. If wholesome foods without additives are consumed, or
    b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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.

For research subject to the revised Common Rule (2018 requirements):

1. Research, conducted in established or commonly accepted educational settings, *that* specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

    i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

    A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

    (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such

benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

    i. The identifiable private information or identifiable biospecimens are publicly available;
    ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
    iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
    iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

NOTE: VAI is not a covered entity and so does not anticipate the use of Category 4.iii. above.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including 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. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies:

   i. If wholesome foods without additives are consumed, or
   ii. 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.

Note: VAI is not adopting the option for broad consent in the revised Common Rule at this time and thus not applying exempt categories 7 & 8.

4.3.3 FDA Exemptions

The following category of clinical investigations is exempt from the requirements of IRB review:

- 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)].

4.3.4 Procedures for Exemption Determination

In order to obtain an exemption determination, PIs must submit:

- The appropriate Initial Application Form (Specimens and Data Only, Interventions or Interactions),
- All recruitment materials (e.g., letter of invitation, recruitment script, flyer),
- Consent form (when appropriate),
- All surveys, questionnaires, instruments, etc.,
- Letter(s) of permission from each non-VAI site of performance,
- Verification of current human research protection training for all members of the research team, including the faculty advisor.

The IRB Chair (or designee) reviews all requests for exemptions and determines whether the request meets the criteria for exempt research.

To document the reviewer's determination of the request for exempt research, he/she completes the *Exemption Determination Checklist.* The reviewer verifies on the form whether the submission meets

the definition of human subjects research (See *Section 1.2*). If the request meets the definition of human subject research, the reviewer then determines whether or not the research is eligible for exemption.

When the research requires limited IRB review or a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review may be conducted using expedited review procedures by the IRB Chair or an experienced Chair-designated member of the IRB. As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities; and to suspend or terminate IRB approval. Actions of disapproval may only be made by the convened IRB. [45 CFR 46.109(a), 45 CFR 46.110]

Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported to the IRB (i.e., within 2 business days). [45 CFR 46.108(a)(3)(iii)]

Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the IRB may determine that continuing review is required for a particular study subject to limited IRB review (continuing review of those aspects of the research subject to limited IRB review), in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter. [45 CFR 46.109(f)(ii), 45 CFR 46.115(a)(3)]

The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report. The reviewer indicates whether the request for exemption was approved or denied. If approved, the rationale for the determination and category under which it is permitted must be indicated. The exempt application, review, and determination letter are recorded and maintained in the same manner and for a minimum of seven years after completion of the study.

Once IRB review is completed, IRB staff will send the determination letter to the PI with the results of the review.

Exempt determinations will include a termination date, with the maximum time allotted being 3 years. If the research extends beyond the termination date, the researcher must submit a new application to request continuation of the study exemption. This process will allow the PI and the VARI the opportunity to review and update the research activity and determine whether the study still qualifies for exemption. PIs must notify the IRB office when an exempt research project is complete so that an accurate database of active research activities is maintained.

4.4 Expedited Review

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

- **For research subject to the revised Common Rule (2018 requirements):**
    - When the research activities involve only procedures appearing on the federal register list of categories of research eligible for expedited review **and** found by the reviewer(s) to involve no more than minimal risk. If the reviewer determines that the research involves more than minimal risk, the reviewer must document the rationale for the more than minimal risk determination and the research must be reviewed by the convened IRB.

- Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

- **For research subject to the pre-2018 Common Rule, or FDA regulations or other requirement that requires reviewer determination of minimal risk:**
  - When the research activities involve only procedures appearing on the federal register list (or when applicable, the FDA list) of categories of research eligible for expedited review **and** found by the reviewer(s) to involve no more than minimal risk
- **Minor changes** in previously approved research during the period (of one year or less) for which approval is authorized.

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

4.4.1 Definitions

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

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

1. The acceptability of the risk-to-benefit analysis (i.e., the change does not increase the level of risk);
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 4.4.2) would be considered more than a minor change);
3. The number of local subjects to be enrolled in greater than minimal risk research (usually not greater than 10% of the total requested);
4. The qualifications of the research team (i.e., the change does not negatively impact the expertise available to conduct the research);
5. The facilities available to support safe conduct of the research; or
6. Any other factor which would warrant review of the proposed changes by the convened IRB.

Minor changes also include the addition of sites to a protocol approved by the convened IRB so long as the investigator(s)/site(s) do not have a conflict of interest, potential compliance concerns (e.g., an unfulfilled Corrective and Preventive Action Plan) or any other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

In addition, if a study is transitioned from the pre-2018 Common Rule to comply with the 2018 requirements, the IRB may consider an investigator modification of the consent form to be consistent with the 2018 requirements to represent a minor change to the research. If such a determination is made, the IRB may use the expedited review procedure to evaluate the consent form changes, as permitted under §46.110(b)(1)(ii).

4.4.2 Categories of Research Eligible for Expedited Review

The categories of research eligible for expedited review were published in a Federal Register on November 9, 1998 (Common Rule: notice 63 FR 60364-60367; FDA: notice 63 FR 60353).

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

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

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

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

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
    b. Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
    a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week, or
    b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. [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.
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
    a. Hair and nail clippings in a non-disfiguring manner;
    b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
    c. Permanent teeth if routine patient care indicates a need for extraction;
    d. Excreta and external secretions (including sweat);
    e. Uncannulated saliva collected either in an unstimulated 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 subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

j. Sputum collected after saline mist nebulization.

k. Vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

   a. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

   b. weighing or testing sensory acuity;

   c. magnetic resonance imaging;

   d. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

   e. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving 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 Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

   Categories 8 and 9 apply only to continuing review.

8. Continuing review of research previously approved by the convened IRB as follows:

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*

b. where no subjects have been enrolled and no additional risks have been identified; *or*

c. where the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure. For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. With respect to category 8(a), "Long-term follow-up" includes research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection *of follow-up* data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk. *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 PI nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]*

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

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

4.4.3 Expedited Review Procedures

Under an expedited review procedure, IRB review may be carried out by the IRB Chair or by one or more reviewers designated by the IRB Chair from among experienced members and alternate members of the IRB. Designated reviewers must be professionally competent (i.e., experienced with and having demonstrated the ability to apply IRB review requirements and with appropriate scientific or scholarly expertise) to conduct expedited reviews.

On an annual basis, the IRB Chair will designate a list of IRB members eligible to conduct expedited review. The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see *Section 3.7*) cannot be selected but may answer questions about the research if requested.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documents that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and protocol modifications.

If the research meets the criteria allowing review using the expedited procedure, the reviewer(s) complete the appropriate review checklist and any applicable addendum checklists. The checklist(s) will assist in determining whether the research meets the regulatory criteria for approval. The same criteria of approval apply to reviews conducted via expedited review as those conducted by the convened board. When a reviewer determines that research subject to the revised Common Rule (the 2018 requirements) falls within the expedited categories but involves more than minimal risk, the reviewer will document the rationale for that determination in the checklist and refer the research for review by the convened IRB. If the research does not otherwise 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 IRB meeting agenda.

In reviewing the research, the reviewers will follow the Review Procedures described in *Sections 4.6* and *4.7* and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review by the convened IRB.

Reviewers will indicate approval, required modifications or requirement for convened IRB review on the checklist and return it to the IRB Office. If modifications are required, the IRB Office staff will inform the PI in writing.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the protocol will be submitted for review at the next convened IRB meeting.

4.4.4 Informing the IRB

Through a list appended to the meeting minutes, IRB members will be apprised of all expedited review approvals, including limited IRB reviews conducted using expedited review procedures. Any IRB member can request review of the protocol at a fully convened meeting, by contacting the IRB Office.

4.5 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all non-exempt research, and exempt research subject to limited IRB review, at convened meetings at which a quorum (see below) of the members is present. Meetings may be in-person or remote.

4.5.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (once per month, as needed, usually on the second Wednesday). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings can be found on the VARI intranet site (vanandelinstitute.sharepoint.com/sites/compliance). Special meetings may be called at any time by the IRB Chair or the Vice Chair in conjunction with the Regulatory Programs Manager.

4.5.2 Preliminary Review

The Regulatory Programs Manager will perform a preliminary review of all protocol materials submitted to the IRB Office for determination of completeness and accuracy. Only complete submissions will be

placed on the IRB agenda for review. The PI will be informed either by e-mail, phone or in person of missing materials or missing information and informed of the submission deadline for this additional information in order for the study to be included on that month's agenda. In the case of a PI who is submitting a protocol for the first time or a PI who may not be well-versed in the protocol submission procedures, consultations can be arranged with the Compliance Staff to assist in this regard.

4.5.3 Primary Reviewer

After it has been determined that the protocol submission is complete, Regulatory Programs Manager will assign protocols for review, paying close attention to potential conflicts of interest, the scientific content of the protocol, the potential reviewer's area of expertise, and representation for vulnerable populations that may be involved in the research. A primary reviewer will be assigned to protocols requiring initial review, continuing review, and review of proposed modifications. When the IRB is presented with a protocol which may be outside the expertise of the IRB members, an outside consultant will be sought (See *Section 3.8*). Protocols for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when that expertise and critique can be provided.

The primary reviewer is responsible for:

- Having a thorough knowledge of the details of the proposed research.
- Performing an in-depth review of the proposed research.
- Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and leading the IRB through the regulatory approval criteria (See *Section 4.6*).
- Making suggestions for changes to the proposed research, where applicable.
- Completing all applicable IRB reviewer checklists.

If the primary reviewer is absent from the meeting, a new reviewer may be assigned, provided the new reviewer has reviewed the materials prior to the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary reviewer. It should be noted that all of the IRB members will receive and are expected to review all studies, not just the ones they are assigned to as a primary reviewer.

4.5.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted 7 business days prior to the convened meeting for inclusion on the following IRB agenda. The meeting agenda will be prepared by the Regulatory Programs Specialist, as necessary, with the assistance of the HRPP Director and distributed to the IRB members prior to the meeting. All IRB members will receive the review materials no later than 3 business days before the scheduled meeting, to allow sufficient time for review of the materials prior to the meeting. The meeting materials typically include:

- Meeting agenda;
- Meeting minutes;
- Applicable business items and audit findings;

- Appropriate continuing education materials; and
- Protocol review materials *(See Section 4.5.5).*

4.5.5 Materials received by the IRB

Each IRB member receives and reviews the following documentation, as applicable, for protocols on the agenda:

- Initial IRB Application Form,
- Protocol that outlines all of the study procedures and requirements,
- Proposed Consent/Parental Permission/Assent Form(s),
- Recruitment materials including advertisements intended to be seen or heard by potential subjects.

Additionally, for HHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the HHS-approved sample informed consent document(s) (when one exists) and the complete HHS-approved protocol (when one exists).

The materials provided to the primary reviewer will also be provided to all IRB members with the exception of the grant application and the PI's Brochure. These materials will be available upon request.

If an IRB primary reviewer requires additional information to complete the review, they may contact the PI directly or may contact the IRB Office to make the request.

If an IRB member requires additional information, they may contact the IRB Office to make the request of the PI.

Reviewers will use the appropriate *Initial Protocol Review Checklist* and any applicable addendums as a guide to complete their review. Checklists completed by the Primary Reviewer will be kept with the IRB files.

4.5.6 Quorum

A quorum consists of a simple majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area.

At IRB meetings, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate quorum is present before calling the meeting to order and will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing the non-scientific member or another required member, the IRB cannot take action or vote on regulatory determinations until the quorum is restored. The IRB Staff will document the time of arrival and departure for all IRB members and notify the IRB Chair if quorum is not present. The minutes of the meeting will also document when an IRB member leaves, the reason for leaving and when the IRB member returns to the meeting room.

In addition to the required attendance of at least one "non-scientist" member, it is generally expected that at least one scientific member, one unaffiliated member, and one member who represents the general perspective of participants (one individual can serve in more than one capacity) will be present

at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception (i.e., generally no more than 2-3 meetings per year).

When the IRB regularly reviews research that involves subjects vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with such subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. When not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in the 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.

4.5.7 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is present. The Chair will remind IRB members to recuse themselves from the final deliberations and vote by leaving the room when 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. If the revisions/corrections are significant and the IRB members vote to have the revised Minutes reviewed at the next meeting, this will be added on to the next agenda.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The primary reviewer presents an overview of the research and leads the IRB through the regulatory criteria for approval in the appropriate review checklist (Initial, Modification, Continuing Review) and any applicable addendums. In order for the research to be approved, it must receive the approval of a majority of the voting members present at the meeting at the time of the review/vote.

It is the responsibility of the IRB Staff to record the proceedings of the meeting, including votes, and to develop Minutes.

4.5.8 Guests

At the discretion of the IRB, the PI may be invited to the IRB meeting to make a brief presentation and/or to answer questions about their proposed or ongoing research. The PI may not be present for deliberations or vote on their research.

Ex-officio guests are individuals who, by virtue of their position and their role at VARI, may regularly attend IRB meetings. Ex-officio guests may include: the General Counsel, VP Research Protections (IO) or the Director of Research. Ex-officio guests may fully participate in the IRB discussion and deliberations so long as they do not have a conflict of interest in the item under review, but may not vote.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the Regulatory Programs Manager. Guests, other than ex-officio guests, may not officially speak unless requested by the IRB Chair and must sign a *Van Andel Institute IRB Member Confidentiality Agreement.*

4.6 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited or by full IRB review, the IRB must determine that the following criteria are satisfied. These criteria are considered and apply to all categories of IRB review, including initial reviews, continuing reviews, and modifications of previously approved research.

0) 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.

1) 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.

2) **For research subject to the pre-2018 Common Rule, or FDA regulations:** 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.

   For research subject to the revised Common Rule (2018 requirements): 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 subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

3) 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 the Federal Regulations.

4) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations.

5) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

6) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

7) 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, individuals with impaired decision-

making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

4.6.1 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 and/or to 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** that are associated with the requirements of the research. In evaluating risks and benefits, the IRB should consider those risks and benefits that may result from the research (as distinguished from the risks of diagnostic treatments or therapies subjects would receive even in not participating in the research).
- **Determine whether the risks will be minimized** to the fullest extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for diagnostic or treatment purposes or by alternative procedures that impart less risk;
- **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 potential benefits, whenever informed consent is required.

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.

4.6.1.1 Scientific Review

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

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

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or that of others, such as reviews by a funding agency or departmental review. When scientific review is

conducted by an individual or entity external to the IRB, documentation of that review must be provided to the IRB for review and consideration.

4.6.2 Equitable Selection of Subjects

The IRB determines, by reviewing the application, protocol and other research project materials, that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates the:

- Purposes of the research;
- Setting in which the research occurs;
- Scientific and ethical justification for including vulnerable populations or subjects vulnerable to coercion or undue influence such as children, prisoners, pregnant women, mentally disabled persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons;
- Scientific and ethical justification for excluding classes of persons who might benefit from the research;
- Inclusion/exclusion criteria;
- The amount and timing of payments to participants;
- Procedures/materials intended for use in identification and recruitment of potential subjects.

At the time of continuing review, the IRB will determine that the PI has followed the subject selection criteria that were originally set forth at the time of the initial IRB approval.

4.6.2.1 Recruitment of Subjects

The PI will provide the IRB with all recruitment materials to be used in identifying subjects including recruitment methods, advertisements, and payment arrangements. The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should ensure the procedures followed adequately protect the rights and welfare of the prospective subjects. See *Section 4.7.6* for a discussion of IRB review of advertisements, *Section 4.7.7* for a discussion of IRB review of payments.

In studies where the research activities will be carried out at an external site(s), the VARI IRB will require the external IRB's approval for recruitment materials.

4.6.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR), in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB 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. The IRB will ensure, as part of its review, that the information in the consent document & process is consistent with the protocol, and, when applicable, the HIPAA authorization. VARI IRB has a template consent document, *Informed Consent Document Template.*

4.6.4 Safety Monitoring

For research that is more than minimal risk, the PI should submit a data and safety monitoring (DSM) plan. The plan 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 providing DSM findings to the IRB. DSM may be performed by a researcher, medical monitor, safety monitoring committee, or other means.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring data to ensure the safety of subjects and for addressing problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan depend on the potential risks, complexity, and nature of the research study.

The principles the IRB applies in evaluating the adequacy of a proposed DSM plan include:

- Monitoring should be commensurate with the nature, complexity, size, and risk of the research
- Monitoring should be timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
- For lower risk studies, continuous, close monitoring by the study PI or an independent party may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies, as applicable.
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB will carefully evaluate the proposed DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of participant safety

Data and Safety Monitoring plans should specify:

- The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
- The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
- The frequency or periodicity of review of safety data
- The procedures for analysis and interpretation of the data to determine whether harm is occurring
- The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
- The conditions that trigger a suspension or termination of the research (i.e., stopping rules), when appropriate
- The procedures for reporting findings to the IRB, including a summary description of what information, or the types of information, that will be provided

For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe the composition of the board or committee. Generally, a DSMB or DMC should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety.

Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.

The National Institutes of Health (NIH) requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants.

When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide 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.

4.6.5 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.

4.6.5.1 Definitions

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

Confidentiality - Methods used to ensure that information obtained by researchers about their subjects is adequately protected from inappropriate access and 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 PI or associated with the information.

4.6.5.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual subjects. In order to make that determination, the IRB must obtain information regarding how the PIs will access the subjects or subjects' private, identifiable information and the subjects' expectations of privacy in the situation. PIs 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 subjects;
- Settings in which an individual will be interacting with an PI;
- Appropriateness of all personnel present for research activities;
- Methods used to obtain information about subjects and the nature of the requested information;
- Information that is obtained about individuals other than the "target subjects," 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.

4.6.5.3 Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the PI, 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. Note that the presence or absence of elements considered identifiers under HIPAA are not typically sufficient, in-and-of themselves, in considering whether the identity of subjects can be readily ascertained. For example, when the subject group is small and the level of detail in the data great, or when the subject group consists of individuals with a rare disorder or characteristic, the likelihood of identifying subjects from the data increases. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from inappropriate or unintentional disclosure.

At the time of initial review and with any applicable amendments, the IRB assesses whether there are adequate provisions to protect subject confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies. The PI will provide the information regarding the procedures in place to protect the confidentiality of research data and sensitive information. Sensitive information is data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information. This information should be reviewed at the time of initial review through the completion of the IRB application forms, any necessary HIPAA authorization forms, research protocol, and/or other submitted applicable materials.

The PI will provide information regarding information security procedures and plans to address the protection of written and paper documents, other physical media (e.g. CDs, tapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the PI and determine whether or not the confidentiality of research subjects is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to further protect research data (See *Section 23.1*).

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that could likely result from the disclosure of information collected outside the research. The IRB shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of data transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA must comply with the information security requirements of 21 CFR 11.

4.6.6 Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other situation, may be at increased vulnerability to accept exposure to risks. At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards are put into place for vulnerable subjects, such as those with diminished decision-making capacity.

For an extensive discussion about the IRB's review and approval process for individual vulnerable populations, please refer to *Section 9*.

4.7 Additional Considerations

4.7.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocol, which will generally be classified as either "minimal" or "greater than minimal" with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a protocol depending on the procedures and risks that subjects will be exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The meeting minutes will reflect the IRB's determination regarding risk levels.

4.7.2 Investigator Qualifications

The IRB reviews credentials, curriculum vitae, resumes, or other relevant materials to determine whether PIs and members of the research team are appropriately qualified to conduct the research.

