VANDERBILT ®

Investigator's Handbook for the Protection of Human Participants in Social and Behavioral Research

May 2021

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Forward

This handbook was prepared to help Investigators comply with the Vanderbilt University and the Vanderbilt University Medical Center's institutional policies, the Human Research Protections Program (HRPP) policies and procedures, and the federal regulations concerning the use of humans in research. Included is detailed information concerning:

- Federal and institutional requirements for the protection of human research participants:
- Role and responsibilities of the IRB;
- Requirements and procedures for initial and continuing IRB review and approval of research;
- Rationale and procedures for proposing the research may meet the criteria for expedited review;
- Requirements and procedures for verifying research is exempt from IRB review;
- Responsibilities of Investigators during the review and conduct of research;
- Requirements and procedures for notifying the IRB of unanticipated problems or events involving risks to the participants or others;
- Informed consent requirements;
- Issues to consider regarding special categories of research and participants;
- Requirements for the use of investigational drugs, agents, biologics, and devices; and the use of radiation and radioactive drugs in research.

All efforts have been made to assure that the information in this handbook is consistent with all applicable federal and state laws and regulations, and with Vanderbilt University and Vanderbilt University Medical Center's policies concerning the use of humans in research. However, as changes in laws and policies occur this handbook will be revised.

If you need more information or would like to discuss specific aspects of your research with someone from the Human Research Protections Program, please contact the HRPP directly at (615) 322-2918 or toll free at (866) 224-8273.

How to Use This Handbook

Each chapter of this handbook addresses specific issues pertinent to Investigators who are engaged in biomedical research at Vanderbilt University or Vanderbilt University Medical Center or an affiliated site. It cannot be stressed enough, the importance of understanding the ethical principles, the federal regulations and the Human Research Protections Program's (HRPP) policies and procedures.

The table of contents has a listing of the topics covered within this handbook. Each is linked to the material to save time in looking for specific guidance.

After reviewing this handbook, Investigators should be better equipped to successfully submit to the IRB and understand the guiding principles to protect humans participating in research.

CHAPTER 1 - Investigator Responsibilities

The Principal Investigator is the ultimate protector of the research participant's rights and safety and is obligated to be personally certain that each participant is adequately informed and freely consents to participate in the research. The Investigator must personally assure that every reasonable precaution is taken to reduce to a minimum any risk to the participant. The Investigator also assumes responsibility for compliance with all federal, state and institutional rules and regulations related to research involving humans and human subject-derived information and materials. Investigators **may not** initiate any research involving humans without prior IRB review and approval.

This handbook will provide each Investigator with the information necessary to successfully submit for review the following types of applications and additional IRB review considerations.

Non-Human/Non-Research Application
Request for Exemption
Expedited Review
Full Committee Review
Request for Review by Another IRB
Site Addition
Informed Consent Documents
Continuing Review
Amendments
Repositories
Adverse Events/Protocol Deviations
Vulnerable Populations
Subject Recruitment - Advertisements
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Conflicts of Interest
HIPAA
Research in Public Schools

All Research Involving Humans Must Be Reviewed by the IRB

All individuals engaged in research that is sponsored by Vanderbilt University (VU) or Vanderbilt University Medical Center (VUMC); conducted by or under the direction of any faculty, staff, student, or agent of Vanderbilt University or Vanderbilt University Medical Center in connection with his or her institutional responsibilities; conducted by or under the direction of any employee or agent of VU or VUMC using any property or facility of VU or VUMC; or involves the use of VU or VUMC's non-public information to identify or contact human research participants or prospective participants must submit an application to the IRB prior to commencement of any research activities.

The implications of engaging in activities that qualify as research subject to IRB review without obtaining such review are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of VU and VUMC policy. It is also against policy to use such data to satisfy thesis or dissertation requirements.

If an Investigator begins a project and later finds that the data gathered could contribute to generalizable knowledge through publication or presentation of the results

of the activities, it is important that the Investigator submit a proposal to the IRB for review and approval prior to release or use of such information.

Investigators who submit an IRB application requesting approval to continue research that was not previously reviewed or to use data that was collected without IRB approval face the possibility that the IRB will administratively withdraw or request the Investigator administratively withdraw his or her application, as the IRB cannot give post-hoc approval.

The IRB may not approve applications where the Investigator has attempted to circumvent HRPP policies and procedures regarding human research by collecting data as non-research and then applying to use them as existing data. It is therefore in the Investigator's best interest to carefully consider the likelihood that he or she will want to use the data for research purposes in the future, and to err on the side of inclusion and seek IRB approval prior to commencing the work.

Oversight of Others Assisting in Research

An Investigator may delegate study related activities but he or she is ultimately responsible for the conduct of the study. It is the responsibility of each Investigator to assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Tennessee and the policies of VU and VUMC.

Every member of the research team is responsible for protecting participants in research. Sub-Investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, adhere rigorously to all protocol requirements, inform Investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, oversee the adequacy of the informed consent process, and take whatever measures are necessary to protect the safety, rights and welfare of participants. Regardless of involvement in research, each member of the research community is responsible for notifying the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

Human Research Protections Training

It is the policy of the Human Research Protections Program (HRPP) that all Investigators and key study personnel conducting human subjects research under the jurisdiction of the VUMC IRB complete initial and ongoing human research protections training. Investigators and study personnel must complete Human Research

Protections training before initiating research and renew the training every three years. The VUMC IRB has designated training options that meet this requirement. Human research protections training must be completed prior to submitting an application for IRB review.

Investigators and study personnel who are conducting clinical trials may submit documentation of **Good Clinical Practice (GCP)** training as documentation of Human Research Protections training. GCP training options are available on the VHRPP website.

The VUMC IRB offers online training options for Vanderbilt University Medical Center and Vanderbilt University researchers through each institution's training platform. Investigators who have not previously completed Human Research Protection training may complete the *IRB Basics* training course.