4.7.3 Investigator Conflicts of Interest

It is VARI's policy to preserve public trust in the integrity and quality of research by minimizing actual or perceived conflict of interest (COI) in the conduct of research. Information regarding federal regulations and VARI policies, procedures, and training relevant to COI is available at www.vai.org.

All PIs and members of the research team are required to submit COI disclosures in accordance with *Conflict of Commitments Policy (COI-POL-002) Conflict of Interest Policy (LEG-POL-001)* and *Institutional Conflict of Interest Policy (COI-POL-003)*. The research application asks protocol-specific questions regarding PI and research team compliance with disclosure requirements, the existence of possible non-financial conflicts, and whether or not any COI management plans are in place. If a potential conflict exists, the Regulatory Programs Manager follows the procedures described in the policies listed above. If it is determined that no conflict exists, or that due to the nature of the conflict or circumstances of the protocol a management plan is not necessary, a report stating that is provided to the IRB reviewers. As part of its review process, the IRB will make a final determination as to whether COI exists with regard to the research under review. If a COI requiring management is identified, a management plan is developed by the VAI Conflicts Committee (CC) and provided to the IRB along with a summary describing the nature and circumstances of the conflict. The IRB reviews the proposed management plan and may accept it as written, make additions to, or otherwise strengthen the management plan. The final IRB-approved management plan is provided to the PI, the Regulatory Programs Manager, and the PI's department chair or direct supervisor. Final IRB approval of a protocol cannot be given until an approved conflict of interest management plan that adequately protects the human subjects enrolled in the protocol is in place.

When research is under the oversight of an external IRB, the conflict of interest procedures outlined in the reliance agreement or related materials are followed. Investigators who disclose interests to external IRBs should ensure that the disclosures are consistent with COI disclosures to VARI.

4.7.4 Institutional Conflicts of Interest

The policy of VARI is to ensure that the health and welfare of human subjects and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. Although VARI policy has separated technology transfer functions from research administration, circumstances may exist in which separation of function is not sufficient to avoid the appearance of institutional conflict of interest.

Institutional financial interests may be created by gifts, payments, royalty income, equity, and other benefits from or interests in for-profit organizations. Institutional financial interests also are created by financial and fiduciary interests of institutional officials.

VARI has established policies and procedures to identify, review, and manage institutional conflicts of interest and to ensure the independence of IRB review. This information can be located in *Institutional Conflict of Interest Policy (COI-POL-003).*

4.7.5 Significant New Findings

During the course of research, significant new knowledge or findings about research, the medication or test article, and/or the condition under study may develop. Upon awareness, the PI must report any significant new findings to the IRB as soon as possible, but no later than 10 business days. The IRB will review these new findings 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 PI contact currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The consent document should be updated for enrollment of new subjects. Currently enrolled subjects may need to be informed in writing of this new information and affirm their desire to continue participation in the study.

4.7.6 Advertisements and Recruitment Materials

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

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

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

The IRB reviews the material to assure that the information is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate, which includes but is not limited to:

- Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
- Claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation.

- Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device.
- Claims, either explicitly or implicitly, about the test article that are inconsistent with the product's labeling.
- Using terms like "new treatment," "new medication," or "new drug" without explaining that the test article was investigational.
- Promising "free medical treatment" when the intent was only to say subjects will not be charged for taking part in the investigation.
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
- The inclusion of exculpatory language.
- Advertisements will not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

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

- The name and address of the clinical PI and/or research facility.
- The condition being studied and/or the purpose of the research.
- In summary form, the criteria that will be used to determine eligibility for the study.
- The time or other commitment required of the subjects.
- The location of the research and the person or office to contact for further information.
- A clear statement that this is research and not treatment.
- A brief list of potential benefits.

The IRB will use the *Advertisements and Recruitment Materials Checklist* in the review of each proposal for utilization of advertisement/recruitment material. The completed checklists will be kept with the IRB files.

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

Directory listings of research such as ClinicalTrials.gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

4.7.7 Payments to Research Subjects

Payments to research subjects are commonly proposed as an incentive for participation in recognition of the time, effort, inconveniences, and discomforts that participation in the proposed research may entail. In contrast to payments, reimbursement is provided to cover actual costs incurred by subjects as a result of participation (e.g., travel, parking, lodging, etc.). Payment arrangements should be

managed separately from reimbursement whenever possible because the ethical considerations differ (as well as the potential tax implications). Reimbursement offsets costs and may decrease financial risks associated with participation and in doing so may facilitate equitable selection of subjects. In contrast, the amount, timing, and nature of payments may unduly influence potential subjects' decision-making, influencing them to accept discomforts or risks that they otherwise would find unacceptable and interfering with truly voluntary informed consent. Payment arrangements may also create issues with equitable selection of subjects, including the societal distribution of research risks and benefits and the generalizability of the research results.

The IRB must consider the proposed amount of payment, the method and timing of disbursement, the subject population, the recruitment methods and materials, and the information provided within the proposed consent form in order to evaluate the acceptability of a proposed payment plan. The IRB does not consider payment as a benefit when weighing the risks and benefits of the research, payment is an incentive not a benefit of the research.

Investigators who wish to pay research subjects must include in their application to the IRB the amount and schedule of all payments and the justification or basis for payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the time and inconveniences associated with study participation and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

When research involves multiple visits or interactions, payment should be prorated and not be contingent upon the participant completing the entire study. Further, any amount paid as a bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment.

Plans to reimburse subjects for incurred expenses must also be outlined in the application to the IRB and described within the consent.

If payment will meet or exceed $600.00 USD, 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. In general, unless the study is sensitive in nature, VARI Finance Department requires identifying information to issue checks, cash, or gift certificates to subjects. For sensitive studies, only name and address are required by the Finance Department, but the PI is required to keep an identity key in a secure place.

Payments in exchange for referrals of prospective participants, sometimes referred to as "finder's fees" or "referral fees" are not permitted. In addition, payments or other incentives designed to accelerate recruitment that are tied to the rate or timing of subject enrollment, e.g., "bonus payments," are prohibited.

4.7.8 Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present issues of undue influence or coercion.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other similar materials, the approximate retail value should be described to the IRB. The IRB must also be provided with a description, photo, or sample product to review.

Non-financial incentives such as extra credit for students and access to services or programs can also create situations that impact a potential subject's ability to fully and freely consider participation in research.

The PI and IRB should be particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing not to participate will not adversely affect an individual's relationship with the institution, its staff or the provision of services in any way (e.g., loss of credits or access to programs).

PIs should carefully structure incentives and methods of disbursement so that they do not unduly influence or coerce participation.

The IRB will use the *Payment and Non-monetary Gifts Checklist* in the review of non-monetary gifts and incentives to research subjects. The completed checklists will be kept with the IRB files.

4.7.9 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on VARI General Counsel for the interpretation and application of Michigan law and the laws of any other jurisdiction where research is conducted, and as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.

4.8 Possible IRB Actions

In conducting its review of research, the IRB may take any of the following actions. With the exception of disapproval, the actions listed below may be used for either expedited or convened board review, including limited IRB review under the 2018 requirements. An action of disapproval can only be taken at a convened IRB meeting.

Approval – The study is approved as submitted.

Approval with Comments or Recommendations - This action is taken when the IRB has determined that the criteria for approval are satisfied and the IRB provides the investigator with comments or recommendations that the investigator may wish to consider.

Approval with Conditions that Must Be Addressed – This action is taken when the IRB has determined that the criteria for approval are satisfied as long as the PI makes prescribed, specific changes to the protocol, consent, or study materials; provides confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted; and/or submits additional documents. For example, the IRB may require:

- Precise language changes to the protocol or consent such as specified wording changes or substitutions;
- Confirmation that the research excludes children;

- Submission of an ethics training certificate; or
- More substantive modifications to the protocol or consent process that must be within clearly stated parameters, such as a requirement to revise the protocol to indicate that consent of prospective subjects will be obtained at least one week prior to an investigational procedure.

For protocols reviewed at a convened IRB meeting, the required, prescribed revisions are agreed upon at the IRB meeting. For protocols reviewed under expedited review, the required revisions are designated by the expedited reviewer(s).

In order to receive approval for a protocol approved with conditions that must be addressed:

- The PI's response, the revised protocol materials and the previously submitted documents are provided to the IRB Chair or other qualified individual(s) designated by the IRB to review the investigator's response. The reviewer(s) verify that the prescribed changes have been made and the conditions have been satisfied. The approval date for the protocol is the date that the IRB took the action of "Approval with Conditions that Must Be Addressed". The date the conditions were determined to be satisfied is the effective date of approval ('final approval').
- As appropriate, the Chair or designated reviewer may request the full Board's review of the investigator's response.

Final approval will not be issued until all conditions are satisfied. An exception to this is allowed when the IRB stipulates that certain components of the research that meet the criteria for approval, may commence or continue while other components of the research that require modification cannot be initiated or continued until the outstanding issues are resolved and final approval is issued.

The outcome of the IRB's deliberations is communicated to the PI in writing.

The Chair or designated reviewer's determination that the conditions for approval have been satisfied will be included in the IRB protocol file and the IRB members are notified via the next meeting agenda that the study has been approved.

Deferred – This action is taken when substantial modification or clarification is required (of the nature or amount that the IRB cannot specify exact changes or parameters), or insufficient information is provided to judge the protocol submission adequately (e.g., the risks and benefits cannot be assessed with the information provided). For example, a justification for use of placebo and withholding currently available treatment is required, or a greater than minimal risk protocol has no description of how the safety of the study will be monitored. IRB approval of the proposed research cannot occur until subsequent review of the investigator's response at the convened IRB meeting.

In order to receive approval for a deferred submission:

- **For full review** - the PI's response must be reviewed at a convened meeting of the IRB. The IRB members are provided with the PI's written response, the revised materials and any other relevant materials necessary for review.
- For studies that initially qualified **for expedited or limited IRB review** and where the designated reviewer found that clarification was needed in order to determine whether the study is approvable, the PI's written response, the revised materials and any other relevant materials necessary for review is provided to the same IRB designated reviewer(s) unless the original reviewer is no longer available. In this case the review is completed by the IRB Chair or other qualified individual(s)

designated by the IRB Chair to conduct expedited or limited IRB review. The designated reviewer's determination that the study has met the criteria for approval is documented in the protocol file.

The protocol application will not be approved until all issues are addressed to the satisfaction of the convened IRB or the expedited reviewer(s).

The outcome of the IRB's deliberations is communicated to the PI in writing.

Disapproved – The IRB has determined that the research cannot be conducted at VARI or by employees or agents of VARI.

Approval in Principle – As per federal regulations, (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. One is if study procedures are to be developed during the course of the research, but human subjects approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the, as yet, undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the PI must submit such materials in sufficient time for IRB review, and secure IRB approval 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 PIs to have access to funding to begin aspects of the project that do not involve human subjects.

4.9 Approval Period

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols.

For research subject to the pre-2018 Common Rule, or FDA regulations: All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year.

For research subject to the revised Common Rule (2018 requirements): The IRB will conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year, except as described in *Section 4.10*.

In some circumstances, such as when the research involves a high likelihood or severity of risks, when the research imparts significant risks without likelihood of direct benefit, when the research population is especially vulnerable, when the investigator is inexperienced or a history of noncompliance, a shorter review interval (e.g. semi-annually, quarterly, or after accrual of a specific number of subjects) may be required (see below). If a maximum number of subjects is used to define the approval period, it is understood that the approval period in no case can exceed one year unless the study does not require continuing review. Or, for a new PI or a PI 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 be required or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first few subjects. For research that is subject to continuing review, the meeting minutes will reflect the IRB's determination regarding review frequency and the reason for shorter review intervals; when applicable, expedited reviewers will document the period of approval on the reviewer's checklist.

For each initial or continuing approval, the IRB will indicate an approval period with specification of the expiration date. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study reviewed and approved by a convened IRB, the approval commences on the date of the convened IRB meeting. If a study reviewed by a convened IRB meeting is approved with

conditions that must be addressed, the IRB can vote to assign a reviewer to assess the PI's response (see *Section 4.8*). When continuing review is required, the expiration date of the initial approval period is the date by which time the first continuing review must occur. For a study approved under expedited review, the approval period begins on the date the IRB Chair or Chair designee(s) gives final approval to the protocol.

The approval date and approval expiration date, when applicable, are clearly noted on all IRB approval letters sent to the PI. PIs should allow sufficient time for development and review of renewal/continuing review submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review is required to occur. This is because continuing review must be conducted by review of the full protocol and any results to date.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur no later than midnight of the date when IRB approval expires.

4.10 Continuing Review

For research subject to the pre-2018 Common Rule, FDA regulations, and any research where continuing review is required by applicable regulations, policy, or other requirements: The IRB will conduct continuing review of research at intervals appropriate to the degree of risk but not less than once per year. The date by which continuing review must occur will be recorded in the IRB electronic document and on initial and continuing review approval letters. There are no exceptions to the requirement for continuing review in the pre-2018 Common Rule, or in FDA or DOJ regulations.

For research subject to the revised Common Rule (2018 requirements): The IRB will conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year, except as described below. When applicable, the date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters.

Unless an IRB determines otherwise, continuing review of research subject to the 2018 Common Rule (the revised Common Rule) is not required in the following circumstances:

- Research eligible for expedited review in accordance with 45 CFR 46.110;
- Research reviewed by the IRB in accordance with the limited IRB review described in Section 4.3;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

The IRB may determine that continuing review is required for any research protocol that falls within the above criteria. For example, the IRB may determine that continuing review is required when:

1. Required by other applicable regulations (e.g., FDA);

2. Required by the terms of a grant, contract, or other agreement;
3. Recommended by Federal guidance (e.g., OHRP recommends that IRB's require continuing review of research that falls within expedited categories 8(b) and 9);
4. The research involves topics, procedures, or data that may be considered sensitive or controversial;
5. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;
6. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
7. An investigator has a history of noncompliance.

When the IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

If continuing review is not required, the IRB staff will request a *Research Status Report* annually from the investigator. This will be tracked by the IRB staff and verification of completion date will also be tracked.

To assist PIs, the IRB Office staff will send out renewal notices to PIs two months and one month in advance of the expiration date. However, it is the PI'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.

PIs must submit the following for continuing review:

- The current protocol;
- The current consent document;
- The most recent report from the DSMB or DMC (if applicable);
- The most recent multi-center progress report (if applicable);
- Any proposed modifications to the protocol, consent, or study; and
- The appropriate Continuing Review Report Form (Specimens or Data Only, Interventions or Interactions).

IRB staff attends the convened meetings and brings the complete protocol file for each protocol on the agenda. IRB members can request the protocol file or any additional materials prior to the meeting, or request to review the file while at the IRB meeting.

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

4.10.1 Key Considerations

In order to re-approve research at the time of continuing review, the IRB must determine that the criteria for approval continue to be satisfied. Since the research was previously found to satisfy the criteria for approval, the IRB focuses on whether any new information is available that would affect the

IRB's prior determination and that the criteria for approval continue to be satisfied. The IRB pays particular attention to four aspects of the research:

- Risk assessment and monitoring;
- Adequacy of informed consent;
- Local Principal Investigators (PI) and institutional issues; and
- Research progress.

4.10.2 Full Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the above materials and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any proposed amendments to the research plan, protocol, or consent. The primary reviewer is responsible for reviewing the materials submitted for continuing review including the complete protocol and is given access to the IRB file and relevant IRB meeting minutes. At the meeting, the primary reviewer leads the IRB through the completion of the regulatory criteria for approval in the *Continuing Review Checklist*.

During the continuing review of research, the consent document (currently approved or newly proposed) must be reviewed. In addition, it should be noted that consent documents are reviewed whenever new information becomes available that may require modification of information in the consent document.

4.10.3 Expedited Review of Continuing Review

In conducting continuing review under expedited review, the designated IRB member receives all of the above material. The reviewer completes the *Continuing Review Checklist* to determine whether the research meets the criteria that allow continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

For research subject to the pre-2018 Common Rule, or FDA regulations:

Generally, if the research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

For research subject to the revised Common Rule (2018 requirements):

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, unless it has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care;

and in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in *Section 4.4.1*).

When continuing review is not required (See *Section 4.10*) for research subject to the 2018 Common Rule and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the checklist.

4.10.4 Possible IRB Actions

As with Initial Review, at the time of Continuing Review, the convened IRB or IRB member conducting expedited review may take any of the following actions (See *Section 4.8* for a detailed description of these actions):

- Approval
- Approval with Comments or Recommendations
- Approval with Conditions that Must be Addressed
- Deferred

Additionally, if the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See *Section 6* for a detailed discussion of suspensions and terminations).

If a research protocol is "Approved with Conditions that Must Be Addressed" at the time of the Continuing Review, the IRB will specify any restrictions or requirements that must be adhered to, until the conditions for approval have been satisfied. For example, if at the time of continuing review, the IRB determines that an additional screening procedure is necessary, the IRB could approve the research with conditions that must be addressed and specify that no new subjects may be screened and enrolled until the PI submits the revised protocol and the condition has been determined to be satisfied. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition to be satisfied.

4.10.5 Lapses in Continuing Review

The regulations permit no grace period or extension of approval date after the specified approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. This will occur even if the PI has provided the continuing review information before the expiration date. Therefore, PIs must allow sufficient time for IRB review before the expiration date.

The IRB Office is responsible for promptly notifying the PI of the expiration of approval and that all research activities must stop.

If research subjects are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval, the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm and a proposal describing and justifying the specific research procedures that should continue in order to avoid harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already

enrolled subjects should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so. If there is insufficient time to obtain approval from the IRB to continue subjects on a lapsed study, the PI can make an initial determination that study activities must continue due to safety of the subjects and promptly inform the IRB.

It should be noted that if the IRB notes a pattern of noncompliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion, the IRB may determine that such a pattern represents serious or continuing noncompliance that will be handled according to the noncompliance policy (See *Section 12*).

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed, the PI must submit a continuing review report and the PI's department chair will be notified of this lapse.

4.11 Amendment of an Approved Protocol

PIs may wish to modify or amend their approved applications. **PIs must obtain IRB approval before making any changes, no matter how minor, in approved research** unless the change is necessary to eliminate any apparent immediate hazard(s) to the subject(s) or others (in which case the IRB must be notified immediately). This includes Protocol Exceptions (proposed changes to research procedures or other aspects of the IRB-approved research plan (e.g., eligibility criteria) for a single subject).

PIs should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new protocol application rather than allow such changes to be made through an amendment to the existing protocol.

PIs must submit documentation to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- Completed *Protocol Modification Request Form*,
- Revised protocol, an updated Initial IRB Application Form (as appropriate), and/or study materials (with tracked changes, with a detailed summary and justification for the changes);
- Revised consent/parental permission/assent documents (if applicable) or other documentation to be provided to subjects when the proposed change(s) to the research might relate to their willingness to continue to participate in the study; and
- Any other relevant documentation provided by the sponsor or coordinating center.

IRB staff will review the submission and make an initial determination regarding 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 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, will refer the protocol for full board review.

4.11.1 Full Board Review of Protocol Modifications

When a proposed change in a research study is not minor, the IRB must review and approve the proposed change at a convened meeting before the modification 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 modification, and a justification provided following its implementation. The IRB Chair or designee will review the change to determine that it is consistent with ensuring the subjects' continued health and welfare. This modification will be placed on the next IRB agenda for full review.

All IRB members are given a copy of all documents provided by the PI as part of their review responsibility.