Basic initial training is obtained through the following options:

A. Oracle. Search for the module "HRPP Basic Module."

B. The CITI Program. Choose either the Basic "Biomedical" or "Social and Behavioral" Research Course.

C. A Good Clinical Practice course.

After completion of the required modules, the IRB will be notified that the Investigator has completed the training. Upon successful completion, the Investigator should print out a certificate for their records. IRB applications will not be accepted from Investigators who have not successfully completed the training. **In addition, the electronic IRB submission system (DISCOVR-E) will not permit the listing of investigators or key study personnel who have not completed the educational training requirements.**

Key Study Personnel - anyone who is responsible for the design or conduct of the study. This list may include sub-Investigators, research assistants, research coordinators, research nurses, etc.

A. Oracle

Links to Oracle are available on VHRPP's website.

Within the Oracle, search for "HRPP" and select HRPP Basic Module for initial human subjects training.

B. A CITI Program Course

Links to the CITI Program are available on VHRPP's website.

Appropriate documentation (certificate of completion) of attendance is required.

C. A Good Clinical Practice Course

Investigators and key study personnel who are involved in NIH sponsored clinical trials are required to complete Good Clinical Practice (GCP) Training.

Email certificates for sessions completed outside of the Vanderbilt Learning Exchange, Oracle and CITI website to TrainingCertificates@vumc.org. Please allow 24 hours for DISCOVR-e to be updated.

Ongoing Training Requirement

The IRB requires that all Investigators and key study personnel have ongoing training in the area of human research protections. As studies are submitted for continuing review to the IRB, the staff will check to see that this requirement is met. The Principal Investigator and key study personnel have an open invitation to attend or complete as many of the following sessions they would like; however, completion of one is mandatory to meet the annual training requirement:

There are several ongoing training options for the Principal Investigator and key study personnel. Any one of the following options will count:

A. Any online VHRPP sessions through Oracle;
B. An in-person training session (e.g., News You Can Use, IRB Basics, IRB Essentials, or departmental in-services);
C. An optional course through the CITI Program (e.g., Good Clinical Practices or Responsible Conduct of Research) or any module relative to human subjects protections;
D. Completion of the OHRP "Investigator 101" training module;
E. Attendance of a local, regional or national conference regarding human subjects protections; or
F. Other training may be approved on a case-by-case basis if the content includes human subjects protections. Approval by an HRPP Manager is required.
G. With the exception of adverse events and reports of noncompliance, the Investigator and key study personnel are unable to submit through the online submission system until they have completed human subjects training and are not approved to conduct the research.

Additionally, a Regulatory Compliance Analyst (RCA) will provide any type of human research protection training at the department's or Investigator's request. To request a tailored training or workshop, Investigators, faculty, or staff may request an In-service on the HRPP website. A member of the Compliance Team will follow up to schedule the activity.

Failure to meet the ongoing training requirement will delay the continuing review process, which may result in expiration of the study.

CHAPTER 2 - Authority of the IRB

Federalwide Assurance (FWA)

Institutions engaged in research involving humans supported or conducted by the Department of Health and Human Services (DHHS) must obtain an Assurance of compliance approved by the Office for Human Research Protections (OHRP).

Assurance - a formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

VU and VUMC currently each have a Federalwide Assurance (FWA) with OHRP assuring that the Institutions and affiliated sites will follow all applicable federal regulations addressing the protection of humans in all research, regardless of sponsorship.

Within these Assurances, and the establishment of Institutional Review Boards (IRBs), certain responsibilities and authority govern the functioning of such boards. The VUMC IRB is the IRB of Record for VU.

Performance Sites

As part of VU and VUMC's Assurances with the Office of Human Research Protections (OHRP), the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.104(d) or 21 CFR 56.104(d).

Regardless of financial support or funding, the VUMC IRB must assure that all performance sites "engaged" in research have approval from the IRB of Record for the proposed research to be conducted at the site. Therefore, it is important for the VUMC IRB to obtain information regarding the locations where research will be conducted. This is commonly referred to as a "performance site" because it is the site of research activities. Depending on the location of the performance site, the type of affiliation with VU or VUMC that may exist (*i.e.,* legal entity or memorandum of understanding) and the activities being performed, the IRB may be required to obtain different types of information to determine if the performance site is "engaged" or "not engaged" in research.

The performance site may either be associated with an institution that holds a Federalwide Assurance (FWA) with the federal government or may hold an FWA directly. It is important to know that holding an FWA allows an institution/performance site to receive federal support for the conduct of research involving humans.

The Investigator must first determine whether the sites where his or her research activities will be conducted are considered "engaged" or "not engaged" as defined by the federal regulations. A performance site becomes "engaged" in research when its employees or agents 1) intervene or interact with living individuals for research purposes, or 2) obtain individually identifiable private information for research purposes. Further, a performance site is considered to be "engaged" in human research when it receives a direct federal award to support the research. A performance site is "not engaged" in research if its employees or agents do not 1) intervene or interact with living individuals for research purposes, or 2) obtain individually identifiable private information for research purposes. If a VU or VUMC Investigator or his or her staff, including site personnel contracted by VU or VUMC, performs all research related activities as well as screening, recruiting, or consenting at the performance site, the performance site would be considered "not engaged" in research, unless the non-VU or VUMC performance site releases identifiable private information to VU or VUMC researchers without first obtaining participants' permission.

Independent Ethics Committee (IEC): A specially constituted review body whose responsibility is to assure the protection of the rights, welfare and safety of research participants. An IEC shares the same composition and operations as an Institutional Review Board.

Institutional Review Board (IRB): A specially constituted review body established or designated by an entity to protect the rights and welfare of human subjects recruited to participate in biomedical or behavioral/social science research.

Performance sites "engaged" in research must have the proposed research reviewed and approved by one of the following:

- Its own OHRP registered IRB/IEC;
- Another designated OHRP registered IRB/IEC; or
- VUMC IRB, provided an approved Reliance Agreement is on file.

Performance sites "engaged" in research with federal support must also hold an Assurance with OHRP.

Reliance Agreement: A formal agreement between Vanderbilt University Medical Center and another institution that identifies the VUMC Institutional Review Board as the IRB of record for that institution and defines the responsibilities for both the IRB and the other institution. Examples of reliance agreements can include Memorandum of Understanding (MOU), Institutional Authorization Agreements (IAA), Institutional Agreement For Institutional Review Board Review (IAIR)

Initiation of research conducted at a performance site "engaged" in research is contingent upon the receipt and review of the IRB/IEC approval from the "engaged" performance site. It is the responsibility of the IRB of record and the Assurance holding institution to assure that the resources and facilities are appropriate for the nature of the research under its jurisdiction.

Note: An IRB is considered the IRB of record when it assumes IRB responsibilities for another institution.

When performance sites are "not engaged" in research and have an established IRB/IEC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for VU or VUMC to conduct the proposed research at the site. When performance sites are "not engaged" in research and the "not engaged" site does not have an established IRB/IEC, the Investigator must obtain a letter of cooperation demonstrating that the appropriate institutional officials are permitting the research to be conducted at the performance site.

It is the responsibility of the VU or VUMC Principal Investigator and the performance site "not engaged" in research to assure that the resources and facilities are appropriate for the nature of the research. It is the responsibility of the VU or VUMC PI and/or the performance site "not engaged" in research to notify the VUMC IRB promptly if a change in research activities alters the performance site's engagement in the research (*e.g.,* employee of performance site "not engaged" begins consenting research participants, etc.).

The Investigator must obtain documentation that approval has been granted for sites "engaged" and "not engaged" in research involving humans. The Investigator will include this documentation in the initial submission to the IRB. If all approvals/letters of cooperation are not available at the time of initial submission, they may be submitted to the IRB with an amendment as they are received by the Investigator.

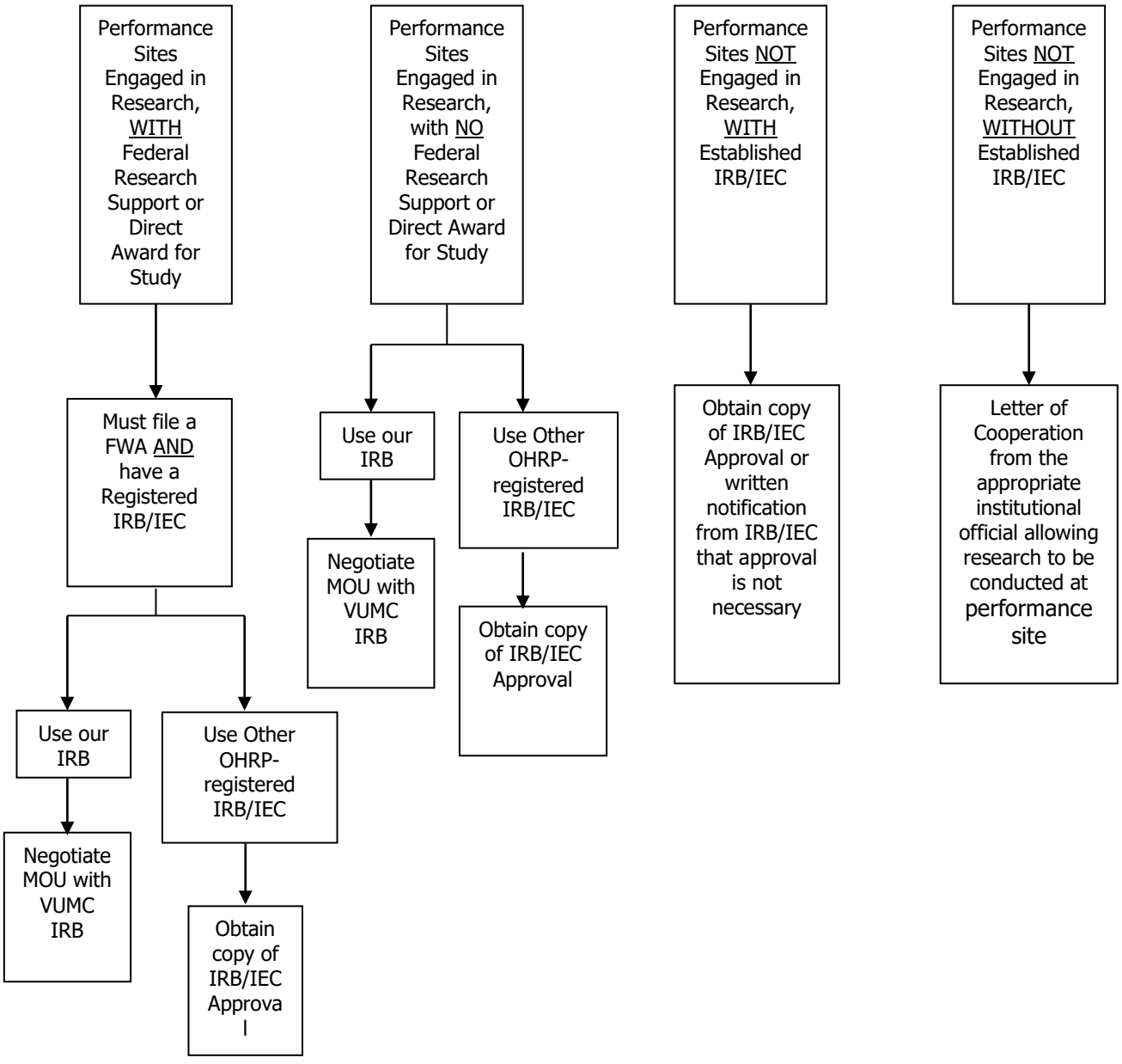
It is the responsibility of the Investigator to maintain current performance site IRB/IEC documentation, (*e.g.* approvals, continuing reviews, updated Assurance, Investigator qualifications, etc.), throughout the course of the research. The Investigator is responsible for assisting performance sites that do not have an IRB and are "engaged" in research in securing the appropriate Assurance and IRB approvals.

Vanderbilt Serving as a Single IRB

Performance sites may be added to the research study with the submission of a site add and the appropriate documents to the IRB for review and approval prior to beginning research activities at the new performance site. The Investigator may begin research activities at each site as it is approved by the VUMC IRB. The IRB is to be notified of closures of performance sites, if they occur. The Investigator will obtain the IRB/IEC approval letters or letters of cooperation for each performance site.

Below is a flowchart of "engaged" and "not engaged" to assist Investigators that are responsible for other sites in the research.