At the meeting, the primary reviewer presents an overview of the proposed modifications and leads the IRB through the completion of the regulatory criteria for approval. The IRB will determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

4.11.2 Expedited Review of Protocol Modifications

An IRB may use expedited review procedures to review changes in expedited research so long as those changes do not impact the eligibility of the research for expedited review and to review minor changes (See *Section 4.1*) in convened board research during the period for which approval is authorized. Expedited review may be carried out by the IRB Chair and/or IRB Chair designee(s).

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

The reviewer will also consider whether information about those modifications might relate to the subjects' willingness to continue to take part in the research and if so, whether to provide that information to subjects.

4.11.3 Possible IRB Actions

As with Initial Review, at the time of Continuing Review, the convened IRB or IRB member(s) conducting expedited review may take any of the following actions (see *Section 4.8* for a detailed description of these actions):

- Approval
- Approval with Comments or Recommendations
- Approval with Conditions that Must Be Addressed
- Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the amendment to the convened IRB for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See *Section 6* for a detailed discussion of suspensions and terminations).

4.12 Closure of Protocols

The completion or termination of the study, whether premature or not, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a closure notice 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.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information [including specimens] are all complete). An example of this is when the only remaining research activity involves the analysis of aggregate data sets without individual subject identifiers.

For multi-center research, the study may be closed once all local research activities (as above) are complete. If the PI is serving as the lead PI or VARI is the coordinating center, the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

PIs may submit study closures to the IRB as part of the *Continuing Review Report Form*. With the submission, the PI must provide a summary of the research activity and any findings. If the study does not require continuing review, the *Research Status Report* can also be used to request closure of a study.

PIs may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. PIs must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study, request additional information or confirmation from the PI.

4.13 Reporting IRB Actions

All IRB actions are communicated to the PI, and designated primary contact person for the protocol, in writing within ten (10) business days via a letter prepared by the IRB staff that is reviewed and signed by the IRB Chair or Chair designee. For approval of a study, along with written notification of approval, a copy of the approved consent form (if applicable), indicating approval period on each page of the consent form will be sent to the PI.

For approval with conditions that must be addressed, the notification will include a list of the contingencies that must be satisfied in order for the research to be approved.

For a deferral, the notification will include the modifications and/or clarifications necessary along with the basis for requiring those modifications.

For a disapproval, termination or suspension, the notification will include the basis for making that decision and an opportunity to respond in person or in writing.

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

The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the VARI Institutional Official, as requested, and are stored permanently and securely in the IRB Office.

4.14 Appeal of IRB Decisions

When an IRB protocol is disapproved or deferred, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary in order to obtain IRB approval. The IRB shall include in its written notification a statement the reasons for its decision and give the PI an opportunity to respond in person or in writing. Similarly, when research is suspended, in part or in full, or terminated, the IRB will notify the PI in writing of the suspension or termination and the reasons for its decision.

In cases where there is disagreement between the IRB and the PI regarding the nature and extent of the requested changes or the necessity of, or basis for a suspension or termination, and these disagreements cannot be resolved, the PI and/or the IRB may make an appeal to the IO for resolution of the matter. The IO may organize a meeting to facilitate discussion between the IRB and the PI. While the IO may provide input and make recommendations to the IRB for expeditious resolution of the matter, final determinations for approval remain under the purview of the IRB.

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

5 Quality Assurance

VARI performs Quality Assurance (QA) activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

5.1 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the PI that no material changes occurred since previous IRB review.

In support of this requirement, the IRB requires the submission of Other Reportable Information (See *Section 14*) including reports from external monitors, auditors, or inspectors (See *Section 5.4*).

The IRB will also determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

1. The nature, probability, and magnitude of anticipated risks to subjects;
2. The degree of uncertainty regarding the risks involved;
3. Whether the research involves novel therapies or procedures;
4. The vulnerability(ies) of the subject population;
5. The projected rate of enrollment;
6. The experience and expertise of the investigators;
7. The IRB's previous experience with the investigators or the sponsor (e.g., compliance history, complaints from subjects, etc.);
8. The probable nature and frequency of changes that may ordinarily be expected in the type of research;
9. Whether the research undergoes routine independent monitoring;
10. Whether concerns about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources; and
11. Any other factors that suggest independent verification is warranted.

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

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

5.2 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 (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or 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 subjects; or
- Other situations when the IRB has concerns that the 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 PI or research project.

If the IRB determines that consent monitoring is required, the IRB Chair and Regulatory Programs Manager 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 affiliated with VARI. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI 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;
- Whether the participant had sufficient time to consider study participation;
- Whether the consent process involved coercion or undue influence;
- Whether the information was accurate and conveyed in understandable language; and
- Whether the subject 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.

5.3 Data Monitoring Reports

Reports describing the outcome of ongoing safety monitoring (such as DMC or DSMB reports) must be submitted to the IRB in a timely manner (typically within 7 business days after receipt). In the event the report recommends modifications to the research or suspension or termination of some or all research activities due to safety concerns, the IRB office should be contacted and the monitoring report submitted immediately.

5.4 External Monitoring, Audit, and Inspection Reports

Reports from external monitors, auditors, or inspectors must be submitted to the IRB for information. The IRB Chair, HRPP Director or designee will review such reports in order to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing noncompliance. If such issues are identified, the report will be forwarded to the convened IRB to determine if additional actions are necessary.

The HRPP Director should be notified in advance of upcoming audits or inspections, whenever possible.

Reports indicative of any negative actions by a government oversight office regarding research conducted at or by VARI, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections must be immediately reported to the HRPP/IRB office by phone or email regardless of whether the research is reviewed by an internal or external IRB. See *Section 16* for more information.

5.5 PI Compliance Reviews

The Regulatory Programs Manager, with the help of the IRB Chair, as needed, is responsible for, but can delegate, random post-approval audits and for-cause audits of protocols. Additionally, the IRB may appoint a subcommittee for the purpose of conducting compliance review audits of one or more protocols under its jurisdiction. The subcommittee may be composed of IRB members and staff from within and outside the organization.

Compliance reviews are conducted to assess PI compliance with federal, state, and local laws, and VARI policies, to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the IRB, and the PI. Any noncompliance will be handled according to the procedures in *Section 12*.

If it is identified that subjects in a research project have been potentially exposed to unexpected serious harm, the reviewer will promptly report such findings to the HRPP Director and the IRB Chair for immediate action.

If issues are identified that indicate possible misconduct in research, the procedures called for in the *RP-POL-001 Reporting and Investigating Allegations of Research Misconduct* will be initiated.

Compliance reviews may include:

- Requesting progress reports from researchers;
- Examining PI-held research records;
- Contacting research subjects;
- Observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
- Reviewing advertisements and other recruitment materials;

- Reviewing projects to verify from sources other than the researcher that no unapproved changes have been implemented since the previous review;
- Monitoring COI concerns to assure adherence to the approved management plan (e.g., related to the protocol and consent document)
- Monitoring HIPAA authorizations; and
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

5.6 IRB Compliance Reviews

The Regulatory Programs Manager, or delegated individual, may require assistance of an outside consultant or organization. The Regulatory Programs Manager will periodically review the activities of the IRB to assess compliance with regulatory requirements to identify areas of potential improvement. This will include a partial review of IRB records at least annually. Review activities may also include:

- Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessment of the documentation surrounding the discussion for protection of vulnerable populations as well as other risk/benefit related issues and consent issues that are included as part of the criteria for approval;
- Review of the IRB minutes to assure that quorum was met and maintained;
- Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and recorded;
- Evaluation of the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- Review of the IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- Review of the IRB database to assure all fields are complete and accurate;
- Verification of IRB approvals for collaborating institutions or external performance sites;
- Assessment of review timelines (metrics), e.g., time from submission to first review, to evaluate the quality, efficiency, and effectiveness of the IRB review process;
- Review of the workload of IRB staff to evaluate appropriate staffing level; and
- Other monitoring or audit activities deemed appropriate by the IRB.

The Regulatory Programs Manager and IRB Chair will review the results of IRB compliance reviews with the IRB and the IO. If any deficiencies are noted in the review, a corrective action plan will be developed by the Regulatory Programs Manager and IRB Chair and approved by the IO. The Regulatory Programs Manager will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the IO.

5.7 HRPP Quality Assessment and Improvement

Quality Assurance reports, including compliance reviews, are reviewed by the Regulatory Programs Manager with the IO available for consultation, in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the Regulatory Programs Manager and other relevant parties such the IO, the IRB Chair, will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

The Regulatory Programs Manager is responsible for tracking internal metrics that are informative in consideration of IRB and PI efficiencies, such as the amount of time from receipt of a submission through pre-review, assignment to the IRB agenda, final approval, and the amount of time it takes PIs to develop and submit responses to post-IRB review requirements and determinations.

Annually, a meeting is held by the IRB Chair, Regulatory Programs Manager, and IO in which a quality improvement plan is put into place, to be carried out by an individual or committee named by the Institutional Official that assesses compliance and achieving targeted levels of quality, efficiency, and effectiveness of the HRPP (e.g., continuous investigator training; use of IRB-approved consent forms, turn-around time of exemption determinations, etc.). The plan will, at a minimum contain:

- The goals of the quality assessment/improvement plan with respect to measuring effectiveness, identifying opportunities for improvement and achieving and maintaining targeted levels of quality, efficiency, effectiveness and compliance are stated.
- At least one objective to achieve or maintain compliance is defined.
- At least one measure of compliance is defined.
- The methods to assess compliance and make improvements are described.
- At least one objective of quality, efficiency, or effectiveness is defined.
- At least one measure of quality, efficiency, or effectiveness is defined.
- The methods to assess quality, efficiency, or effectiveness and make improvements are described.

Results of the plan report are reviewed by the IRB Chair, Regulatory Programs Manager and the IO, in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the Regulatory Programs Manager and other relevant parties such the IO and the IRB Chair will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

The Regulatory Programs Manager is responsible for tracking internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, assignment to the IRB, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. Metrics reports will be provided to the IRB Chair and IO, as requested.

6 Study Suspension or Termination

6.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See *Section 11* for a discussion of unexpected problems and *Section 12* for a discussion of noncompliance). The IRB's authority to suspend or terminate research applies to all research subject to IRB approval, including exempt research with limited IRB review and research for which continuing review is no longer required.

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

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

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The PI shall be provided with an opportunity to respond in person and 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 consider notification of subjects and any actions necessary to ensure the rights, safety, and welfare of subjects.

PIs are required to continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor despite the suspension. All events that need to be reported during a study must continue to be reported during the suspension period.

Suspension or termination of protocols approved by the IRB can also be issued by VARI officials acting outside of and unrelated to the interests of the IRB (i.e., not necessarily related to protecting the rights and welfare of study subjects). Such VARI actions can be made by the VAI Chairman and Chief Executive Officer, VARI General Counsel, Director of Research and Chief Scientific Officer or IO. The PI must report any suspension or termination of the conduct of research by VARI officials to the IRB. The IRB will review the circumstances to determine the impact of the suspension on the study and on the research subjects. The IRB will then determine if suspension or termination of IRB approval is warranted and any actions necessary to notify or to protect human subjects.

6.2 Protection of Currently Enrolled Subjects

Before a suspension or termination is put into effect the Chair, Vice Chair, Regulatory Programs Manager, or IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current subjects. Such procedures might include:

- Transferring subjects to another PI;
- 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 subjects for safety reasons;
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor;
- Notification of current subjects; and
- Notification of former subjects.

7 Documentation and Records

VARI prepares and maintains adequate documentation of the IRB's activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

7.1 IRB Records

IRB records include, but are not limited to:

- Written operating procedures;
- IRB membership rosters;
- A resume, CV, or other documentation of experience for each IRB member;
- Training records: documenting that researchers, IRB members, and IRB staff have fulfilled VARI's human subject training requirements;
- IRB correspondence including reports to regulatory agencies;
- IRB Protocol Records (Study Files) including correspondence with PIs and research team;
- Documentation of exemptions including when limited IRB review is a condition of exemption);
- Documentation of convened IRB meeting minutes;
- Documentation of review by another institution's IRB, when appropriate;
- Documentation of IRB reliance and cooperative review agreements (e.g. Memoranda of Understanding (MOUs);
    - For nonexempt research involving human subjects covered by the 2018 revised Common Rule (or exempt research for which limited IRB review takes place as described in *Section 4.3*) that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy [the Common Rule] (e.g., in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol);
- Documentation of independent or external investigator agreements;
- Federal Wide Assurances;
- IRB Registrations; and
- Documentation of complaints and any related findings and/or resolution.

7.2 IRB Study Files

The IRB maintains a separate IRB study file for each research application (protocol) that it receives for review. Protocols are assigned a unique identification number by the IRB 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 study file. VARI IRB maintains a separate file for each research protocol that includes, but is not limited to:

- Protocol and all other materials submitted as part of a new protocol application;
- Protocol and all other materials submitted as part of a request for continuing review, progress reports, or closure of research, including the rationale for conducting continuing review of research that otherwise would not require continuing review under the revised Common Rule as described in *Section 4.10*;
- Materials submitted and reviewed after the study has been approved, including modification requests, proposed advertisements, data and safety monitoring reports, and reports of protocol violations, complaints, noncompliance, subject injuries, and unanticipated problems;
- Significant new findings;
- IRB-approved Consent Form(s);
- IRB reviewer forms;
- Documentation of scientific review (if conducted by an entity other than the IRB and available);
- Documentation of type of IRB review. For exempt determinations and expedited review, this will include justification for conducting exempt or expedited review (qualifying factors and category(ies);
- For expedited review, IRB records document the name of the person reviewing the expedited protocol, and documents 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, and research involving children.
    - **For research subject to the pre-2018 Common Rule, or FDA regulations:** IRB records include documentation that the reviewer determined that the research involves no more than minimal risk and a determination of the frequency of continuing review for each study.
    - **For research subject to the revised Common Rule (2018 requirements):** For expedited review, the rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk. The rationale for requiring continuing review of research that otherwise would not require continuing review.
- For exempt research records document the name of the person making the exempt determination and, when applicable, limited IRB review determination;

- Documentation of all IRB review actions;
- Notification to the PI of expiration of IRB approval and requirements related to the expiration;
- Notification of suspension or termination of research;
- Copies of IRB determination letters (e.g., approval, conditions, deferral, etc.);
- IRB correspondence to and from the PI; and
- All other IRB correspondence related to the research;

7.3 The IRB Minutes

Proceedings are written and available for review at a regularly scheduled IRB meeting. Once approved by the members at a subsequent IRB meeting, the minutes cannot be altered by anyone, including a higher institutional authority.

A copy of IRB-approved minutes for each IRB meeting will be distributed to the IO, as requested.

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
    a. Each member's (or alternate's) full name;
    b. Each member's (or alternate's) representative capacity (e.g., scientist, non-scientist, unaffiliated, member who represents the general perspective of research subjects)
    c. The names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending remotely received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions;
    d. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or categories of members only as designated on the official IRB membership roster);
    e. Names of any consultants present, a brief explanation of their expertise, and documentation to support that the consultant(s) did not vote;
    f. The names of non-members and guests in attendance, such as IRB staff, investigators, and study coordinators

        Note: The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the numbers of members present for the vote on that item.
2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area;
3. When both a member and an alternate are present, the minutes will reflect if and when the alternate substituted for the member. Generally, the member votes, but an alternate may

substitute when appropriate (e.g., the member has a conflict of interest, the alternate has needed expertise, etc.);

4. Business items discussed and any in-service education provided;
5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing review by the convened IRB;
6. Vote counts on these actions (Total Number Voting; Approve (number voting for); Disapprove (number voting against); Abstain (number abstaining); Recused (number of members recused). When a member is recused due to conflict of interest, the name of the member and reason for the recusal will be noted;
7. Basis or justification for actions related to disapproval or requiring changes in research;
8. Summary of controverted issues and their resolution.
9. Approval period for initial and continuing reviews, when applicable, including identification of research that warrants review more often than annually and the basis for that determination.
10. **For research subject to the revised Common Rule (2018 requirements):** The rationale for requiring continuing review of research that otherwise would not require continuing review as described in *Section 4.10*;
11. Risk level of initial and continuing approved protocols, and modifications when the modification alters the prior risk determination.
12. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the HHS-approved sample consent document.
13. Protocol-specific findings supporting that the research meets each of the required criteria 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 altogether.
14. Protocol-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived.
15. Protocol-specific findings supporting that the research meets each of the criteria for approval under any applicable Subparts.
16. Determinations of conflict of interest and acceptance or modification of conflict of interest management plans.
17. Identification of any research for which there is need for verification from sources other than the PI that no material changes have occurred in the research.
18. Review and determinations related to interim reports (e.g., unanticipated problems or safety reports, serious or continuing noncompliance, suspensions or terminations, etc.);
19. A list of research approved under expedited review procedures, including limited IRB reviews conducted using expedited procedures, since the time of the last such report;
20. An indication that, when an IRB member or alternate member has a conflicting interest (see *Section 3.7*) with the research under review, the IRB member or alternate member was not present during the final deliberations or vote, and that the quorum was maintained.

21. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.
22. Discussion of statements of any significant new findings provided by the investigator.

A primary reviewer is assigned to each agenda item and completes any applicable reviewer worksheets prior to the IRB meeting. The worksheet(s) are projected during IRB meetings to guide discussion and determinations. Worksheets are updated as needed at or immediately following the meeting to reflect the convened IRB's final determinations and appended to the minutes. Comments within the IRB's e-system are reconciled as needed to reflect the final determinations of the IRB.

7.4 IRB Membership Roster

A membership list of IRB members must be maintained; and must contain the following information:

- Name;
- Earned degrees;
- Employment or other relationship (affiliated or non-affiliated) between each member and VARI - neither the member nor an immediate family member of the IRB member may be affiliated with VARI;
- Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist;
- 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; at a minimum which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, prisoners and other vulnerable populations or other subjects vulnerable to coercion or undue influence commonly involved in VARI research, as appropriate;
- Role on the IRB (Chair, Co-Chair, etc.);
- Voting status;
- For alternate members, the primary member or class of members for whom the member could substitute.

The IRB office must keep the IRB membership list current. The Regulatory Programs Manager or designee will report changes to the IRB Chair or Human Subjects Administrator to the OHRP, HHS within 90 days of the change.

7.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exempt category and written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exempt category as detailed in *Section 4.3*. When an exemption includes limited IRB review under the revised Common Rule (2018 requirements), the documentation will include this fact and the IRB action taken on those aspects of the research subject to limited IRB review in accordance with the procedures described for the review procedures used (expedited or convened board) elsewhere in this manual.

7.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: reference to the specific permissible category(ies) or status as exempt but requiring limited IRB review; that the activity described by the PI satisfies all of the criteria for approval; the approval period (when applicable), and any determinations required by the regulations including protocol-specific findings justifying the following determinations:

- Approving a procedure which waives or alters the informed consent process;
- Approving a procedure which waives the requirement for documentation of consent;
- Approving research involving pregnant women, human fetuses, or neonates;
- Approving research involving prisoners; and
- Approving research involving children.

7.7 Access to IRB Records

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

- All IRB records are kept secure within the IRB Offices. The IRB files are locked when the office is unattended;
- Ordinarily, access to all IRB records is limited to the Regulatory Programs Manager, IRB Chair, IRB members, IRB staff, authorized institutional officials, and officials of Federal and state regulatory agencies (OHRP, FDA). PIs are provided reasonable access to files related to their own 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 access needs, as determined by the IO and Regulatory Programs Manager;
- 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; and
- All other access to IRB study files is prohibited.

7.8 Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained at the facility for at least seven (7) years after completion of the research.

IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at VARI for at least 3 years after closure.

After that time those records will be shredded or otherwise destroyed.

8 Obtaining Informed Consent from Research Subjects

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 VARI. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB of record. When informed consent is required, it must be sought prospectively, and properly documented. Except as provided in *Sections 8.13 and 8.14* of these procedures, informed consent must be documented using a written consent form approved by the IRB.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants. The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach by an investigator and continuing through the completion of the research study. The process of obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB. See *Section 8.13.1* for an exclusion for certain screening and recruitment activities.

If someone other than the principal investigator obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. Consent delegates must be knowledgeable about the research to be conducted and the consent process and must have the expertise be able to answer questions about the study including those regarding risks, procedures, and alternatives.

The VARI IRB application solicits information regarding who will obtain consent; proposed changes to the personnel authorized to obtain consent must be submitted to the IRB for approval.

Sample or draft consent documents may be developed by a sponsor or network. However, the IRB of record is the final authority on the content of the consent documents that are presented to prospective subjects.

The following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of VARI. When the VARI IRB is serving as the IRB of record for external sites or personnel, the below requirements may be adapted as appropriate based upon the local context where the research will occur (e.g., who may serve as a LAR).

8.1 General Requirements

Except as provided elsewhere in these Standard Operating Procedures:

For research subject to the pre-2018 Common Rule, or FDA regulations:

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized

representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

For research subject to the revised Common Rule (2018 requirements):

1. Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or the subject's LAR
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence
3. The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR
4. The prospective subject or the LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information
5. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension
6. Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate
7. No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that have additional requirements for informed consent to be legally effective.

8.2 Additional Requirements

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be

obtained from a legal guardian with appropriate authority to make decisions regarding the activities called for in the research or a legally authorized representative (LAR);

2. The informed consent information must be presented in language that is understandable to the subject (or LAR/guardian). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population;
3. For subjects with Limited English Proficiency (LEP), informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the IRB requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent, and, in most circumstances, that consent materials are translated; and
4. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

8.3 Legally Authorized Representative

A Legally Authorized Representative (LAR) is defined by 45 CFR 46.102(c) and 21 CFR 50.3 as *"an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."* If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Who may serve as LAR is determined by state law. Michigan law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research. Thus, the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

For the purposes of this policy, a LAR includes a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC) or as patient advocate under a Patient Advocate Designation, a court appointed guardian of the person, and next-of-kin in the following order of priority: spouse, adult child, parent, adult relative with whom the person has been residing for the previous 6 months. The order of priority of a LAR is: court ordered representative, then patient advocate designation, then the above-stated priority of next-of-kin.

When the VARI IRB serves as the IRB of record for external sites and the use of LARs is proposed, information regarding relevant state law and local policy will be sought (local context information) and applied.

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB determines whether the use of LARs is appropriate for a given research study.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in *Section 8.5*.

8.4 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 VARI IRB. PIs are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) 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 a critical communication link between the prospective human subject and the PI, beginning with the initial recruitment approach and continuing through the completion of the research study. PIs must have received the appropriate training in the informed consent requirements and processes and be knowledgeable about the study protocol in order that they may answer questions to promote an understanding of the study to the potential study subject. The exchange of information between the PI and study subject can occur via one or more of the following modes of communication; face-to-face contact, mail, telephone, video-conferencing, or fax. Obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and have their questions answered to their satisfaction. PIs must obtain consent prior to enrolling a subject into a study and prior to initiating any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the PI will obtain consent from a potential subject, the PI needs to formally delegate this responsibility and obtain IRB approval for this delegation. The person approved to obtain consent must have had the appropriate training on how to obtain consent, the consenting process, must be knowledgeable about the research to be conducted, and must be able to answer any question about the study.

In requesting approval to delegate consenting responsibilities, the PI must provide an explanation of how the proposed consenting individual has been trained to obtain consent by addressing the following:

- What qualifies this individual to obtain consent;
- What specific training has this individual had or will this individual have to assure that he/she knows the protocol and can answer any question posed by potential subjects; and
- What ongoing supervision/training will be provided for this individual?

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 are 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.

8.5 Determining a Potential Adult Subject's Ability to Consent to Research

For the purpose of this section, a subject has the capacity to consent to his or her own participation in a research activity if s/he demonstrates an understanding:

- That the activity is research, not standard treatment
- Of the risks and benefits of the study
- Of the alternatives that are available if s/he does not participate
- That, if s/he chooses not to participate, this decision will be accepted without penalty, and will not jeopardize clinical care

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals. To highlight this distinction, a person who is suffering with severe depression may be able to demonstrate an understanding of a, b, c and d above, but may not care, or may actually want to put themselves at risk. Such individuals should not be considered able to provide consent for themselves.

For further discussion regarding adults who cannot consent for themselves, see *Section 9.9*.

8.6 Basic Elements of Informed Consent

To be valid, the consent process must include the following basic elements of information to potential subjects:

- 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 that may reasonably be expected from the research;
- A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will 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 on the research team** for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
- **Contact information for someone independent of the research team** for problems, concerns, questions, or input. At VARI, **contact information for the IRB** is provided 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.
- 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 that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- For research subject to the revised Common Rule (2018 requirements): One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
    - A statement that **identifiers might be removed** from the identifiable private information or identifiable biospecimens **and that**, after such removal, the information or biospecimens **could be used** for future research studies or distributed to another investigator for future research studies **without additional informed consent** from the subject or the legally authorized representative, if this might be a possibility; or
    - A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, **will not be used or distributed** for future research studies.

  For studies subject to the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, a statement regarding the posting of clinical trial information at ClinicalTrials.gov (or other accepted database for basic experimental studies) is required.

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

1. 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 are not well known.)
2. 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.)
3. Anticipated circumstances under which the subject's participation may be terminated by the PI without regard to the subject's consent. (For example: Include anticipated circumstances under which the PI may terminate participation of a subject.)

4. Any additional costs to the subject that may result from participation in the research. (For example: Include information regarding additional costs that subject may incur.)
5. When applicable, the amount and schedule of all payments;
6. The consequences of a subject's decision to withdraw from the research. (For example: Include information that withdrawal from the research may be associated with adverse consequences.)
7. Procedures for orderly termination of participation by the subject. (For example: Include information when the protocol describes such procedures.)
8. 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 if interim information is likely to be developed during the conduct of the research.)
9. The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)
10. **For research subject to the revised Common Rule (2018 requirements):**
    a. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
    b. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
    c. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

8.8 VARI Requirements

In addition to the federal elements of consent described above, VARI has defined specific additional information that must be included in consent documents when applicable to the research (e.g., 1099 language). A list of these requirements is provided on the IRB's website (vai.org/compliance/hrpp) for investigator and reviewer reference.

8.9 Documentation of Informed Consent

Except as provided in *Section 8.14* of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

For research conducted in accordance with ICH-GCP E6 or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form.

Informed consent is documented by the use of a written consent form approved by the IRB and signed (including in an electronic format) and dated by the subject or the subject's LAR at the time of consent.

A written copy of the signed and dated consent form must be given to the person signing the form. The PI should retain the signed original or a copy in the research records.

The consent form may be:

1. **For research subject to the pre-2018 Common Rule, or FDA regulations:** A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's LAR, but the subject or LAR must be given adequate opportunity to read it before it is signed;
2. **For research subject to the revised Common Rule (2018 requirements):** A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's LAR;

VAI does not currently utilize the option for short form documentation of consent described at 45 CFR 46.117**.**

8.10 Special Consent Circumstances

8.10.1 Electronic Informed Consent (eIC)

The ethical obligation to obtain informed consent for participation in research is fundamental; however, U.S. regulations do not specify a particular method for the informed consent process. Recognizing the increased interest in using electronic informed consent (eIC) to replace or supplement the traditional paper-based process, OHRP and FDA issued joint guidance on the topic in 2016. Per the guidance, eIC refers to *"the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent."* Investigators planning to use eIC should review the guidance in advance to ensure that the eIC process and platform meet OHRP and FDA (as applicable) expectations.

Investigators proposing to use eIC should submit copies of all forms and informational materials (e.g., video content, hyperlinked webpages) that the potential subject will review during the eIC process. If the eIC includes questions or other methods to gauge subject comprehension, these should also be provided. Investigators are responsible for periodically reviewing any linked to materials to ensure that the content remains available and is unchanged. Any changes to the eIC or any of the supplemental information must be submitted to the IRB for review and approval.

Whether the eIC process takes place in person or remotely, the responsibility for obtaining informed consent remains with the investigator and any appropriately delegated study team members. When the eIC process takes place remotely and is not witnessed by the investigator or study team members, the eIC generally should include a method to ensure that the person electronically signing the eIC is the subject or their LAR, when applicable. Exceptions to this general rule may be acceptable in certain circumstances (e.g., minimal risk research).

As with any other form of consent, the eIC process must allow for sufficient time for the potential subject to consider whether to participate and must include a mechanism for potential subjects to ask questions and have them answered. A copy of the eIC must be provided to participants, including copies of any supplemental materials. The copy provided to participants may be hardcopy or electronic.

Electronic signatures must be compliant with applicable legal requirements, including those of the jurisdiction where the research is to be conducted, and the FDA's requirements, when applicable.

8.10.2 Enrollment of persons who do not speak English or who have Limited English Proficiency

Expected enrollment: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document and other subject materials, as applicable. In order to assure that the translation is accurate, the consent document must be either a certified translation or be independently reviewed by an IRB member or other person who is fluent in that language before it is approved. When non-English speaking subjects enroll, the subject and the witness sign the translated document. The subjects are given a copy of the signed translated consent document.

Unexpected enrollment: If a person who does not speak or read, or has limited proficiency in, English unexpectedly presents for possible enrollment, an IRB-approved translated version of the written consent document may not be available for use. PIs should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. 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, may not be effective. If this is the case, the subject should not be entered into the study.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must receive IRB approval to enroll the participant and to ensure that they receive consent information in their preferred language.

Use of interpreters in the consent process: Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter is required to deliver information in the IRB-approved consent form and to facilitate the consent conversation. Someone who is independent of the subject (i.e., preferably not a family member) should assist in presenting information and be a part of the consent process. Whenever possible, interpreters should be provided copies of the IRB-approved consent script well before (24 to 48 hours if possible) the consent conversation with the subject. A consent note should be written for the research record documenting the use of an interpreter to support understanding and facilitate the subject's ability to ask questions and have them answered as well as the subject's agreement to participate (or decision to decline). The interpreter should sign the consent form and/or consent note and note "Interpreter" under the signature line.

8.10.3 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure 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.

8.10.4 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in *Section 9*.

8.10.5 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) has 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 whether he/she wants to enroll in the study.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in *Section 8.14*.

For more than minimal risk research, the consent form must be read to the potential subject and the subject must be given an opportunity to ask questions. An audiotape approved by the IRB may be used and is strongly encouraged where possible. If capable, the subject signs, or marks an X to signify consent. If this is not possible, the potential subject will provide verbal consent. The person obtaining consent and a witness will sign the written study consent form with a statement that specifies that an oral process was used and that the subject gave verbal consent. The consent process will also be documented in the research record. 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.

8.11 Physically Challenged Subjects

A person who is physically challenged (e.g., physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with oral consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

8.12 Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or a PI may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participation. In these circumstances, questions sometimes arise about: (1) whether the PI may use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the PI; and (2) whether the PI can continue to obtain data about the subject and, if so, under what circumstances. PIs must plan for the possibility that subjects may withdraw from research and include a discussion of what withdrawal means and how it is to be handled in their research protocols and informed consent documents.

Regulatory requirements regarding the retention and use of data after subject withdrawal or termination differ between FDA regulations and research not subject to FDA regulations. Under applicable FDA regulations, data collected on human subjects enrolled in FDA-regulated research up to the time of subject withdrawal must remain in the trial database in order for the study to be scientifically valid. For research not subject to FDA regulations, PIs, in consultation with the funding agency, can choose to honor a research subject's request that the PI destroy the subject's data or that the PI exclude the subject's data from any analysis.

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

- For FDA-regulated studies and 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 this previously collected data removed.
- For research not subject to FDA regulations, the PI should inform subjects whether the PI intends to either: (1) retain and analyze already collected data up to the time of subject withdrawal; or (2) honor a research subject's request that the PI destroy the subject's data or (3) the PI exclude the subject's data from any analysis.

Sometimes, a subject wants to withdraw from the primary interventional component of a study, but is willing to allow the PI to continue other research activities described in the IRB-approved protocol and informed consent, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social worker. 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. The PI 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 continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

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

If a subject (a) withdraws from the interventional portion of a study, (b) does not consent to continued follow-up of associated clinical outcome information, and (c) does not request removal of their data, the PI cannot access, for purposes related to the study, the subject's medical record or other confidential records requiring the subject's consent. However, a PI may review study data related to the subject that was collected prior to the subject's withdrawal from the study, and may consult public records, such as those that establish survival status.

8.13 Waiver or Alteration of Informed Consent

General Waiver or Alteration:

For research subject to the pre-2018 Common Rule, or FDA regulations:

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

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

Note: Prior to January 22, 2024, waivers or alterations for certain FDA-regulated research may have been granted by an IRB in accordance with these criteria based on the July 25, 2017 FDA guidance" IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects" (82 FR 34535)

For research subject to the revised Common Rule (2018 requirements) and/or FDA §50.22 (effective January 22, 2024):

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent in accordance with the revised Common Rule and refused.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration"), provided that the IRB finds and documents that the below criteria are satisfied. An IRB may not omit or alter any of the general requirements for informed consent (See *Section 8.1*).

1. The research of clinical investigation involves no more than minimal risk to the subjects;
2. The research or clinical investigation could not practicably be carried out without the requested waiver or alteration;
3. If the research or clinical investigation involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

5. Whenever appropriate, the subjects or LARs will be provided with additional pertinent information after participation.

Public Benefit or Service Programs Waiver or Alterations

Note: VARI does not conduct research at this time that would involve Waiver or Alteration of Consent for Public Benefit or Service Programs. This content is included in the event that VARI engages in such research in the future.

For research subject to the revised Common Rule (2018 requirements):

(Note: this option is <u>not</u> available to research subject to FDA regulations)

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent and refused.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration") (See *Sections 8.6 and 8.7*), provided that the IRB finds and documents that the below criteria are satisfied. An IRB **may not** omit or alter any of the general requirements for informed consent (See *Section 8.1*).

1. 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:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

8.13.1 Screening, recruiting, or determining eligibility

For research subject to the revised Common Rule: An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

1. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

*Note: The provisions described in this section do not apply to research subject to the **pre-2018 Common Rule**. These provisions do not appear in FDA regulations, however, the FDA does not consider records review or oral communication with potential subjects prior to obtaining consent to be part of a clinical investigation, therefore waivers are not required. See FDA Guidance on Informed Consent for more information.*

8.14 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the PI to obtain a signed consent form for some or all subjects if it finds **any** of the following:

- Only record linking the subject and the research would be the informed consent form and the major risk would be potential harm resulting from a breach of confidentiality *(Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)*;

  Note 1: Each subject (or LAR) must be asked whether they want documentation linking them with the research, and their wishes must govern.

  *Note 2: This option **does not** apply to FDA-regulated research.*

OR

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers (e.g., marketing surveys, telemarketing).

  *Note: This option **does** apply to FDA-regulated research (most commonly in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in a clinical trial).*

OR

- If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

  *Note: This option **does not** apply to research subject to the **pre-2018 Common Rule or to FDA** regulations.*

Unless the IRB has granted a full waiver of informed consent, PIs who seek and receive approval for a waiver of documentation of consent still must perform an adequate consent process.

In cases in which the documentation requirement is waived, the IRB requires the PI to provide in the application materials a written summary of the information to be communicated to the subject. The IRB will consider whether the PI is required to provide subjects with a written statement regarding the research. If a written statement is required, this document must be approved by the IRB.

8.15 Posting of Clinical Trial Consent Forms

For research subject to the revised Common Rule (2018 requirements):

*Note: The provisions in this section **do not apply** to research subject to the **pre-2018 Common Rule.***

For each clinical trial conducted or supported by a Federal department or agency, one IRB approved informed consent form used to enroll subjects **must be posted by the awardee or the Federal department or agency component conducting the trial** on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

At this time, two publicly available federal websites that will satisfy the consent form posting requirement have been identified: ClinicalTrials.gov and a docket folder on Regulations.gov (Docket ID: HHS-OPHS-2018-0021). Additional federal websites that would satisfy the revised Common Rule's clinical trial consent form posting requirement might be identified in the future.

OHRP's website includes guidance and instructions for posting clinical trial consent forms for research conducted or supported by HHS: https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/index.html.

9 Vulnerable Subjects in Research

When some or all of the subjects in a research study conducted under the auspices of VARI are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these subjects. The IRB must ensure that the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable subjects in research under the auspices of VARI.

9.1 Definitions

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. According to Michigan State Law, minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, VARI IRB generally defines children as persons under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example:

- Emancipated minors, Michigan law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc.);
- Mature minors—Michigan law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or
- Certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment.

Because Michigan law does not specifically address consent of children with majority status in relation to research, VARI IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than Michigan, the research must comply with the state laws regarding the legal age of consent in all relevant jurisdictions. VARI's General Counsel will be consulted with regard to the laws in other jurisdictions.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Michigan, a guardian of a minor has the powers and responsibilities of a parent, including the duty to take reasonable care of the minor's physical well-being and protect the minor's property; facilitate the minor's education and social or other activities; and authorize medical or other professional care, treatment, or advice. (MCL 700.5215)

NOTE: For research conducted in jurisdictions other than Michigan, the research must comply with the State laws regarding guardianship in all relevant jurisdictions. VARI's General Counsel will be consulted with regard to the laws in other jurisdictions.

Fetus means the product of conception from implantation until delivery.

Dead fetus means a fetus that does not exhibit heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord.

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

Neonate means a newborn.

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.

Nonviable neonate means a neonate after delivery that, although living, is not viable.

Pregnancy encompasses the period of time from implantation until delivery. A woman shall be 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.

Prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Surrogate Consent is consent obtained from a legally authorized representative (LAR) on behalf of a research subject who is determined to lack decision-making capacity.

9.2 Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of subjects 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 subjects. 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. These are:

- 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

HHS-funded research that involves any of these populations must comply with the requirements of the relevant Subparts. Research funded by other federal agencies may or may not be covered by the Subparts. For example, FDA regulations include additional protections only for children as subjects in research.

When following DoD regulations, research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C. and D.

- For purposes of applying Subpart B, 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 included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Research involving prisoners cannot be reviewed by the expedited 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 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 participant. VARI limits the application of the FWA to federally funded research. Consequently under VARI’s FWA the Subparts only apply to HHS-funded research and research funded by another federal agency that requires compliance with the Subparts (FDA regulations include Subpart D, which applies to all FDA-regulated research). The following policies and procedures, which are based on the Subparts, apply to all research regardless of funding. The individual sections describe how the Subparts apply to HHS-funded research.

9.3 Procedures

The following policies and procedures apply to all research involving vulnerable populations *(subjects vulnerable to coercion or undue influence)* under the oversight of the IRB regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study;
2. The investigator describes safeguards to protect the subject’s rights and welfare in the research proposal;
3. IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
4. The IRB evaluates the proposed inclusion of vulnerable population(s) in the research and the safeguards proposed by the investigator, taking into consideration the following factors, as applicable to the research:

a. Whether inclusion of vulnerable populations is ethically and scientifically appropriate;
b. Whether the proposed plans, including the settings and circumstances, for the identification and recruitment of subjects, and for obtaining consent or parental permission, ensure equitable selection of subjects and promote voluntariness;
c. Whether the proposed research confers any direct benefit, whether the benefit is available outside of the research, and whether access to the benefit may unduly influence participation by vulnerable populations;
d. Whether any costs or plans for subject reimbursement or compensation, may exclude or unduly influence participation by vulnerable populations;
e. Whether the provisions for privacy and confidentiality adequately protect vulnerable populations; and
f. Other relevant considerations as appropriate for the population(s) and the circumstances of the research

5. The IRB will determine whether the inclusion of the vulnerable population(s) is appropriate and whether the proposed plan adequately safeguards the rights and welfare of these subjects. When appropriate, the IRB may restrict or disallow the inclusion of vulnerable subjects or may require modifications to the research plan to enhance protections or to monitor the effectiveness of protections. For example, the IRB could require review more than annually, periodic HRPP QA/QI reviews, independent routine monitoring, or the use of a research subject advocate or consent monitor.

Modifications to Research

1. When an investigator proposes to add inclusion of a vulnerable population after research has already been approved by the IRB, the investigator must submit a modification request to the IRB identifying the population they would like to add, justification for inclusion of the population, and any modifications to the research plan to ensure protection of the subjects' rights and welfare;
2. The IRB staff and IRB will follow the procedures outlined for initial review above.

Continuing Review

1. At continuing review, the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare. When research does not include any interaction or intervention with subjects, and such information is not gathered, this should be noted on the continuing review report;
2. IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
3. The IRB reviews the continuing review information, and any relevant information reported to the IRB during the period of approval, and determines whether the inclusion of vulnerable populations and the plans to protect the rights and welfare of vulnerable subjects remains appropriate.

9.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research regardless of funding source. Since, according to VARI FWA, Subpart B of 45 CFR 46 applies only to HHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

VARI does not currently, nor does it foresee engaging in research involving neonates. If VARI were to be presented with a research proposal involving neonates, VARI would develop appropriate policies and procedures to ensure protection of this population.

9.4.1 Research Involving Pregnant Women or Fetuses

9.4.1.1 Research Not Funded by HHS

For research not funded by HHS, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research where the risk to the pregnant women and fetus is no more than minimal.

Pregnant women or fetuses may be involved in research not funded by HHS **involving more than minimal risk** to fetuses 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 risks 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;
- 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, or the prospect of a direct benefit both to the pregnant woman and the fetus, 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 paragraph 4 or 5 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;
- 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; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

9.4.1.2 Research Funded by HHS

For HHS-funded research, 45 CFR 46 Subpart B applies to all research involving pregnant women. Under 45 CFR 46 Subpart B, pregnant women or fetuses may be involved in research funded by HHS 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 or 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 paragraph 4 or 5. 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 in *Section 9.8.2*;
- 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; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

9.4.2 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.

9.5 Research Not Otherwise Approvable

9.5.1 Research Not Funded by HHS

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 detailed above, 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 pregnant women, fetuses or neonates; and
    - 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.

9.6 Research Funded by HHS

HHS-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 HHS review.

9.7 Research Involving Prisoners

Prisoners are one of three classes of individuals deemed vulnerable to exploitation in research and therefore special rules protect them. In the past, prisoners were viewed as a convenient research population. In general, prisoners are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, all the things that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation.

Subpart C and this policy based on Subpart C attempt to address whether prisoners have a real choice in research participation, or whether incarceration prohibits free choice.

The following applies to all research involving prisoners, regardless of funding source (unless the research is subject to the revised Common Rule, qualifies for exemption, and only incidentally includes prisoners (See *Section 4.3.1*). The requirements in this section are consistent with 45 CFR 46 Subpart C, which applies to HHS-funded research.

While VARI does not anticipate engaging in research involving prisoners, should such a study be submitted for IRB consideration or if a subject on a VARI protocol becomes incarcerated, we will follow the procedures outlined below.

9.7.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of VARI involving prisoners as subjects. Even though the VARI IRB may approve a research protocol involving prisoners as subjects according to this policy, PIs are still subject to the Administrative Regulations of the Michigan Department of Corrections and any other applicable State or local law (45 CFR 46.301).

9.7.2 Minimal Risk

The definition of minimal risk in the Subpart C is different than in the rest of the federal regulations. According to 45 CFR 46.303, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

9.7.3 Composition of the IRB

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

- The IRB (exclusive of prisoner members) must have no association with the prison(s) involved in the study, apart from membership on the IRB.
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
- The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count towards quorum when he or she is in attendance and reviewing studies covered by Subpart C.

9.7.4 Review of Research Involving Prisoners

The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.

The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)

The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.

Modifications. Minor modifications to research may be reviewed using the expedited procedure. Modifications involving more than a minor change must be reviewed by the convened IRB using the same procedures for initial review, including review by the prisoner representative.

Continuing review. Continuing review must use the same procedures used for initial review, including review by the prisoner representative.

Expedited Review. If research involving prisoners is reviewed by expedited review, prisoner representation will be included in the review when possible.

9.7.5 Incarceration of Enrolled Subjects

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, Subpart C now applies and the IRB must:

- Confirm that the subject meets the definition of a prisoner;
- Terminate enrollment or review the research study under Subpart C if it is feasible for the subject to remain in the study;
- Before terminating the enrollment of the incarcerated subject, the IRB should consider the risks associated with terminating participation in the study. If the subject cannot be terminated for health or safety reasons, one of two options are available:
    - Keep the subject enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification;
    - Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.;
    - If a subject is incarcerated temporarily while enrolled in a study:
    - If the temporary incarceration has no effect on the study, keep the subject enrolled; and
    - If the temporary incarceration has an effect on the study, handle according to the above guidance.

9.7.6 Additional Duties of the IRB

In addition to all other responsibilities prescribed for the IRB in other sections of this manual, the IRB will review biomedical or behavioral research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following **permitted categories** (45 CFR 46.306):
    - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- Research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research.
- The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research (68 FR 36929, June 20, 2003). The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. Prisoners cannot be a particular focus of such research, and the research must present no more than minimal risk and no more than inconvenience to the prisoner-subjects.

- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB, justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or

care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

9.7.7 Certification to HHS

Under 45 CFR 46.305(c), institutions engaged in research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research. Certification is not required for exempt research that only incidentally includes prisoners.

When VARI is responsible for submitting certification to OHRP, the HRPP/IRB office will do so using the web-based certification form available on OHRP's website. The certification form must be accompanied by the "research proposal" which OHRP defines as including:

- the IRB-approved protocol, including consent forms;
- any IRB application forms required by the IRB; and
- any other information requested or required by the IRB to be considered during IRB review.

DHHS-conducted or supported research involving prisoners as subjects may not proceed until OHRP reviews the certification and issues its authorization on behalf of the Secretary.

9.8 Research Involving Children

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

9.8.1 Allowable Categories

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

1. Research not involving greater than minimal risk. Provided that the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in *Section 9.8.2*.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Provided that the IRB finds and documents that:
    a. The risk is justified by the anticipated benefit to the subjects;
    b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
    c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 9.8.2*.

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. Provided that the IRB finds and documents that:
    a. The risk represents a minor increase over minimal risk;
    b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
    c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
    d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 9.8.2*.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
    a. Federally-funded research in this category must be approved by the Secretary of Health and Human Services;
    b. FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs.
    c. For non-federally-funded, non-FDA research, 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:
        (1) That the research satisfies the conditions of the previous categories, as applicable; or
        (2) 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
            - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 9.8.2*.

9.8.2 Parental Permission and Assent

9.8.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in *Sections 8.6 and 8.7*.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 & 2 above. The IRB's determination of whether permission must be

obtained from one or both parents will be documented in the reviewer's notes when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 & 4 above 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.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver in *Section 8.13*; or
- 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 requirement to protect the subjects (for example, neglected or abused children), the IRB may waive the parental permission requirements provided that 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 only be waived for research covered by the FDA regulations if the criteria for an exception from the general requirements for informed consent under 21 CFR 50.23 or for emergency research under 21 CFR 50.24 are satisfied.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by *Section 8.9*.

9.8.2.2 Assent from Children

When children are to be enrolled in research, the IRB is obligated to determine that adequate provisions are made for soliciting the assent of children when, in the judgment of the IRB, the children are capable of providing assent. "Assent" is defined as a child's affirmative agreement to participate in research. Mere failure on the part of a child to object, absent affirmative agreement to participate, should not be construed as providing assent.

In determining whether children are capable of providing assent, the IRB should take into consideration the ages, maturity, and psychological state of the children to be involved. The IRB has the discretion to judge children's capacity to assent for all of the children to be involved in a proposed research activity, for some, or to make the determination on an individual basis.

Likewise, in evaluating the provisions for obtaining assent, the IRB should take into account the nature of the proposed research activities and the ages, maturity, and psychological state of the children to be involved. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should 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, and whether it might involve any pain or discomfort. The assent procedure should incorporate provisions to ensure that the child is enabled to make a free choice about participation.

9.8.2.3 Waiver of Assent

The IRB may waive the requirement for assent of children if it determines and documents that:

1. The capability of an individual child, some, or all children to provide assent is so limited that they cannot reasonably be consulted;
2. The interventions or procedures involved in the research hold 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; or
3. That even though the children are capable of providing assent:
    a. The research involves no more than minimal risk;
    b. The waiver will not adversely affect the rights and welfare of the subjects;
    c. The research could not practicably be carried out without the waiver; and
    d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

9.8.2.4 Documentation of Assent

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the researcher should provide the IRB with a proposed script and any materials that they intend to utilize in explaining the research.

When the research targets children who are likely able to read and write, researchers should propose a process and 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; and
- Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when the potential to enhance comprehension may exist. Studies involving older children or adolescents should include more information and may use more complex language.

9.8.2.5 Disagreement between the Parent and Child

Parents and children will not always agree on whether the child should participate in research. Unless the requirement for child assent or parental permission has been waived by the IRB, both child assent and parental permission are necessary prerequisites for a child to participate in research. Objection by either the parent(s) or child must be respected and neither should be subjected to coercion or undue influence.

9.8.2.6 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 (Categories 3 & 4 in *Section 9.7.1*), 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 PI(s), or the guardian organization.

9.9 Adults with Impaired Decision-Making Capacity

The requirements in this section apply to all research involving persons with mental disabilities or persons with impaired decision-making capacity regardless of funding source.

Research involving adults with impaired decision-making capability may only be approved when the following conditions apply:

- Only persons with impaired decision-making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The PI must demonstrate to the IRB that there is a compelling reason to include persons with impaired decision-making capacity as subjects. Persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

- The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. Persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
- Procedures have been devised to ensure that subject's LAR is well informed regarding their roles and obligations to protect persons with impaired decision-making capacity. LAR, or guardians, must be given descriptions of the proposed research studies and the obligations of the person's LAR. The LAR must be informed that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the best interest of the potential research subject.

9.9.1 Determination of Decision-Making Capacity

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the potential subject may not be capable of making voluntary and informed decisions about research participation.

The PI and research staff must have adequate procedures in place for assessing and ensuring the potential subjects' capacity, understanding, and ability to provide informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent or assent is adequate including consideration of state and local laws and VARI policy.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the PI can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require PIs to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision-making capacity, the IRB may ensure that PIs establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third-party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the potential subject to consider the information that has been presented. If in doubt, researchers should not seek participation from the subject.

It is often possible for PIs and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audio-visual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, video-taping or audio-taping of consent interviews, second opinions, use of independent consent observers, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision-making process.

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

Although unable to provide informed consent, some persons may resist participating in a research protocol approved by their LAR. Under no circumstances may subjects be forced or coerced to participate.

In the event research subjects become impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the PI is responsible for notifying the IRB of the situation. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above.

9.9.2 IRB composition

The IRB membership must include representation via a member or consultant with expertise in issues of impaired decision-making capacity, e.g., a family member of such a person or a representative of an advocacy group for that population. If the IRB regularly reviews research that involves persons who with impaired decision-making capacity, consideration shall be given to the inclusion of one or more IRB members who are knowledgeable about and experienced in working with these subjects. When inclusion of subjects with impaired decision-making capacity has not been approved by the IRB and the PI wishes to enroll one or more subjects with impaired decision-making capacity in an active protocol, the PI must seek IRB approval from the IRB prior to proceeding with the enrollment.

9.9.3 IRB Review

In reviewing research involving persons with impaired decision-making capacity, the IRB considers whether the following are required and appropriate:

- Whether subjects with diminished capacity can be included in the research, as the target of the research;
- The rationale for including subjects who do not have the ability to consent (e.g. risk/benefit relationship);
- The method used to assess the subject's consent capacity;
- The process for obtaining surrogate permission for subjects who do not have the ability to consent;
- The process to seek assent according to the capacity of the subject and to respect dissent;
- Additional safeguards to protect the rights and welfare of these subjects (e.g. third-party observation of the consent/permission/assent process, consent modifications, more frequent continuing review, research subject advocate); and
- Situations which may involve fluctuating capacity (e.g. intermittent capacity, drug-related capacity), regaining capacity, or progressively diminishing capacity and re-consenting processes, when appropriate.

10 FDA Regulated Research

VARI is not a clinical facility, therefore, VARI IRB will not engage in review of emergency use of a test article, research involving Humanitarian Use Devices, expanded access and compassionate use trials, or planned emergency research studies. FDA regulations apply to any research that involves a *test article* in a *clinical investigation* involving *human subjects* as defined by FDA regulations. Any such research that VARI investigators engage in (off site with a clinical partner) is reviewed by the IRB of record for the clinical site(s). The VARI IRB may either cede review to the off-site IRB or review the components of the research that VARI is engaged in (e.g., laboratory, data analysis). When conducting a component review, VARI IRB will apply the FDA criteria relevant to the VARI activities (e.g., 21 CFR 50 and 21 CFR 56). VARI investigators are responsible for fulfilling their responsibilities as investigators under the applicable regulations (e.g., 21 CFR 50, 56, 312, 812, etc.) and for adhering to the ICH-GCP E6 guidelines, if applicable to the trial.

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR 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 at 21 CFR 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research by the VARI IRB and summarize key investigator responsibilities under FDA regulations.

10.1 Procedures

During the pre-review process, the Regulatory Programs Manager will confirm whether FDA regulations are applicable to clinical studies being conducted off-site and whether the VARI IRB is ceding review or conducting component review. If FDA regulations apply and the VARI IRB is conducting IRB review of the components of the research that VARI is engaged in, the Regulatory Programs Manager will indicate on the IRB agenda that the protocol is an FDA-regulated study. The VARI IRB will conduct its review of the research in accordance with 21 CFR 50 and 56 and apply the criteria outlined in 21 CFR 56.111 to the review of the VARI components of the research, and make any other necessary determinations relevant to the VARI components of the research (e.g., for waivers of consent) in accordance with FDA's regulations. Ongoing oversight of the research, including the requirement for continuing review, will comply with FDA's requirements. Likewise, any mandated reporting (e.g., of suspensions, terminations, noncompliance, and unanticipated problems) will conform with FDA's requirements. When reviewing the protocol and consent form, the VARI IRB will focus its review on the aspects of the research that VARI is engaged in. When the VARI IRB identifies a need for changes to documents such as the consent form that are approved by the IRB of a clinical site, or has recommendations, the investigator will be informed on the IRB determination letter and will be responsible for ensuring that the necessary changes are submitted, or recommendation communicated, to the IRB(s) with jurisdiction over the relevant activities (e.g., consent). The investigator is responsible for providing the VARI IRB with documentation confirming IRB approval (e.g., the IRB approval letter and a copy of the approved consent form).

10.2 Investigator Responsibilities

The PI holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other substances. These responsibilities include, but are not limited to the following:

- The PI is responsible for reading and understanding the information in the PI's brochure, including the potential risks and side effects of the drug or device.
- The PI is responsible ensuring that a clinical investigation is conducted according to the signed PI statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
- The PI is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by a PI, the PI is responsible for providing adequate supervision to research staff to whom tasks are delegated.
- The PI must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. A PI should maintain separate lists for each study that he/she conducts.
- The PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
- The PI is responsible for protecting the rights, safety, and welfare of subjects under his/her care during a clinical trial. This responsibility includes:
    - Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention,
    - Providing reasonable access to needed medical care, either by the PI or by another identified, qualified individual (e.g., when the PI is unavailable, when specialized care is needed),
    - The PI is responsible to maintain adequate and accurate records in accordance with FDA regulations and to make those records available for inspection by the FDA. These records include drug and device accountability, case histories, consent forms and documentation that consent was obtained prior to any participation in the study. Records must be maintained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
- The PI shall furnish all reports, including reports of adverse events, to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
- The PI is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, as applicable.

- The PI proposing the drug/device research will be required to provide a plan, to be evaluated by the IRB that includes storage, security, and dispensing of the drug/ biologics/device.
- The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
- The PI may delegate the responsibility for drugs/biologics accountability to the Pharmacy Service at the external clinical site.
- 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 under the PI'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 PI shall furnish all reports required by the sponsor of the research including progress reports, safety reports, final reports, and financial disclosure reports.
- The PI will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under organizational policy, contractual agreement, or regulation.

11 Unanticipated Problems Involving Risks to Subjects or Others

VARI complies with HHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems (UAPs) involving risks to subjects or others to the IRB, institutional officials and relevant federal agencies and departments.

This section provides definitions and procedures for the reporting of UAPs to the VARI IRB. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 2.5.*

In conducting its review of protocol deviations, noncompliance, subject complaints, and other reportable events, the VARI IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UAP.

11.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UAPs). UAPs refer to any incident, experience, outcome, or new information that:

- Is unexpected; and
- Is at least possibly related to participation in the research; and
- Indicates that subjects or others may be at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

Unexpected. 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. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event (AE). For the purposes of this policy and procedure, and in accordance with OHRP guidance, an AE means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

11.2 Reporting

PIs must report possible UAPs to the sponsor, if applicable, and the IRB as soon as possible, but in no event later than 7 working days after the PI first learns of the event using the *Event Reporting Form*.

PIs must promptly report the following problems to the IRB:

- AEs that appear to have caused direct harm to subjects under the oversight of the local investigator that in the opinion of the PI or sponsor may represent an UAP
- An unanticipated event (including AEs) related or possibly related to the research that appears to have exposed subjects under the oversight of the local investigator to new or increased risk but that does not involve direct harm to subjects.
- External AEs that appear to meet the definition of an UAP. Such submissions should include an analysis by the sponsor or lead site/coordinating center explaining why the AE qualifies as a UAP, any planned actions as a result, and whether the UAP has been reported to regulatory authorities (when applicable)
- An unanticipated event related or possibly related to the research that may have exposed individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk or caused harm.
- New information that indicates increased risk, new risk(s), or decrease to potential benefits of the research from what was previously understood. For example:
    - An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms may be different than initially presented to the IRB.
    - A report or publication that indicates that the risks, benefits, or merit of the research are different from what was previously understood.
- Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
- A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen).
- Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities.
- Any other issue or event related or possibly related to the research that indicates that participants or others might have experienced or be at increased risk of harm.

11.3 Review Procedures

1. Upon receipt of the Event Report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UAP. If needed, the Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).
3. If the reviewer determines that the problem does not meet the definition of an UAP, they will determine whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB

for review. The results of the review will be recorded in review notes and communicated to the investigator.