PERFORMANCE SITES ENGAGED IN RESEARCH AND NOT ENGAGED IN RESEARCH



Examples of Research Meeting Requirements for "Engaged" vs. "Not Engaged"

EXAMPLE	IRB DECISIONS BASED ON REGULATIONS
VU Investigators are allowed to come into the classroom to observe, audio/video tape, or distribute surveys/questionnaires for research purposes. The students and teachers of the school are consented by the VU Investigator to participate.	The school would be considered "not engaged" in research. The students and teachers of the school are participants in a study for which they have been consented.
A teacher is administering a standardized test at his/her school for a VU Investigator as part of a Vanderbilt University research project. The teacher is not administering the informed consent or performing data analysis.	The school would be considered "not engaged" in research. The teacher is functioning as a contract provider and is performing a task that they are trained and qualified to perform.
A teacher conducts his/her own research program in his/her classroom. The intervention is not part of the curriculum.	The school would be considered "engaged" in research as the intervention is not part of the standard curriculum performed in the everyday activities of the teacher.
The school system performs its own research, which is completed by school personnel. Investigators at VU will analyze the data. The data will not have identifiers. However, the VU Investigator will be included in the publication.	The school system and VU would be "engaged" in research. Although VU is contracted to perform a service, it will be included in the publication and therefore, considered "engaged."
In an educational trend toward collaboration, teachers and VU Investigators may be paired together to provide teachers with a voice in the literature and provide Investigators access to the field experience.	Both organizations would be "engaged in research" as both would be collecting data and involved in the publication of the results.
Vanderbilt receives an award and obtains a letter of cooperation from Metro Schools to perform research, which involves students. The teacher does not obtain consent from the students but will be administering surveys to the students as part of the research.	VU would be considered "engaged in research" as VU received funding to conduct the research. The school is "not engaged" in research as the teacher is not obtaining consent, but performing a task that they are trained and qualified to perform. Teachers may also be research subjects, which may require informed consent.

Authority of the IRB

The IRB has the authority and responsibility to approve and monitor for compliance with institutional policy all research involving humans conducted by Vanderbilt University or Vanderbilt University Medical Center faculty, staff, students or agents. In particular, the IRB has the authority to:

- Approve, require modification in, or disapprove an application for research;
- Monitor the involvement of humans in a study and require progress reports; and
- Suspend, impose restrictions, require modification to a study as a condition for continuation, or terminate a study.

The IRB does not have the authority to grant retroactive approval should a research study be initiated without prior IRB review.

No institutional administrator, faculty, or staff can reverse IRB Committee decisions that involve disapproval, deferral, suspension or termination of a research study.

Jurisdiction of IRB

VU and VUMC's Assurances with the federal government define their jurisdiction over the review of human subjects research. Regardless of sponsorship, the HRPP and/or the IRB must review <u>all</u> human subjects research if one or more of the following apply:

- The research is sponsored by VU or VUMC;
- The research is conducted by or under the direction of any employee, faculty, staff, student, or agent of VU or VUMC in connection with his or her institutional responsibilities;
- The research is conducted by or under the direction of any employee or agent of this institution using any of its property or facilities;
- The research involves the use of non-public information maintained by VU or VUMC to identify or contact human participants or prospective participants;
- VU or VUMC receive a direct federal award to conduct human subject research, unless all activities involving human subjects are carried out by a subcontractor or collaborator and another IRB(s) will review all of the activities and protocols under the grant; and/or
- The research is where the VUMC IRB is designated as the IRB of Record through an established Memorandum of Understanding or Reliance Agreement; or

- The research is conducted at VU or VUMC but where another IRB is designated as the reviewing IRB through an established MOU or Reliance Agreement.

If it is the intent of the Investigator to publish or disseminate data collected for non-research purposes, IRB review and approval is required prior to accessing the data for research purposes.

If an Investigator begins a non-research project and later finds that the data gathered could contribute to generalizable knowledge, the Investigator must submit a proposal to the IRB for review and approval prior to publication or presentation of the data (*e.g.,* journal article, poster session, public speech or presentation, or project report).

The implications of engaging in activities that qualify as research that is subject to IRB review without obtaining such review are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of HRPP policy. It is also against policy to use such data to satisfy thesis or dissertation requirements.

Investigators who request approval to continue human subjects research that was not previously reviewed or to use data that was collected without IRB approval face the possibility that the IRB will administratively withdraw or request the PI administratively withdraw his/her application, as the IRB cannot give post-hoc approval.

The IRB may not approve applications where the Investigator has attempted to circumvent IRB policies and procedures regarding human subjects research by collecting data as non-research and then applying to use them as existing data. It is therefore in the Investigator's best interest to consider carefully the likelihood that he or she will want to use the data for research purposes in the future, and to err on the side of inclusion and seek IRB approval prior to commencing the work.

Suspension or Termination of Research

The IRB has the authority and responsibility to suspend or terminate approval of research that is not being conducted in accordance with the policies and procedures of the institution or that has been associated with unexpected harm to participants or others. Any letter of suspension or termination of approval to an Investigator must include a statement of the reasons for the action by the IRB.

An example of suspensions or terminations for cause might include inappropriate involvement of humans in research, serious or continuing noncompliance with Federal regulations or IRB policies, and/or new information regarding increased risk to research participants or others.

All suspensions or terminations of approval for cause must be promptly reported to the HRPP Directors. The IRB will notify the Executive Vice President for Research, the Vice Provost for Research, the Chair of the Investigator's Department, the Office of Sponsored Programs, when applicable, the Chairpersons of the IRB Committees, and the Faculty Advisor, if appropriate, for any suspensions or terminations for cause initiated by the IRB.

Audits and Monitoring of Research

The IRB has the authority to initiate periodic post-approval monitoring and/or directed audits when requested by the HRPP Director, the Chairpersons of the IRB Committees, and/or designee. When necessary to assure protections of humans in research, the IRB may appoint a designee to observe the informed consent process of IRB approved research.

When issues of noncompliance or situations in which a participant in a research project has been exposed to unexpected serious harm are identified through an audit or compliance review, the IRB will promptly address such findings to assure that all research is being conducted according to federal regulations, institutional policies and HRPP policies and procedures.