4. If the reviewer determines that the event may be an UAP, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UAP and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees). The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
    a. Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB;
    b. Revising the continuing review timetable;
    c. Modifying the consent process;
    d. Modifying the consent document;
    e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's rights, welfare, or willingness to continue participation);
    f. Providing additional information to past participants;
    g. Requiring additional training of the investigator and/or study staff;
    h. Requiring that current subjects re-consent to participation;
    i. Monitoring the research;
    j. Monitoring consent;
    k. Reporting or referral to appropriate parties (e.g., the IO, General Counsel);
    l. Suspending IRB approval;
    m. Terminating IRB approval;
    n. Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UAP, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in *Section 15*. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

12 Noncompliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the VARI IRB. Research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 2.5*.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

12.1 Definitions

Noncompliance is defined as any failure to follow:

- Applicable federal regulations, state or local laws, or institutional policies governing human subject protections, or
- The requirements or determinations of the IRB, including the requirements of the approved investigational plan (i.e., protocol deviations).

Noncompliance can result from performing an act that violates these requirements or failing to act when required. Noncompliance may be minor or sporadic or it may be serious or continuing.

Serious Noncompliance is defined as noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research.

Continuing Noncompliance is defined as a pattern of repeated noncompliance which continues after it has been determined that noncompliance occurred, including inadequate effort to take corrective actions or comply with IRB requirements within a reasonable timeframe.

Allegation of Noncompliance is defined as an unproven assertion of noncompliance.

Apparent Noncompliance describes an event that appears to constitute noncompliance, but the IRB has not yet made a formal assessment of the event. For example, a finding on an audit of an unsigned consent document, or an admission of a PI that the protocol was willfully not followed, would represent reports of noncompliance. In these instances, no further action is required to determine their truth and would therefore represent apparent noncompliance. Once a finding of noncompliance is proven, it must be categorized as serious, non-serious, or continuing.

12.2 Reporting

PIs and their study staff are required to report instances of possible noncompliance to the IRB within 7 working days of discovery using the *Event Reporting Form*. Additionally, anyone may report concerns of possible noncompliance to the HRPP or IRB verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the Regulatory Programs Manager or IRB Chair

directly to discuss the situation informally. If an individual, whether PI, study staff or other person, is uncertain whether there is cause to report noncompliance, he or she may contact the Regulatory Programs Manager or IRB Chair directly to discuss the situation informally via email or phone.

Complainants may also make reports via email or phone to the Regulatory Programs Manager, IRB Chair or through Ethics Point at https://secure.ethicspoint.com/domain/media/en/gui/25544/index.html. Ethics Point is an external reporting service that provides a confidential method to bring concerns to the attention of management. All reports submitted through EthicsPoint are handled as promptly and discreetly as possible by staff at EthicsPoint, who will make the facts available only to those at VARI who need to know to investigate and resolve the matter and will protect the complainant's identity unless the complainant chooses not to remain anonymous. Any HRPP problems or complaints reported via EthicsPoint will be reviewed in accordance with VARI procedures.

12.2.1 Review

1. Upon receipt of the Event Report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the report came from someone other than the investigator verbally, by email, or by other means, the Regulatory Programs Manager or assigned staff will develop a written report summarizing the available information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the IRB Chair, and, when appropriate, the IO, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents noncompliance, and, if so, if the noncompliance may be serious or continuing. If needed, the reviewer may request additional information from the investigator or others. When circumstances warrant, the Regulatory Programs Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, they will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system and communicated to the investigator.
4. If the reviewer determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions, such as those outline below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.

5. When the IRB determines that an event is serious or continuing noncompliance, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
    a. Requiring modifications to the protocol or research plan
    b. Revising the continuing review timetable
    c. Modifying the consent process
    d. Modifying the consent document
    e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
    f. Providing additional information to past participants
    g. Requiring additional training of the investigator and/or study staff
    h. Requiring that current subjects re-consent to participation
    i. Monitoring the research
    j. Monitoring consent
    k. Reporting or referral to appropriate parties (e.g., the IO, Compliance, Risk Management, Privacy)
    l. Suspending IRB approval
    m. Terminating IRB approval
    n. Other actions as appropriate given the specific circumstances
6. When the IRB determines that an event is serious or continuing noncompliance, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in *Section 15*. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.
7. Investigators may request that the IRB reconsider its determination by following the procedures in *Section 4.14*.

12.3 IRB Noncompliance

When a complaint, concern, QA finding, or other report or issue indicates that the IRB may be in serious or continuing noncompliance, the IO will review the issue, and when merited, convene others (e.g., General Counsel, Chief Scientific Officer, Regulatory Programs Manager) to investigate the allegation and provide a report summarizing the findings, an analysis of whether the findings represent serious or continuing noncompliance, and, when appropriate, recommendations for corrective and preventative actions for the IO's consideration. The IO will review the report, determine whether serious or continuing noncompliance has occurred, determine corrective and preventative actions, when appropriate, and initiate any mandated or required reporting to federal agencies, sponsors, and others.

13 Complaints

VAI will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 2.5*. Investigators conducting research under the oversight of the VARI IRB report complaints using the *Event Reporting Form*. Investigators are encouraged to contact the Regulatory Programs Manager or IRB Chair when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP/IRB office is the direct recipient of complaints or concerns, staff will do the following:

1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
2. Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
3. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
4. Convey the information to the IRB of record in a timely manner.
5. When appropriate, contact the investigator for additional information or to assist with resolution.
6. When appropriate, engage other resources to assist with information-gathering or resolution.

For research under the oversight of the VARI IRB, the IRB Chair or designee will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the next available meeting if the research is subject to convened IRB review, or provided to the designated expedited reviewer if the research is eligible for expedited review. When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UAP or noncompliance, and, if so, will follow the relevant procedures. The IRB Chair or designated expedited reviewer may refer any complaint for review by the convened IRB. The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP receives a complaint, or identifies information while investigating a complaint, that is

indicative of possible misconduct in research. VARI's Research Integrity Officer will be notified as quickly as possible.

14 Other Reportable Information

When research is under the oversight of the VARI IRB, in addition to UAPs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within 7 working days of discovery using the *Event Reporting Form*, as applicable. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 2.5*.

Other reportable information includes, but is not limited to, the following:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s);
2. Protocol Deviations - any variation from the IRB-approved research plan that happens without prior review and approval of the IRB and isn't necessary to eliminate apparent immediate hazards to the subject(s);
3. Monitoring, audit, and inspection reports in accordance with *Section 5.4* of this manual;
4. Notice of:
    a. Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after FDA has had the opportunity to review the responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and any corresponding compliance actions taken under non-US authorities related to human research protections.
    b. Any litigation, arbitration, or settlements initiated related to human research protections.
    c. Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding human subjects research conducted at or by VARI's program for the protection of human research participants.

NOTE: The above events (4.a, b, and/or c) must be reported to the HRPP/IRB office by phone or email **as soon as anyone becomes aware**, with the formal submission within the 7-day timeline as noted above. See *Section 16* for more information.

5. Sponsor or coordinating center reports;
6. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others;
7. Enrollment or inclusion of vulnerable populations not previously approved by the IRB for the study (e.g., prisoner, pregnant woman, child, adult with impaired decision-making capacity);
8. When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (e.g., incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject);

9. Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others;
10. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently;
11. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees;
12. New information that may impact the rights, welfare, or willingness of subjects to continue in the research.

14.1 Review Procedures

1. Upon receipt of the report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the Regulatory Programs Manager, IRB Chair, and, when appropriate, the IO, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Chair or designated reviewer receives and reviews the report and if the report may represent an UAP or noncompliance, reviews the report as described in *Section 11 or 12*. When circumstances warrant, the Regulatory Programs Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance or an UAP, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be communicated to the investigator and records placed in the protocol file.

15 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 the applicable regulations or, the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. VARI IRB complies with this requirement as follows.

When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

15.1 Procedures

IRB staff will initiate the procedures outlined in *Section 15.1.1* as a result of the following, the IRB:

- Determines that an event may be considered an unanticipated problem involving risks to subjects or others;
- Determines that noncompliance was serious or continuing; or
- Suspends or terminates approval of research.

15.1.1 IRB Office Procedures

The Regulatory Programs Manager or designee is responsible for preparing draft reports in accordance with the instructions of the Federal department or agency (e.g., OHRP, FDA).

Following the preparation of the draft report/letter, the following will take place:

- The IRB Chair, General Counsel and the IO review the letter and report for appropriateness.

Once finalized, the Regulatory Programs Manager or designee sends a copy of the report to:

1. The IRB Chair
2. The IRB, as part of the next agenda packet as an informational item
3. The IO
4. Federal departments or agencies, as follows:
    a. OHRP, if the research is conducted or supported by DHHS, or if an engaged institution's FWA has been voluntarily extended to all non-exempt human subjects research
    b. If the research is conducted or supported by a Common Rule Dept. or Agency other than DHHS, the report is sent to the party identified by the Dept. or Agency. A list of contacts is available on OHRP's Reporting Incidents webpage.
    c. If the study is conducted or supported by a federal dept. or agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the dept. or agency.
    d. FDA, if the study is subject to FDA regulations.

Reports are not submitted to federal departments or agencies such as OHRP or FDA unless the research is subject to federal regulations or another mandate that necessitates such reporting.

5. The Sponsor, if applicable
6. The Principal Investigator, when applicable
7. The Chair or Supervisor of the PI
8. Others as deemed appropriate by the IO, Regulatory Programs Manager, or CLO.

The Regulatory Programs Manager ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, and as appropriate, the Regulatory Programs Manager will expedite reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report.

16 Reporting to AAHRPP

VARI's HRPP is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In addition to the information that VARI routinely provides to AAHRPP in annual reports and the re-accreditation application, AAHRPP requires that any of the following are reported to AAHRPP asap but generally within 48 hours after the organization or any researcher (if the researcher is notified rather than the organization) becomes aware:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding VARI's HRPP.

The Regulatory Programs Manager (or designee) is responsible for ensuring that such reports are made to AAHRPP and for informing appropriate organizational officials. Investigators, research staff, HRPP/IRB staff, IRB members, and other organizational officials or offices (e.g., the IO, Legal, etc.) are responsible for informing the HRPP/IRB office as soon as they become aware of any of the above so that these reporting obligations may be fulfilled.

17 Investigator Responsibilities

PIs are ultimately responsible for the conduct of research. PIs may delegate research responsibility. However, PIs must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

The following procedures describe PI responsibilities in the conduct of research involving human subjects.

17.1 Investigators

17.1.1 Principal Investigator (PI)

Individuals who can serve as PI or co-principal investigator (Co-PI) on Institution-based grants, contracts or cooperative agreements are full-time employees of VAI, VARI, VAEI or VAIGS, or are individual scientists who hold a fully-executed VARI-based joint faculty appointment. Eligibility to act as a PI or Co-PI on externally sponsored projects is granted by the Research Director, the VAEI Director, or the Dean of the Graduate School. To further clarify, the Institution provides the following information:

- Those authorized to submit grant or contract-based proposals or cooperative agreements for external funding as PI or Co-PI include VARI employees who hold the rank of Research Assistant Professor, Assistant Professor, Associate Professor, or Professor, and VAEI employees who hold the rank of Director, Associate Director, Dean, Associate Dean, Assistant Dean, Science Education Specialist, Evaluation Specialist, or Curriculum Specialist.
- Postdoctoral Fellows are permitted to submit fellowship-based applications with the approval of their supervisor.
- VAIGS graduate students in good standing may submit student-based applications with the approval of their academic supervisor and the Dean of the Graduate School.
- Submission of applications by jointly appointed faculty is subject to the terms and conditions of individual appointment agreements and the operational protocol established between their home institution and the VAI Office of Sponsored Research representing VAI, VARI, VAEI, or VAIGS as applicable.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the PI must be modified to meet the PI's skills or have one or more additional qualified faculty as co-investigator(s).

17.1.2 Investigators

Within the regulations, the term “investigator” to be any refers to individuals involved in the design, conduct, or reporting of the research. Such involvement would include:

- Designing the research

- Obtaining information about living individuals by intervening or interacting with them for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary informed consent of individuals to be subjects in research; and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

For FDA regulated research, investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug or device is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the PI is the responsible team leader. "Sub-investigator" includes any other individual member of that team.

17.1.3 Research Team

The research team includes the PI and other individuals 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 for the express purposes of the research, or who analyze data and/or tissue derived from humans for the purposes of the research.

17.2 Responsibilities

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 principles in the Belmont Report;
- Develop a research plan that is scientifically sound and minimizes risk to the subjects;
- Incorporate into the research plan, a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
- 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;
- Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
- Ensure that there are adequate provisions to protect the privacy interests of subjects;
- Ensure that there are adequate provisions to protect the confidentiality interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;
- 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.
  - Necessary equipment.
  - A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.
  - When appropriate, a plan to ensure availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in 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 applicable laws of Michigan and the policies of VARI;
- Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
- Assure that all persons assisting with the research are adequately trained and informed about the protocol and their specific duties and functions.
- Promptly report to the IRB for evaluation and approval any changes in, additions to, or loss of investigators or research staff;
- Protect the rights, safety, and welfare of research subjects;
- Ensure that when protected health information is used that legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the authorization. This requirement does not apply when VARI research is not conducted under the auspices of a covered entity;
- Ensure that the language in the consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization;
- Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining their consent or consent/permission from their legally authorized representative, unless a waiver of consent has been approved by the IRB;
- Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;
- Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
- Ensure that all research involving human subjects receives IRB approval in writing or a determination of exemption before commencement of the research;
- Ensure that all research involving human subjects is reviewed by other experts and organizational components and other regulatory committees as applicable to the research;

- Comply with all IRB decisions, conditions, and requirements;
- Ensure that protocols receive timely continuing IRB review and approval;
- Report unanticipated problems, deviations, complaints, noncompliance, suspensions, terminations, and any other reportable events to the IRB;
- Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research;
- Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
- Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
- Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.
- Additional investigator responsibilities when engaged in FDA-regulated research are described elsewhere in this document.

17.3 Training/Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. VARI is committed to providing training and an on-going educational process for PIs and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

17.3.1 Initial Education

PIs, key personnel, and other members of the research team must complete VARI Required Core Modules in CITI in the Protection of Human Research Subjects including the module on Conflicts of Interest. Evidence of current training (date of completion within 3 years of application date) for each member of the research team must be included in every new protocol application and application for continuing review.

Research protocols and applications for continuing review will be accepted and reviewed if the PI holds current certification of training, but prohibit the participation of individuals named on the protocol who have not completed the mandatory human subjects training.

New research protocols and applications for continuing review, may be approved by the IRB, but cannot accrue new subjects unless the PI has completed the initial or refresher training requirement. This is verified by our in-house training tracker system.

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subjects research training during the past two years that is equivalent to that required by VARI, the individual may request a waiver of the requirement for Initial Education. However, all PIs or members of their research team must complete the requirements of Continuing Education at least triennially.

17.3.2 Continuing Education and Recertification

PIs, key personnel, and other members of the research team must meet VARI 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 approved PRIM&R, OHRP, or FDA web-based training site. Other training may be acceptable. In these cases, the researcher should check with the IRB Office for a determination. If other training is found to be acceptable, the individuals must provide certificates of completion. New research protocols and applications for continuing review, may be approved by the IRB, but cannot accrue new subjects unless the PI has completed the initial or refresher training requirement.

PIs who are also IRB Chair, IRB members, or IRB staff will satisfy the training requirements for IRB members and staff described under *Section 3.11*.

17.4 Investigator Concerns

PIs who have concerns or suggestions regarding VARI's HRPP or IRB(s) should convey them to the IO or other responsible parties (e.g. Director of Research/ Chief Scientific Officer, or Department Chair), when appropriate. The IO will review the issue, and when deemed necessary, convene the individuals involved to form a response to the PI or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair or the Regulatory Programs Manager will be available to address PIs' questions, concerns and suggestions. Information regarding the concern will be shared with the IRB as appropriate. The IRB has final authority on protocol specific decisions.

18 Lead Investigator/Coordinating Center

When VARI IRB is serving as the IRB of record for a PI or site who is serving as the lead investigator or lead/coordinating center of a multi-site or collaborative research project, the PI must describe within the protocol and IRB application how the research will be overseen and how issues relevant to the protection of human subjects (e.g., IRB initial and continuing approvals, study modifications, reports of unanticipated problems, interim results, data-safety monitoring, etc.) will be coordinated and communicated among participating sites and investigators.

The lead PI or lead/coordinating center is responsible for serving as the liaison with other participating sites and investigators and for ensuring that all participating investigators obtain IRB review and approval prior to initiating the research, maintain approval, and obtain IRB approval for modifications to the research. The VARI IRB will evaluate whether the plan for research oversight and management of information that is relevant to the protection of human subjects is adequate.

19 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 primary impact of the Privacy Rule is on the routine provision of health care and billing, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information (IIHI) transmitted or maintained by a covered entity in any form (electronic, written or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

VARI, while not a covered entity itself, does receive PHI from covered entities for research and is committed to the protection of this information in accordance with the provisions described in the applicable authorization, waiver or alteration of authorization, and/or any applicable agreements (i.e., data use agreement, business associate agreement). As an appropriately constituted IRB, VARI IRB has the authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Under the Privacy Rule, an Authorization may be combined with the consent document for research. When a VARI researcher is leading or otherwise participating in collaborative research involving the authorized use of PHI, and the proposed consent document is combined with an Authorization, VARI IRB will conduct review of the research and the Authorization language to verify the presence of all required elements and statements.

19.1 Definitions (per HIPAA Privacy Booklet for Research)

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered Entity. A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set (LDS) that establishes the ways in which the information in the LDS may be used and how it will be protected.

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information. Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Health Insurance Portability and Accountability Act of 1996 (HIPAA, The Privacy Rule). This Act requires, among other things, under the Administrative Simplification subtitle, the adoption of standards, including standards for protecting the privacy of individually identifiable health information.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set (LDS). Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

Minimum Necessary. The least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

Protected Health Information (PHI). PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from a researcher or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

19.2 The IRBs Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research.

The Privacy Rule does not change the composition of the VARI IRB. The Privacy Rule permits a covered entity to accept documentation of a waiver or alteration of Authorization from any qualified IRB or Privacy Board.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the HHS Protection of Human Subjects Regulations (45 CFR 46) and/or, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review process.

When a request for a waiver or an alteration of the Authorization is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of Authorization to be effective, it must be approved by a majority of the IRB members present at the convened meeting. HHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review process. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the HHS or FDA list of approved expedited categories and involves no more than minimal risk. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review process to review minor changes in previously approved research. For example, a modification to a previously approved research project, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review process. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or designated IRB member reviewer (See S*ection 4.4*). Regardless of the type of review, a member of the IRB who has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration of Authorization is being sought, may not participate in the review.

VARI will not release PHI to researchers without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

Waivers or alterations approved by a non-VARI Privacy Board or IRB will be reviewed by the VARI IRB.

19.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that covered entities obtain authorization from research subjects for the use or disclosure of his/her PHI to be utilized in the research. This authorization is distinct from the subject's consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements (45 CFR 164.508(c)).

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the PI and the covered entity (e.g., the clinical site) for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Researchers are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, researchers may continue to use and disclose PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source of the research), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other Federal and State laws may establish continuing protections for the disclosed information. Under the HHS or the FDA Protection of Human Subjects Regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
4. A description of each purpose of the requested use or disclosure.
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository).
6. Signature of the individual and date. If the individual's legally authorized representative (LAR) signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

19.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the Authorization in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of Authorization occurs when the IRB or Privacy Board determines that the institution does not need authorization for PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an Authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

- The use or disclosure of PHI 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 health information identifiers from improper use and disclosure.
    - An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
    - Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
- The research could not practicably be conducted without the waiver or alteration or Authorization.
- The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project. However, HHS also recognizes that "covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers" (67 *Federal Register*

53232, August 14, 2002). At VARI, PHI may not be disclosed for the purposes of research pursuant to a waiver provided by a non-VARI Privacy Board without the approval of the VARI IRB.