IMPACTT

The Research Support Services group has developed, through a grant award, a quality improvement program designed to assist Investigators in increasing the level of protection for research participants through improvement of the research process. IMPACTT (IRB Measured Performance and Collaborative Training Techniques) is a program that offers support, consultation, and collaboration with the goal of strengthening VU and VUMC's Human Research Protections Program.

To accomplish this goal, the HRPP invites Investigators to schedule a consultation with the IMPACTT team. In addition, some research programs will be selected at random for this initiative.

The consultation will include an on-site visit, preliminary interview and an on-site assessment. The purpose of the short preliminary interview with the Investigator and coordinator(s) is to communicate the goals of the IMPACTT program. These goals are three-fold: to assist the research team in identifying strengths and weaknesses, to provide education, and to make recommendations for improvement. Following the preliminary interview, an on-site assessment will be performed on a single protocol utilizing a comprehensive assessment tool developed to examine the necessary elements involved in managing a research study.
At the conclusion of the on-site assessment, an exit interview will be conducted. A final

report, which includes the findings and recommendations, will be issued by the IMPACTT team.

Investigators interested in voluntarily initiating this process may submit a request by downloading an "IMPACTT Program Request" form. The completed form should be sent to the IRB IMPACTT Team at the IRB office address.

CHAPTER 3 - Purpose and History of the Institutional Review Board

Federal Requirements for the Protection of Human Research Participants

The formal requirements for the establishment of Institutional Review Boards (IRB) first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status the National Institute of Health's (NIH) Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the IRB as one mechanism through which human research participants would be protected. In 1981, both the Department of Health and Human Services (HHS, formerly DHEW) and the FDA promulgated significant revisions of its regulations involving human research participants. The HHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. Those basic regulations became final on January 16, 1981, and were revised effective March 4, 1983, June 18, 1991, December 13, 2001 and January 19, 2019. The June 18, 1991 revision involved the adoption of the **Federal Policy for the Protection of Human Subjects**, or **"Common Rule"** as it is sometimes called. A number of federal agencies that conduct, support, or otherwise regulate research involving human research participants adopted the provisions of the regulations. The FDA also adopted some of its provisions. As is implied by its title, the "Common Rule" is designed to make uniform the human research protection system in these Federal agencies and departments.

Governing Principles Established in *The Belmont Report*

The three basic principles that govern the protection of human research participants in biomedical and behavioral research as set forth in *The Belmont Report* and adhered to by the HRPP are:

- Respect for Persons - recognition of the personal dignity and autonomy of individuals and special protection of those persons with diminished autonomy;

- Beneficence - obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm; and

- Justice - fairness in the distribution of research benefits and burdens.

These principles designed to protect the rights and welfare of human participants are the basic tenets underlying the HRPP policies and procedures. Statements supporting these ethical principles and standards adopted by the HRPP can be found in the following major documents:

- The Nuremberg Code
- The Declaration of Helsinki
- The Belmont Report

In summary, the HRPP policies are based on the following general ethical principles as established in the federal regulations (criteria for approval, 45 CFR 46.111):

- The rights and welfare of all subjects must be adequately protected to safeguard the physical and psychological well-being of a subject and to preserve the subject's rights of privacy and self-determination;

- Risks must be minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk;

- Risks must be reasonable in relation to anticipated benefits to subjects or to the importance of the knowledge that may be gained;

- Recruitment and selection of subjects must be equitable within the confines of the purposes and design of the study. Subjects must not be arbitrarily included or excluded on the basis of gender, race, national origin, religion, creed, education or socioeconomic status;

- If informed consent is required, it must be obtained from each subject or the subject's legally authorized representative, prior to the subject's participation in any activity performed solely for research purposes;

    - The informed consent process must be documented by a signed written consent form, a copy of which must be given to the subject.
    - The subject's consent must be based upon an understanding of the research, the risks, possible discomfort, and alternative procedures.
    - The informed consent document must provide for the subject's ability to refuse participation or to discontinue participation at any time without prejudice.

- Provisions must be made to monitor the data to assure the safety of subjects;

- Provisions must be made to protect the privacy of subjects and the confidentiality of data; and

- Additional safeguards must be included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence.

Additional guidelines for research involving humans, such as those formulated by professional organizations and societies, can be supplemental, but do not supersede or

diminish the protections and requirements outlined above. Local and state laws and regulations often supplement the protections and guidelines outlined above and where more restrictive, supersede the federal protections.

VU and VUMC Oversight of the Protection of Human Participants

VU and VUMC, their staff, employees, faculty and students are guided by the ethical principles regarding all research involving humans as set forth in The Belmont Report established by the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**. These ethical standards guide all research activities regardless of whether the research is subject to federal regulation, who is conducting the research, or the source of support (*e.g.,* sponsorship).

The IRB is an administrative body established to protect the rights and welfare of humans recruited to participate in research activities conducted at VU or VUMC and its affiliated sites by assuring institutional compliance with those ethical considerations contained in the federal regulations. The IRB maintains guiding principles and operating policies demanding the highest professional standards and reviews all research projects involving humans to assure that appropriate standards are met, and research procedures do not infringe upon the safety, health, or welfare of participants.

The Executive Vice President for Research, the Vice Provost for Research, the HRPP Medical Director, and the HRPP Director are responsible for exercising appropriate administrative oversight to assure that HRPP's policies and procedures designed for protecting the rights and welfare of humans participating in research are effectively implemented in compliance with its Assurance with the Office for Human Research Protections (OHRP), which oversees compliance of all registered IRBs with the federal regulations.