VARI IRB documentation of approval of a waiver or alteration of the authorization includes:

- The identity of the approving IRB;
- The date on which the waiver or alteration was approved;
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met;
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity;
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
- The required signature of the IRB chair or the chair's designee.

19.5 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research protocol.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See *Section 19.4* of this policy manual for a discussion of waivers of authorization.

While VARI is not a covered entity itself, the clinical entities with which VARI researchers commonly collaborate typically combine consent for research and authorization for use and/or disclosure of PHI in one document. As with any research activity, the combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The researcher and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the consent/authorization for future research is combined with another research consent/authorization, the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide

individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

19.6 Corollary and Sub-studies

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

"This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization." and "an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals."

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

- The authorization clearly differentiates between the conditioned and unconditioned research activities;
- The authorization clearly allows the individual the option to opt-in to the unconditioned research activities; and
- Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

19.7 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

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

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to

identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subjects data under the Common Rule, particularly when working with a small data set that can be further broken down into smaller subsets. Additionally, while coded information may be de-identified under HIPAA, if the researcher holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

19.8 Limited Data Sets and Data Use Agreements

Limited data sets (LDS) are data sets stripped of certain direct identifiers. LDSs may be used or disclosed only for public health, research, or health care operations purposes. Because LDSs may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, PHI in LDSs may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a LDS: (1) Names; (2) postal address information, other than town or city, state, and ZIP code; (3) telephone numbers; (4) fax numbers; (5) email addresses; (6) social security numbers; (7) medical record numbers; (8) health plan beneficiary numbers; (9) account numbers; (10) certificate or license numbers; (11) vehicle identifiers and license plate numbers; (12) device identifiers and serial numbers; (13) URLs; (14) IP addresses; (15) biometric identifiers; and (16) full-face photographs and any comparable images.

Before disclosing an LDS a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the LDS, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA.

While VARI is not a covered entity, investigators at VARI will abide by any written agreements with any covered entity, including DUAs, when applicable.

19.9 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial.

20 Information Security

VARI has established standards and safeguards to protect research subject's information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, USB drives, and other non-VARI devices for storage of research data is discouraged. In the instances when a non-VARI computer or device must be utilized for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by Information Technology Department and a User Agreement must be completed. Additionally, any potential or known breach of research data or a device storing research data must be immediately reported to both the IRB, the Compliance Department and the HIPAA Security Officer so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Lost or stolen VARI devices must also be reported to the Physical Security and IT Departments, so that tracking mechanisms to remotely wipe or protect data can be activated.

Provisions for Data Security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security Numbers or PHI including data considered sensitive is to be transferred outside of VARI, the provisions for data security may be subject to further review and approval by the HIPAA Security Officer.

Sensitive information refers to data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information.

See the VARI Information Technology Policies on SharePoint for further information.

21 Databases, Registries, & Repositories

Databases, registries, and biospecimen repositories (all referred to as repositories throughout this section) are used to store data and/or biospecimens for future use.

There are two type of repositories:

- Non-research repositories created and maintained for purposes that are unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

21.1.1 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB approval is required for the research use of identifiable private information or identifiable human specimens from non-research repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of VARI that includes the use of coded private information or specimens, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See *Section 4.2*).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied. PHI held by a covered entity in non-research repositories may not be used or disclosed for research purposes without written authorization or an IRB waiver of authorization. The IRB review process should include how and what information will be given when proposing to provide de-identified specimens.

21.1.2 Research Repositories

Research repositories involve three distinct activities:

1. Collection of data/specimens;
2. Storage and management of data/specimens; and
3. Distribution of data/specimens.

Collection

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
    - What data/specimens will be collected;
    - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured;
    - Whether the data/specimens will be identifiable, coded, or deidentified;
    - The types of research to be conducted and any limitations or restrictions on such; and
    - The conditions under which data/specimens will be released to recipient-investigators.
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request)
- When appropriate, the plan for management of incidental findings and sharing of results

Storage and Management

Repositories should have written policies describing:

- The conditions under which data/specimens will be accepted (e.g., inclusion criteria)
- Informed consent
- IRB review
- The sources of data/specimens
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key; and
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens

Distribution

Repositories should have written policies describing:

- How data/specimens may be requested and by whom;
- Any requirements associated with a request for data/specimens (e.g., verification of IRB approval or that approval is not required);
- Any limitations or restrictions on how data/specimens may be used;
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will have access to or be provided with the key or other means to re-identify; and

- Agreements with recipient investigators specifying the terms of use.

21.1.3 IRB Oversight

Establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable, and its data management center is under the auspices of VARI, is subject to oversight by the VARI IRB. In general, private information or specimens are considered individually identifiable when the identities of the subjects are known to investigators/repository operators or when the data/specimens can be linked to specific individuals either directly or indirectly through coding systems. Proposals to establish a repository must be submitted to the IRB using the appropriate *Initial Application Form* specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves the repository protocol that describes the collection process, informed consent document and process, researcher request and approval process to provide specimens and/or data, and any requirements for approval from external IRBs. HIPAA applies to submission of PHI to a research repository and authorization is required when appropriate. See *Section 19* for a detailed discussion of authorization, waivers, limited data sets, and de-identification. HIPAA allows authorization for future research when sufficient information is provided to the subject on potential future research scope (e.g., research on cancer, Alzheimer's disease, and other chronic diseases, including their genetic basis), but that also enables the subject to be able to make an informed choice. Authorization for future research can be combined with an authorization for other research activities as described in *Section 19.5*.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of VARI that includes the use of coded private information or specimens, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See *Section 4.2*). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

22 Research Involving Biological Specimens or Coded Human Data

22.1 Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB-approved research protocol, exemption, or determination that IRB approval is not required. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

22.1.1 Regulatory Oversight

For research subject to the pre-2018 Common Rule requirements:

A human subject is a living individual about whom an investigator conducting research obtains:

- Data through intervention or interaction with the individual; or
- Identifiable private information.

For research subject to the revised Common Rule (2018 requirements):

A human subject is a living individual about whom an investigator conducting research:

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

Whether research involving biological specimens meets the definition of human subjects research is based on: a) how the specimens were obtained; and b) whether the specimens include identifiable private information or will be used to generate identifiable private information.

If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information or will be used to generate identifiable private information (See below for policies on coded specimens).

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device. HIPAA does not directly address biological specimens but does apply to protected health information (PHI) linked to the specimens (See *Section 19* for more detail on HIPAA).

Note: With the implementation of the revised Common Rule, the requirement of the Newborn Screening Saves Lives Reauthorization Act of 2014 that federally-funded "research on newborn dried blood spots shall be considered research carried out on human subjects" is eliminated. Whether such research involves human subjects shall now be considered using the

same standards as are used for other research involving human biospecimens (e.g., whether the identity of subjects may be readily ascertained, whether the specimens are coded and who has access to the key, whether the research involves the evaluation of the safety or effectiveness of an FDA-regulated device, etc.).

State and local laws will also be considered and followed.

If the research meets the definition of human subjects research, then all of the requirements of this document apply.

22.1.2 IRB Review

- **For research subject to the pre-2018 Common Rule requirements:** Research involving only biological specimens may be exempt under Exemption Category #4: "Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects." However, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB.
- **For research subject to the revised Common Rule (2018 requirements):** Research involving biological specimens may be exempt under Exemption 4(i), 4(ii), 7, or 8 as described in *Section 4.3.2*.
- Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:
    - Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
    - Prospective collection of biological specimens for research purposes by noninvasive means.
    - Research involving materials that have been collected, or will be collected solely for non-research purposes
- All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.
- For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB.

22.2 Coded Human Data or Biological Specimens

This section is based on the OHRP guidance document entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" (October 16, 2008). This document:

1. 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).

2. Reaffirms OHRP policy that, under certain limited conditions, research involving ***only*** coded private information or specimens is not human subjects research.
3. Clarifies the distinction between (a) research involving coded private information or specimens that do not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.
4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices requires assessment according to the FDA regulations and guidelines. Investigators should contact the IRB office for guidance.

For purposes of this policy, ***coded*** means that: (1) 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 (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens. At VARI, research with specimens with one-way linkages maintained by an investigator outside of VARI is considered on a case by case basis to determine whether the research involves human subjects as defined in the Common Rule.

Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. ***Obtaining*** identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and

2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were 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 per the Common Rule definition if both of the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; **and**
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

a. 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) At VARI, this agreement must be reviewed and approved by the IRB.

b. 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

c. There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased. While decedents are not considered "human subjects" under the Common Rule, other requirements and regulations, such as HIPAA, may still apply. Investigators should contact the VARI IRB office with any questions regarding research using decedent information and/or specimens.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) 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 *Section 4.3*), 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 *Section 8.13*).

22.2.1 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or Regulatory Programs Manager will determine if the research involving coded information or specimens requires IRB review.

23 Special Topics

23.1 Certificate of Confidentiality (CoC)

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in 42 U.S.C. 241(d) and in written policies and requirements of certain Federal agencies such as NIH and CDC and are summarized below.

CoC's are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- CoCs are issued automatically when research is conducted or supported by the CDC and involves the collection of identifiable, sensitive information.
- CoCs are issued automatically when research is conducted or supported by BARDA and falls within the scope of the BARDA policy.
- CoCs are issued automatically when research is conducted or supported by HRSA and falls within the scope of the HRSA policy.
- CoCs are issued automatically when research is funded by the FDA in whole or in part and involves the collection or use of identifiable, sensitive information as defined in 42 U.S.C. 241(d).
- Other agencies like SAMHSA and IHS still require a CoC application for research that they fund. NIH maintains a list of CoC Coordinators and Contact Information for Non-NIH HHS Agencies that Issue Certificates.
- Research that is not supported by NIH, CDC, BARDA, HRSA, SAMHSA, IHS, or FDA may still benefit from the protections afforded by CoCs through successful application to the NIH, FDA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for research not covered by the NIH policy is available on the NIH CoC Website. Information about discretionary CoC's issued by FDA is available in the FDA guidance document: Certificates of Confidentiality.

23.1.1 Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and

1. Through which an individual is identified; or
2. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

23.1.2 Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

1. In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
2. To any other person not connected with the research, unless:
    a. Required by Federal, State, or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in "1" above;
    b. Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
    c. Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
    d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity. If identifiable, sensitive information covered by a CoC is shared with other researchers or organizations, the researchers or organizations must be informed that the information is covered by a CoC and of their responsibility to protect the information accordingly.

Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

23.1.3 NIH, CDC, BARDA, and HRSA

The NIH Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

The CDC requirements for CoCs apply to *"CDC supported research commenced or ongoing after December 13, 2016 and in which identifiable, sensitive information is collected, as defined by Section 301(d)."*

The BARDA Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by BARDA, whether supported through contracts, cooperative agreements, grants, other transaction awards, or research ("Awards") that collects or uses Covered Information"* (i.e., identifiable, sensitive information) that was commenced on or after July 17, 2023.

The HRSA Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by HRSA, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by HRSA staff, that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH, CDC, BARDA, or HRSA funded activity falls within the scope of the NIH, BARDA, or HRSA policies or CDC's requirements. Investigators and institutions are responsible for determining when research with NIH, CDC, BARDA, or HRSA support are covered by a CoC.

NIH, CDC, BARDA, and HRSA expand upon 42 U.S.C. 241(d) by explaining that they consider research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects);
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained;** or

  Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

If the NIH, CDC, HRSA, or BARDA funding ends, the study will no longer be deemed issued a CoC. While CoC protections remain in perpetuity for already collected or used information, a new CoC will need to be obtained in order to cover any new data collected from already enrolled

participants or any new participants. In this case, investigators should request a new CoC following the process for non-federally funded research.

23.1.4 FDA

The FDA requires, as a term and condition of all FDA funding and grant awards, compliance with the requirements of 42 U.S.C. 241(d) when research is funded in whole or in part by the FDA and involves the use or collection of identifiable, sensitive information. Certificates are deemed issued through FDA funding/award terms and conditions and are not issued as a separate document.

Investigators and institutions are responsible for determining when research with FDA support is covered by a CoC and for ensuring compliance with the requirements of 42 U.S.C. 241(d). Awardees are expected to ensure that any investigator or institution not funded by FDA who receives a copy of identifiable, sensitive information protected by these requirements, understand they are also subject to the requirements of 42 U.S.C. 241(d). Awardees are also responsible for ensuring that any subrecipient that receives funds to carry out part of the FDA award involving a copy of identifiable, sensitive information protected by these requirements understand they are also subject to subsection 42 U.S.C. 241(d).

When research is not funded by the FDA but involves an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

23.1.5 NIH, CDC, BARDA, HRSA, and FDA CoC Determination

At VARI, Office of Sponsored Research staff will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH, BARDA, or HRSA policies or CDC or FDA requirements apply to research with NIH, BARDA, HRSA, CDC, or FDA involvement or support. The questions outlined in the NIH, BARDA, HRSA policies and CDC requirements will be used to guide the analysis for research conducted or supported by NIH, BARDA, HRSA, and CDC. The definitions and text of 42 U.S.C. 241(d) will be used to guide the analysis for research supported by FDA funding/awards. When it has been determined that the NIH, BARDA, or HRSA policies or CDC requirements do not apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with OSR whenever they are proposing changes to the supported activity that may impact or change the analysis.

The NIH, BARDA, and HRSA policies and CDC requirements include additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act. Likewise, FDA requires awardees ensure that recipients of identifiable, sensitive information protected by an FDA CoC understand that they are also subject to the requirements of 42 U.S.C. 241(d).

23.1.6 Application Procedures for Research Not Automatically Issued a CoC

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH, an

investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

When a researcher is conducting a research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299c-3(c)), a CoC is not needed (AHRQ notice NOT-HS-18-012). While the AHRQ statute does not define "identifiable", AHRQ applies the PHS Act definition of "identifiable, sensitive information". Investigators should consult with AHRQ when they believe that data might be considered "non-identifiable" or when otherwise uncertain whether a research project falls within the scope of the statute.

When a researcher is conducting a research project that is covered by the Department of Justice (DOJ) confidentiality statute, 28 CFR 22, and/or a NIJ Privacy Certificate, a CoC is not needed because the Privacy Certificate makes identifiable data immune from any legal action.

When research is not funded by the FDA but involves "the use or study of a product subject to FDA's jurisdiction and subject to FDA's regulatory authority" (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can request a discretionary CoC from the FDA. When FDA funds or conducts research, a CoC is automatically issued.

CoCs may also be issued by other Federal agencies and departments, such as SAMHSA or IHS. For research that is supported by SAMHSA or IHS, researchers must contact the respective CoC Coordinator to request a SAMHSA-issued or IHS-issued CoC. Information about the SAMHSA CoC application process, including the extension of protections and amendments to certificates can be found at https://www.samhsa.gov/grants/gpra-measurement-tools/certificate-confidentiality. The IHS CoC contact can be found on the NIH Coc website at CoC Coordinators and Contact Information for Non-NIH HHS Agencies that Issue Certificates.

For more information, see the NIH CoC Website.

23.1.7 IRB Review

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted or is pending. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit a *Modification Request* to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH, BARDA, or HRSA policies or CDC requirements.

When reviewing research under a CoC, the VARI IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and, when consent will be obtained, whether the proposed consent language or other form of notification properly discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the NIH CoC Website and in the template consent forms available on VARI's HRPP/IRB website.

When research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect subjects' privacy and the confidentiality of subjects' information or specimens.

23.2 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, Michigan law mandates that certain persons who suspect child or elder abuse or neglect report this to the Michigan Department of Health and Human Services.

In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known via the consent process and form to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect. Michigan Compiled Law (MCL) 722.623 outlines the individuals required to report child abuse under the Michigan Child Protection Law. MCL 400.11a outlines the individuals required to report adult/elder abuse and neglect under the Michigan Social Welfare Act.

23.3 VARI Students and Employees as Subjects

When VARI students and/or employees 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 primary and without undue influence on their decision. Researchers must emphasize to subjects that their academic status, grades, or their employment, will be affected by their decision to participate or not.

To minimize coercion, PIs should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic in nature. In these latter situations, PIs should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g. administer a survey, PIs should do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

23.4 Student Research

23.4.1 Human Subjects Research and Course Projects

Learning how to conduct ethical human subjects research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are NOT *designed to develop or contribute to generalizable knowledge* may not require IRB review and approval if all of the following conditions are true:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., not made available on the internet, not published in a journal, etc.).
- Research procedures are no more than minimal risk.

- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that the subjects are not identifiable. Images in videotapes and photographs, and voices on audiotape are considered identifiable.
- When appropriate, an informed consent process is in place.

Responsibility of the Course Instructor: The course instructor is responsible for communicating to the students, the ethics of human subjects research, for ensuring the protection of human subjects (including that a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents;
- Plan appropriate strategies for recruiting subjects;
- Identify and minimize potential risks to subjects;
- Assess the risk-benefit relationship for the project;
- Establish and maintain strict guidelines for protecting confidentiality, and
- Allow sufficient time for IRB review (if necessary) and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor should err on the side of caution and to contact the IRB office for assistance.

Individual Research Projects Conducted by Students. Independent study projects, senior theses, undergraduate research projects, masters and advanced degree research, and similar exercises must be independently submitted for IRB review. It is important to keep in mind that any human subjects research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

23.4.2 Independent Study, Theses and Dissertations

These research activities are considered to meet the federal definition of human subjects research and must be independently submitted to the IRB by the student-researcher. However, when students conduct research as part of a course of study, *a faculty member ultimately is responsible for the protection of the subjects*, even if the student is the primary researcher and actually directs the project. Advisers assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course.

Students may not serve as PI. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as PI and faculty advisor on the study. (See *Section 17.1.1*)

23.5 Research Involving or Generating Genetic Information

Research that generates or uses genetic information may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, and may result in stigmatization and discrimination. Information about one's own genetic make-up may also provide information about family members.

In studies involving genetic testing or analysis of genetic information, several questions should be addressed to ensure that potential risks are well understood and that the rights and interests of subjects and their family members are carefully considered and planned for. For example:

1. Is the testing intrinsic to the study? If not, has participation in the genetic testing component been provided as an opt-in?
2. Will test results be given? Is there an appropriate plan for return of results?
3. Will the subject or family member be provided the option to receive or not receive results? How will this decision be recorded?
4. Could the results provide information about individual disease risk? Disease risk for family members?
5. Could other clinically relevant information or incidental findings be uncovered by the study? Is there a plan for the management of such findings?
6. Will testing that could produce clinically relevant information occur in a CLIA-certified lab? If not, are there tests available that could validate or support findings?
7. Could a change in a family relationship be disclosed, such as mistaken paternity?
8. Could/will the research provide information about the origins, ancestry, or natural history of families, indigenous peoples, tribal populations, or other populations? What are the possible risks?
9. Could/will the research generate information that could place subjects or family members at risk or be stigmatizing?
10. Could/will the research generate information of other value or importance to subjects/families?
11. Are there any practical limitations on the subject's right to withdraw from the research, withdraw data, and/or withdraw biological materials (e.g., specimens, cell lines, extracted genomic DNA)? If so, what are they?
12. How will the information and/or biological materials be protected and who will have access?
13. What is the potential for re-identification of individual subjects (e.g., through the combination of their genetic information and/or materials with other sources of

information (e.g., public records))? What measures can be taken to mitigate these risks?