The Roles and Responsibilities of the VUMC IRB

The IRB is responsible for the operational support, initial and ongoing training, and oversight of the Health and Behavioral Sciences IRB Committees, the Institutional Biosafety Committee for Human Subjects, the Stem Cell Committee, and the Radioactive Drug Research Committee. Committee membership is based upon credentials, areas of expertise, and diversity of ethnicity and gender to assure the protection of rights and welfare of research participants. Committee members are nominated by the HRPP Director to the Executive Vice President for Research or the Vice Provost for Research based upon the specific needs of the IRB Committees (*e.g.,* scientific specialty, diversity, non-scientist, non-affiliated). Committee Chairpersons are requested to serve a minimum of three years to include at least one year as Chair and may be asked to serve an additional year to mentor the newly appointed Chairperson in

an effort to promote consistency. Committee members and Chairpersons receive training and are given copies of the federal regulations, institutional policies, and HRPP procedures relating to research involving humans.

All research proposals involving human participants must be reviewed and approved by the IRB. The involvement of human participants in research is not permitted until the IRB has reviewed and approved the research proposal, informed consent document(s), recruitment materials/advertisements, survey or study instruments, full grant when applicable, and any additional study related documentation.

Once the research proposal has been approved, any additions or changes must be submitted, in the form of an amendment request, for review by the IRB prior to implementation (*See* Chapter 7 – Amendments).

In accordance with the federal regulations, continuing review must be conducted at least annually to include all appropriate documentation regarding the activity of the research, copies of current informed consent documents, and any changes to the risk/benefit ratio and/or the research plan (*See* Chapter 6 – Continuing Reviews).

The IRB is responsible for maintaining copies of all research protocols with supporting documentation, minutes of IRB Committee meetings, documentation of continuing review activities, any significant new findings to be provided to participants, and correspondence between the IRB, administration, Investigators, affiliates, and any appropriate federal and/or state agency. The IRB serves as a liaison for regulatory or institutional information between Investigators, affiliates, sponsors, institutional administration, and OHRP.

To meet its obligations, the IRB:

- maintains guiding principles and operating policies demanding the highest professional standards in working with human research participants, and

- reviews all research projects involving humans to assure that appropriate standards are met and the research procedures do not infringe upon the safety, health or welfare of those participants.

The Use of a Single IRB and the VUMC IRB

The VUMC IRB is required to act as a single IRB or to rely on another single IRB for all federally funded, multi-site, non-exempt research.

NIH Policy: Multi-site, domestic studies, which involve non-exempt human subjects research for grants funded by the NIH submitted on or after January 25, 2018, is required to use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects.

Common Rule: All federally-funded domestic, cooperative research that is ready for IRB submission on or after January 20, 2020 is required to use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects.

It is important to contact the IRB as early as possible in the development of a grant to assure the appropriate selection of an IRB as well as the appropriate language to be included in the grant. Investigators who wish to use Vanderbilt as the Single IRB should submit the Vanderbilt Reliance Interest Form to facilitate initial communication prior to submitting an IRB application.

CHAPTER 4 - IRB Review Determinations: Non-Human/Non-Research, Exempt, Expedited and Full Committee

An Investigator may often question whether his or her proposed activities meet regulatory requirements for IRB review. In general, if the proposed activities **do not** meet the definition of "human subject", "research," or "clinical investigation" review and approval by the IRB is not required.

Determination of "Non-Human"

The federal regulations define a **human subject** as a living individual about whom an Investigator (whether professional or student) conducting research obtains:

- information or biospecimens through intervention or interaction with an individual and uses, studies, or analyzes the information or biospecimen;
- obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens; or
- identifies a subject as either a recipient of a 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. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

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

Interaction includes communication or interpersonal contact between an Investigator or his/her research staff and the research participant or their private identifiable 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. It includes information, which has been provided for specific purposes by an individual, and which the individual can reasonably expect will not be made public (*e.g.,* a medical record). Private information must be individually identifiable in order to constitute research involving human participants. This may include identifiable private information obtained from a primary participant about a third party.

Identifiable Private Information: Private information for which the identity of the subject is or may be readily ascertained by the investigator or associated with the information.

Identifiable Biospecimens: Biospecimens for which the identity of the subject is or may be readily ascertained by the investigator or associated with the biospecimen.

A study does not qualify as "non-human" if data is obtained through intervention or interaction with an individual. Interaction or intervention involves direct human contact with individuals or manipulation of an individual's environment. To qualify as "non-human" the data cannot contain any of the following 18 identifiers that may be linked to an individual:

- names;
- geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;
- all elements of dates (except year) for dates directly related to an individual (*e.g.,* date of birth, admission);
- telephone numbers;
- fax numbers;
- electronic mail addresses;
- social security numbers;
- medical record numbers;
- health plan beneficiary numbers;
- account numbers;
- certificate/license numbers;
- vehicle identifiers and serial numbers, including license plate numbers;
- device identifiers and serial numbers;
- web Universal Locators (URL's);
- Internet Protocol (IP) address numbers;
- biometric identifiers, including finger and voiceprints;
- full-face photographic image and any comparable images; and
- any other unique identifying number, characteristic, or code.

To qualify as "non-human" the Investigator must receive the data or specimens without any of the 18 unique identifiers as described. A code or link cannot exist that could allow the Investigator to establish identity

If an Investigator's research project meets the definition of "non-human," the IRB does not require review and approval. However, because most funding agencies require that the IRB review a project prior to releasing monies, the IRB has developed a mechanism for review and verification that the study does not meet the definition of "human subject." If however, the non-human research project is federally funded (e.g. National Institutes of Health) and VU or VUMC are the direct recipient of the federal funding, and the monies are to support research involving human subjects at an outside institution (i.e., non-VU or VUMC site), an Umbrella Application should be submitted instead.

Determination of "Non-Research"

As defined by the federal regulations, **research** is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

A **systematic investigation** involves a predetermined method for studying a specific topic, answering a specific question, testing a hypothesis, or developing a theory. Activities that develop or contribute to **generalizable knowledge** are such that the activity is intended to be extended beyond the institution through publication or presentation or could otherwise influence current theory or practice.

If an Investigator's project meets the definition of "non-research," the IRB does not require review and approval. However, as with the above determination, because most funding agencies require that the IRB review a project prior to releasing monies, the IRB has developed a mechanism for review and verification that the study does not meet the definition of "research." For federally funded research, please submit an umbrella application request. This process is reviewed following the same procedures described under exempt research addressed later in this chapter.

Levels of IRB Review

All research involving humans that falls under the jurisdiction of the IRB for review and approval must meet the criteria for one of the following methods for review:

- Exempt from IRB Committee Review
- Expedited Review
- Committee Review

Exempt Research

Research activities involving human participants that are exempt from the requirement for full Committee or expedited review are identified in the federal regulations at 45 CFR 46.104(d)(1)-(6) and 21 CFR 56.104(d). Only the IRB may determine which activities qualify for an exempt review and may not create new categories. Investigators do not have the authority to make an independent determination that research involving humans is exempt. If there are any questions regarding the appropriateness of the *Request for Exemption*, a Regulatory Compliance Analyst (RCA) will refer the study to the Chairperson or designed Committee Member. Results of this review will be promptly conveyed in writing to the Investigator.

The *Request for Exemption* must meet one (1) of six (6) specific categories of activities (46.104). If the proposed research activities do not meet the criteria for exemption, the IRB will promptly correspond with the Investigator outlining any additional information needed and the proper type of review (*e.g.,* expedited or full Committee).

Request for Exemption **must be approved prior to initiation of the research or contacts with participants.**

Categories of Research Eligible for Exempt Review

Research is eligible for exempt review if all research activities are encompassed in one or more of the following six categories:

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

2 Research that only includes interaction involving the use of 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 is met:

- information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot be readily ascertained, directly or through identifiers linked to the subjects; or
- any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation; or
- the information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained, directly or through identifiers linked to the subjects and the IRB conducts a limited IRB review.
- Children may only be included in research under this exemption when involving educational tests or observation of public behavior if the investigator(s) do not participate in the activities being observed and the information obtained is recoded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained directly or through identifiers linked to the subjects.

OHRP has traditionally considered "public behavior" to be that generally open to view by any member of a community and/or which would not involve any special permission to observe, such as, at a park, in a mall, at a movie theater, etc. Under this interpretation, what occurs in a classroom would not generally be considered observation of public behavior.

3 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 collected meets one of the following:

1. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained, directly or through identifiers linked to the subjects; or
2. Any disclosure of the 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
3. The information is recorded by the investigator in such a manner that the identity of the subjects can be readily ascertained, directly or through identifiers and the IRB conducts a limited IRB review.

For this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing (e.g., playing an online game, solving puzzles, etc.).

Note: Children may not be included in this exemption. Research involving deception cannot be included unless the subject authorizes the deception prospectively and is informed that they will be unaware 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 are met:

1. The identifiable private information or identifiable biospecimens are publicly available; or
2. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; or
3. The research involves only information, collection and analysis involving the investigator's use of identifiable health information that is regulated under HIPAA, for the purposes of healthcare operations, research, or public health activities and purposes as defined by HIPAA; or
4. The research is conducted by, or on behalf of a Federal department or agency using government-generated or government-collected information obtained for non-research activities.

5 Research and demonstration projects which are conducted by or subject to the approval of Federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

- public benefit or service programs;
- procedures for obtaining benefits or services under those programs;
- possible changes in or alternatives to those programs or procedures; or
- possible changes in methods or levels of payment for benefits or services under those programs.

Note: Exemption for public benefit or service programs applies only for federally-supported projects and requires authorization or concurrence by the funding agency. The following criteria must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs:"

(1) 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 Americans Act);

(2) The research or demonstration project must be conducted pursuant to specific Federal statutory authority;

(3) There must be no statutory requirement that the project be reviewed by an Institutional Review Board; and

(4) The project must not involve significant physical invasions or intrusions upon the privacy of participants.

6 Taste and food quality evaluation and consumer acceptance studies,

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

There are limitations when applying the exempt categories when vulnerable populations are included in the research.

Exemption of Research Involving Children

Research that involves children and falls into all categories described above except category 2 may be found to be exempt by the IRB. The exemption category 2 above, pertaining to educational tests may also be considered for exemption. However, research involving survey or interview procedures or observations of public behavior, does not apply to research involving children, except for research involving observation of public behavior when the Investigator(s) does/do not participate in the activities being observed.

Exemption of Research Involving Prisoners

Research under categories 1-6 is not exempt if it involves prisoners. These applications must be submitted for IRB Committee review.

Procedures for Requesting Exemption

To apply for approval for a *Request for Exemption*, an Investigator must complete and submit through the electronic IRB submission system DISCOVR-e. As stated earlier, the exempt requests are reviewed by a designated RCA for verification. Should the RCA have questions regarding the research, the study is then forwarded

to the appropriate IRB Chairperson or designed Committee Member for review. The same conditions for approval apply. The IRB may approve, approve pending modifications, defer or request that the study be reviewed through expedited procedures or by the Committee. With an exempt approval there are no submission deadlines and the study is not subject to continuing review requirements.

Amendments to Exempt Research

Any changes that are made to the approved *Request for Exemption* within the first year of approval must be submitted for review by the IRB prior to implementation. Amendments will be accepted up to one year from the date of approval. Modifications requested after the first year of approval require a new *Request for Exemption* application. Some modifications to the research may change the review status and require the Investigator to submit an application for expedited or Committee review.

Limited IRB Review

Review will be conducted by the IRB sub-Committee or designee:
(1) For exempt categories 2, 3, 7 and 8 to verify adequate provisions to protect the privacy of subjects and to maintain confidentiality of the data are assessed.
(2) For exempt category 7 and 8, to verify broad consent or a waiver of documentation for broad consent is appropriate. Any change in the way identifiable private information or identifiable biospecimens are stored or maintained will also require review.

There are two categories 7 and 8 which are specific to Broad Consent. At this time, VU and VUMC are not adopting broad consent.

Expedited Review

Expedited review does not mean "fast" but rather, certain research, meeting the specified criteria, may be reviewed by the IRB Chairperson or designed Committee Member, not at a convened Committee meeting. All expedited protocols must meet the conditions of "minimal risk." Additionally, the standard requirements for informed consent or its waiver/alteration apply.

Research Eligible for Expedited Review

Use of expedited review by the IRB is restricted to those applications that both present *no more than minimal risk* to human participants and fulfill one of the nine (9) specific categories (46.110).