14. Is a Certificate of Confidentiality (CoC) in place or should one be considered? (See *Section 23.1*)
15. Will the specimens, cell lines, or genetic information be stored and/or made available for future research? Is this provided as an opt-in when not intrinsic to the study?

Investigators should carefully consider the above and other factors relevant to their specific study when developing the protocol, consent process, and consent form. The President's Bioethics Commission, the National Academies of Sciences, Engineering, and Medicine, and others have produced reports, recommendations, and materials that investigators and the IRB may find helpful in protocol development and review, including:

- Returning Individual Research Results to Participants: Guidance for a New Research Paradigm
- Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts
- Privacy and Progress in Whole Genome Sequencing
- Genetics Research and American Indian and Alaska Native Communities
- National Human Genome Research Institute:
    - Human Subjects Research in Genomics
    - Return of Research Results
    - Data Sharing and Privacy
    - Informed Consent for Genomics Research

In addition to the ethical considerations, investigators must ensure that research involving genetic testing or use of genetic information is consistent with applicable law (e.g., GINA, HIPAA, EU GDPR, state law) and policy (e.g., NIH).

23.5.1 Genetic Information Nondiscrimination Act (GINA)

GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against individuals based on their genetic information. This law protects individuals, including research subjects, in the following ways:

- Health insurance companies and health plans are generally prohibited from requesting or requiring genetic information of an individual or their family members, including genetic information generated from research;
- If health insurance companies and health plans do receive such genetic information, they may not use it to make decisions regarding coverage, rates, or preexisting conditions; and
- Employers with 15 or more employees generally may not use genetic information for hiring, firing, promotion, or other decisions regarding terms of employment.

GINA's protections do not extend to life insurance, disability insurance, or long-term care insurance.

GINA defines genetic information as information about:

- An individual's genetic tests;
- Genetic tests of an individual's family members;
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

GINA includes a "research exception" that allows health insurers and health plans who are engaged in research to request, but not require, that an individual undergo a genetic test so long as certain requirements are satisfied. Additional information on GINA and this exception are available on this OHRP website.

The IRB will consider the protections and limitations of GINA when it assesses the risks of research generating or using genetic information and the adequacy of the measures to protect privacy and maintain confidentiality. Generally, the IRB will also require that the protections and limitations of GINA are disclosed in the consent process when applicable. Sample language for GINA is provided in VARI's template consent form.

23.5.2 Genetics and State Law

Investigators must ensure that the research they conduct conforms with applicable law. When developing and conducting research involving genetic testing in Michigan, the following should be considered:

Michigan law requires obtained written, informed consent to be obtained before pre-symptomatic or predictive genetic testing. Researchers/Providers are responsible for providing information to patients about the purpose, risks, benefits and limitations of genetic testing and the appropriate interpretation of test results. When conducting research in other jurisdictions, investigators must ensure that the research conforms with applicable law in that jurisdiction. Investigators should be prepared to provide information on relevant law and their plans to ensure compliance to the IRB of record for the study, whether it is VARI's IRB or another. Investigators may consult with the IRB Office.

23.6 Genomic Data Sharing (GDS)

VARI complies with the NIH GDS Policy, which allows for "broad and responsible sharing of genomic research data", via submission of said data into an NIH-designated data repository. The intent of NIH's policy is to speed discoveries to diagnose, treat, and prevent disease. **To ensure consistency in the protection of human subjects, VARI applies the NIH principles for informed consent and for a genomic data sharing plan to all research that involves or contemplates genomic data sharing.**

The NIH policy applies to grant activities requesting support from NIH for research involving the generation of large-scale human (and/or non-human) genomic data, regardless of funding level, such as:

- Research project grants (Rs);
- Program projects (Ps) and SCORs (Ss);
- Cooperative agreements for research (Us);
- Individual career development awards (Ks) that include a research component;
- S activities that include a research component; and
- All other activities that include a research component.

Also covered under this policy is research involving data derived from these activities for subsequent research. All basic and clinical research, including clinical trials, supported by NIH that involves the generation or use of large-scale genomic data fall within the scope of the policy.

The policy does not apply to:

- Institutional training grants (T32s, T34s, T35s, and TL2s);
- K12 career development awards (KL2s);
- Individual fellowships (Fs);
- Resource grants and contracts (Ss);
- Linked awards derived from previously reviewed applications (KL1, KL2, RL1, RL2, RL5, RL9, TL1, UL1);
- Facilities or coordinating centers funded through related initiatives to provide genotyping, sequencing, or other core services in support of GDS.

Because of the potential for re-identification of genomic data, Certificates of Confidentiality (CoCs) are automatically issued by the NIH for any research it supports, in part or in whole, that involves *"the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46)."* Research covered by the NIH policy and/or the underlying PHS Act is protected by the CoC in perpetuity; as such any downstream recipients of such information must comply with the requirements of the PHS Act.

Investigators without NIH support who intend to submit genomic data to a NIH repository are encouraged to obtain a CoC. Investigators conducting research generating or using genomic data are encouraged to obtain a CoC when one is not already in place (e.g., for downstream use of data that was collected under a CoC.

For more information on CoCs, see *Section 23.1*.

23.6.1 Definitions

Genomic data: information derived from study of an organism's genome, i.e., the set of DNA (including all the genes within) in every cell that provides all of the information needed to build and maintain that organism.

Genomic Summary Results (GSR): GSR (also referred to as "aggregate genomic data" or "genomic summary statistics") are results from primary analyses of genomic research that convey information relevant to genomic associations with traits or diseases across datasets rather than associations specific to any one individual research participant (e.g., genotype counts and frequencies; allele counts and frequencies; effect size estimates and standard errors; likelihood; and p-values). **Sensitive GSR** refers to GSR where the privacy risks may be heightened for study populations (e.g., populations from isolated geographic regions or with rare traits) or the study populations may be more vulnerable to group harm (e.g., because the data includes potentially stigmatizing traits). Information regarding NIH's updated policy on the access, use, and management of GSR may be found here: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-023.html

Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Examples of genomic research projects that are subject to the Policy and the timeline for submission and sharing of data from such projects may be found here: https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf

NIH-Designated Data Repository: any data repository maintained or supported by NIH either directly or through collaboration. Examples of such repositories is available here: https://osp.od.nih.gov/scientific-sharing/data-repositories-and-trusted-partners/. Data may be unrestricted or controlled access:

- **Unrestricted-Access ("Open Access"):** data are publicly available to anyone (e.g., The 1000 Genomes Project). Non-sensitive GSR are made available through unrestricted access.
- **Controlled-Access:** the data are available to an investigator for a specific project only after the investigators and institution certify to abide by specified terms and conditions and NIH has approved the use. Sensitive GSR are made available through controlled access.

23.6.2 Procedures

IRB Submissions and GDS

For any cell lines created or specimens to be collected, analyzed, and shared subject to the GDS Policy, the IRB expects that informed consent will be obtained from the research subject for the future research uses and broad sharing of data required under the policy, including GSR. **This is the case even if the specimens or cell lines are de-identified.** If there are compelling scientific or legal reasons that necessitate the use of genomic data from cell lines or clinical specimens that lack consent for research use and data sharing, investigators will need to provide a justification in the funding request to NIH for their use. The funding NIH institute/center will review the justification and decide whether to make an exception to the consent expectation. Exceptions from the NIH are not required if only some participants decline to consent to broad sharing, rather an exception request must be granted by NIH for research when consent for broad sharing has not or will not be sought.

Subjects asked to allow for future research uses and broad sharing of their genomic data have the ability to decline, and still remain in the research (however their data cannot be placed into a repository or otherwise broadly shared). The only exception to this is when sharing of the data is intrinsic to the study (e.g., the purpose of the study is to establish a repository for sharing biological specimens and/or data for future research).

Guidance regarding consent language for studies subject to GDS is available in the consent template, from the HRPP/IRB Office. NIH and NHGRI also provides guidance and resources to assist in the development of appropriate consent forms for research involving or generating genetic or genomic data.

Applications to the IRB should include information about the proposed generation or use of genomic data including, as applicable:

- Whether the research will generate or use data subject to the NIH GDS policy;
- The name of the NIH data repository/database, or other repository or database, that data will be submitted to or acquired from;
- Whether the data is or should be classified as restricted access or unrestricted access;
- Whether the data is or should be classified as sensitive (e.g., studies involving populations from isolated geographic regions or with rare traits, studies that include data on potentially stigmatizing traits, etc.)
- Whether there are any data use limitations or modifiers (e.g., use limited to a specific disease, restricted to not-for-profit organizations, IRB approval requirement, etc.);
- The plan for informed consent and the proposed consent language;
- *Supplement Form – Storing Data or Specimens for Future Use*; and
- A copy of the genomic data sharing plan.

The IRB will review the proposal for genomic data sharing or subsequent use of such genomic data in accordance with the criteria for approval of research and the guidelines for IRBs provided by NIH.

When VARI is responsible for NIH Institutional Certification (see below), the IRB review will specifically address the required assurances outlined on the Extramural Institutional Certification. When appropriate, if the IRB is unable to confirm that a certification element is satisfied (e.g., because the IRB has not yet granted final approval), Provisional Institutional Certification will be provided.

Grant Applications and GDS

Investigators planning to apply to NIH for research that will generate large-scale human genomic data as defined above should contact the appropriate NIH Program/Project officials to discuss expectations and timelines for complying with this policy. Along with the grant, the following will need to be submitted:

- **Notification in a cover letter** of the intent to generate large-scale human genomic data
- **A genomic data sharing plan,** within the grant's resource sharing plan section (NIH guidance on these plans is available here: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidance_Developing-GDS_Plans.pdf)

- **Institutional Certification** from the Office of Sponsored Research (templates available here: https://osp.od.nih.gov/scientific-sharing/institutional-certifications/). Certification must be provided for all sites contributing samples. If more than one site is contributing samples, the primary site may submit one certification on behalf of all collaborating sites (or each site may provide their own certification if this is the site's preference). This certification assures that:
    - The data submission is consistent, as appropriate, with applicable national, tribal, and state laws and regulations as well as relevant institutional policies;
    - Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated within the certification;
    - The identities of research participants will not be disclosed to the repositories;
    - An IRB and/or Privacy Board has reviewed the investigator's proposal for data submission and assures that:
        - the protocol for the collection of genomic and phenotypic data is consistent with 45 CFR 46;
        - data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
        - consideration was given to the risks to individual participants and their families associated with data submitted to the repositories and subsequent sharing, including unrestricted access to GSR; and
        - the investigator's plan for de-identifying datasets is consistent with the standards outlined in the NIH Genomic Data Sharing (GDS) Policy (See section IV.C.1).

- **In situations where the sharing of human data is not possible** (i.e., the Institutional Certification criteria cannot be met), a justification is required to explain why these data cannot be shared, and an alternative data sharing plan will need to be provided. Exceptions to NIH expectations for data submission to an NIH-designated data repository will be considered on a case-by-case basis by the NIH funding Institute or Center (IC).

Investigators who wish to use controlled-access human genomic data from NIH-designated data repositories should briefly address their plans for requesting access to the data and state their intention to abide by the NIH Genomic Data User Code of Conduct in the Research Plan of the application. The code of conduct is available here: https://osp.od.nih.gov/wp-content/uploads/Genomic_Data_User_Code_of_Conduct.pdf . Access to controlled-access data is dependent on an approval process that involves the relevant NIH Data Access Committee(s). Applicants may wish to secure access to the data prior to submitting their application for NIH support. Secondary users of controlled-access data are not expected to deposit their findings into NIH-designated data repositories, unless appropriate.

Investigators who wish to use/download data NIH unrestricted-access repositories, including non-sensitive GSR, should use the data to promote scientific research or health; and should not use the data to re-identify individuals or generate information that could allow participant's

identities to be readily ascertained, and, in all oral and written presentations, disclosures, or publications, acknowledge the specific dataset or accession numbers and the repository through which the data were accessed.

Procedures for submitting data into, or requesting access for data from an NIH-designated repository, are available here: https://osp.od.nih.gov/scientific-sharing/researchers-institutional-certifications/.

23.7 Case Reports Requiring IRB Review

Although VARI does not have a clinical center, in general, an anecdotal report on a small series of patients seen in a clinician's private 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.

23.7.1 Definitions

Single Case Report. 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, post treatment follow-up, 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.

23.8 International Research

The IRB will review all international research utilizing human subjects to assure adequate provisions are in place to protect the rights and welfare of the subjects. 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.

For international research, VARI IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or Ethics Committees (EC), which may or may not hold an approved FWA, and/or local letters of support. The source of this information will depend on the nature of the study, on the country, and on the resources available to the PI.

Where there is a local IRB/EC, VARI IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to the commencement of the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the VARI IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ECs, other VARI researchers with knowledge of the region, or other experts on the region. These individuals may either provide a written review of a particular protocol or attend an IRB meeting to provide VARI IRB with recommendations based on his or her expertise.

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/EC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/EC or provide documentation that the site's IRB/EC 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/EC, 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/EC determination, or letter of cooperation, as applicable.

23.8.1 Responsibilities

It is the responsibility of:

- VARI investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
- VARI investigator and the foreign institution or site to confirm the qualifications of the researchers and research staff for conducting research in that country(ies).
- VARI 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, noncompliance and unanticipated problems involving risk to subjects or others.

- VARI 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 subjects, etc.).

VARI IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

23.8.2 Consent Documents

The informed consent documents must be in a language understandable to the proposed subjects, see *Section 8.1*.

23.8.3 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 IRB/ECs.

The IRB will require documentation of regular correspondence between the VARI Investigator and the foreign institution or site and may require verification from sources other than the VARI Investigator that there have been no substantial changes in the research since its last review.

23.9 Incidental Findings

In developing research, investigators should consider the types and likelihood of incidental findings that may occur and plan accordingly. Likewise, the IRB should consider the same in conducting its review and ensuring that human subjects are appropriately protected. Not all incidental findings, however, can be anticipated, and investigators and IRBs must be prepared to consider such findings and take action as appropriate, given the circumstances. The following summarizes recommendations specific to research that are included in the Presidential Commission for the Study of Bioethical Issues 2013 report "*Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*".

23.9.1 Definitions

Incidental Findings. Results that arise that are outside the original purpose for which a diagnostic test or procedure was conducted.

Anticipated Incidental Findings. Findings that are known to be associated with a test or procedure.

Unanticipated Incidental Findings. Findings that could not have been anticipated given the current state of scientific knowledge.

Secondary Findings. Findings that are actively sought out by a researcher but are not the primary target.

23.9.2 Research Plan

The research plan should contain sufficient information to enable the IRB to evaluate the risks associated with participation in research, the likelihood and significance of risks that can be anticipated, and the adequacy of any steps taken to minimize the likelihood, severity, and impact of those risks.

Investigators should thus include within their research plan that provides information regarding potential for anticipated incidental findings and secondary findings, and a plan to manage such findings, including a plan for validation of results, when appropriate. Likewise, investigators should include within their plan a process for evaluating and managing unanticipated incidental findings, including consultation with subject matter experts, when appropriate, and the IRB.

The research plan should include specific information about disclosure of incidental and secondary findings, and whether disclosure is planned, the basis for that decision, and, when applicable, the methods for disclosing findings (i.e., inclusion of clinicians and/or genetic counselors in the disclosure discussion, referrals to clinical specialists, etc.).

23.9.3 Consent

The consent process should include a description of the types of incidental findings that might arise including anticipated incidental findings, deliberately sought secondary findings, and the possibility of unanticipated incidental findings. The consent process should also communicate to subjects the plan for disclosing and managing anticipated incidental findings and secondary findings, and whether and how subjects might opt out of receiving such information. This communication is essential to ensure that subjects understand what to expect as a result of their decision to participate in the research; e.g., informed consent.

Despite best efforts to develop, in advance, a comprehensive plan for the management of incidental and secondary findings, VARI recognizes that circumstances do arise that may fall outside of the original plan or that warrant special consideration. For example, a clinically actionable finding significant to the health of a subject arises but the initial plan did not include disclosure of results due to de-identification of samples or another factor.

In these instances, investigators should contact the VARI IRB for guidance and assistance. It should be noted that investigators would likely also be required to coordinate and work with the IRB at the collaborating clinical site in this regard.

23.10 Outreach Activities

As an institution currently focused on basic research involving Epigenetics, Parkinson's Disease and Cancer and Cell Biology, VARI holds annual conferences, symposia and meetings that focus on recent scientific research and invites public participation for some events, including:

- Grand Challenges in Parkinson's disease is a meeting for people with Parkinson's, advocates and caregivers that explores how the Parkinson's community can impact and accelerate research.
- Origins in Cancer is a one-day symposium that brings together students, scientists and medical professionals to discuss the latest breakthroughs in cancer research.

- Han-Mo Koo Memorial Award and Lecture was established to honor the memory and scientific contributions of Dr. Koo whose research focused on genetic targets for anti-cancer drug development for melanoma and pancreatic cancer. Since 2010, awardees have been selected based on scientific achievement and peer recognition. The researchers and the public are invited to the pre-award reception and the Memorial Lecture.

  When feedback is solicited from participants, the results are shared with the HRPP Office. As a result, if there is opportunity to make suggestions, these are made to the Symposium planners. As a component of the IO's annual evaluation of the HRPP, the Regulatory Programs Manager provides the IO with a summary of outreach activities that took place during the prior year, any feedback from those activities, and any suggestions for new or modified outreach activities from IRB members, the research community, and others. The IO determines whether the outreach program is adequate or whether changes are warranted.

23.11 ICH-GCP E6

To facilitate the acceptance of data for regulatory review in participating countries, clinical trials subject to ICH-GCP should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and applicable regulatory requirements. Among other ICH-GCP guidelines, ICH-GCP E6 outlines guidelines for investigators, IRBs, sponsors, and others on how to do so.

The VARI IRB does not review research subject to ICH-GCP E6, but rather relies upon the IRBs associated with or selected by the clinical sites to do so. However, VARI investigators who engage in or direct off-site research subject to ICH-GCP E6 must be familiar with and abide by the Investigator Responsibilities outlined in ICH-GCP E6 guidance.

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor;
3. The investigator should be aware of, and should comply with GCP and applicable regulatory requirements;
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities;
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties;

6. The investigator must have adequate resources to conduct the trial, including:
    a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period;
    b. Sufficient time to properly conduct and complete the trial within the agreed trial period;
    c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
    d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions;
7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site;
8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated;
9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions;
10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware;
11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed;
12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights;
13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects;
14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB;

15. During the trial the investigator should provide to the IRB all documents subject to review;
16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol;
17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects;
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor;
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol;
20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6;
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding;
22. Additional requirements for Informed Consent -
    a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented;
    b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR;
    c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR;
    d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial;

e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion;

f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects;

g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.

h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;

i. The consent discussion and written informed consent form should include the following additional elements:

    i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment;

    ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights);

    iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/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 informed consent form, the subject or LAR is authorizing such access;

    iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial;

    v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;

vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this;

vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and

viii. A statement that the trial has the approval of the IRB.

23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6;

24. Investigators must comply with the requirements for safety reporting outlined in Sections 3.3.8 and 4.11 of ICH-GCP E6 (to the extent required by FDA regulations and the IRB of record) including the redaction of personally identifying information; and

25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 of ICH-GCP E6 including the requirements for sponsor and IRB reporting.