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

The expedited review procedure may not be used where identification of the participants and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participants' 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 government classified research involving human participants. The expedited review procedures may not be used for research involving prisoners.

In addition to being determined to be minimal risk, all expedited studies must fit into one of the following nine categories. The categories apply regardless of the age of participants, except as noted. The nine categories should not be deemed to be of minimal risk simply because they are included on the list. Inclusion on the list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human participants.

Categories of Research Eligible for Expedited Review

The following categories pertain to both initial and continuing IRB expedited review:

1. Clinical studies of drugs and medical devices only when at least one of the following conditions is met:
   - ✓ Research on drugs for which an investigational new drug application (*See* 21 CFR Part 312) is not required. (Note: Research on marketed drugs

that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

- ✓ Research on medical devices for which (i) an investigational device exemption application (*See* 21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2 Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- ✓ from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
- ✓ from other adults and children, 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 are considered. 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.

3 Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

- hair and nail clippings in a non-disfiguring manner;
- deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- permanent teeth if routine patient care indicates a need for extraction;
- excreta and external secretions (including sweat);
- uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
- placenta removed at delivery;
- amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
- supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
- mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
- sputum collected after saline mist nebulization.

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

- physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
- weighing or testing sensory acuity;
- magnetic resonance imaging;
- electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography;
- moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5 Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt. 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. This listing refers only to research that is not exempt.)

Investigators should remember that even though research may be eligible for expedited review it still remains subject to the requirements of informed consent.

Procedures Required for Expedited Review

Because a study meeting these criteria is reviewed by the appropriate IRB Committee Chairperson or designed Committee Member, there are no deadlines for submission. However, in reviewing the research, the Chairperson or designed Committee Member may exercise all of the authorities of the full Committee except he or she may not disapprove the research. The Chairperson or designed Committee Member may refer the application to the Committee for a standard review or request that the study be reviewed by another IRB Committee member with an appropriate area of expertise.

The following documents are required for expedited review:

- A completed IRB application with a list of all key study personnel, a signature page and conflict of interest statement;
- A full investigator's or sponsor's protocol;
- All proposed informed consent document(s) and/or script as appropriate;
- A copy of all forms of recruitment materials, in final form (*e.g.,* TV ads, radio spots, mass e-mail communications);
- A copy of all research related measures (*e.g.,* surveys, questionnaires, tests, interview question outline);
- When applicable, a copy of the grant application;
- All letters of cooperation or IRB approval letters, when appropriate, for performance sites not engaged in research;
- All IRB letters of approval from performance sites engaged in research; and
- When applicable, an Investigator's brochure (typically submitted with industry sponsored research).

Please submit all materials through DISCOVR-e.

Once the above materials have been submitted to the IRB, an RCA from the designated Health Science Team will complete a pre-review of the application. Should there be any additional materials or modifications needed as required by the federal regulations and HRPP policies and procedures, the RCA will contact the Investigator either through the DISCOVR-e pre-review system, by e-mail or by phone. Upon completion of the pre-review changes, the study will be routed to the IRB Chairperson or designed Committee Member. The process of expedited review may take 7 to 10 working days to complete.

Results of Expedited Review

Following the review by the IRB Chairperson or designated Committee Member, the Investigator will receive a letter addressing one of the following possible determinations:

- The study is approved, in which case a copy of all approved working documents including the consent documents with the stamped approval date will be sent with the final approval letter and the study may begin.

- The study requires specified, non-substantive revisions to secure approval. The Investigator will receive a letter clearly indicating the required modifications. Upon receipt of the changed documents, the Committee Chairperson will verify that the appropriate additions/corrections were made and will approve the study. A link to the final approval letter will be sent to the Investigator with all approved working documents, including the consent documents stamped with the corresponding approval date.

- The study is deferred, in which case the Investigator will be asked to make substantial modifications and/or provide additional information.

- The IRB Chairperson or designed Committee Member may refer the study to another reviewer with the required expertise or to the IRB Committee. Whenever possible, the proposal will be included on the agenda for the next regularly scheduled Committee meeting. The Reviewers may also request additional information, to be included for Committee review and, when appropriate, may request that the Investigator be present at the meeting.

No human participants may be enrolled or recruited prior to receipt of written final IRB approval of the research.

Full Committee Review

The standard review of protocols may occur only at a convened meeting of the IRB Committee at which a *quorum* (a majority of the voting members) is present. Additionally, there are requirements for the make-up of the Committee (46.107). Each Committee must have at least five members of varying backgrounds with one member from the scientific community and one non-scientist. At least one member should not be affiliated with the institution. This person is referred to as a "community member" and is focused on the interests of the community. The federal regulations require a majority of the members to be present for the discussion and vote of each review.

The IRB currently has three Health Sciences Committees and one Social and Behavioral Sciences Committee. In order to have timely reviews of proposals requiring Committee review, each Health Sciences Committee meets weekly and may review ten to fifteen proposals, on average. The Social and Behavioral Committee meets every other week and may review four to six proposals on average.

Criteria for Approval by Full Committee Review

Committee review is necessary for all research that does not qualify for exempt or expedited review. The Investigator can help facilitate the approval of his or her application by considering in the development of the IRB application the following requirements, as established in the regulations (46.111). Specifically, the Committee may only approve an application when it finds that:

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

- 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 Committee will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.

- Selection of subjects is *equitable*. In making this assessment the IRB Committee will 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 considerations of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

- *Informed consent* will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the federal regulations and Institutional policies and procedures including the IRB.

- Informed consent will be appropriately *documented* in accordance with, and to the extent required by the federal regulations and Institutional policies and procedures including the IRB.

- When appropriate, the research plan makes adequate provision for *monitoring* the data collected to assure the safety of subjects.

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

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Procedures Required for Full Committee Review

The IRB uses a primary reviewer system for all studies submitted for full Committee review. Each study will be assigned a Primary and Secondary Reviewer. The Reviewers assigned will have expertise in the area of the research adequate to the scope and complexity of the research. The Reviewers should conduct an in-depth review of all pertinent documentation. Each Reviewer receives a copy of all of the following study related documents:

- A completed IRB application with a list of all key study personnel, a signature page and conflict of interest statement;
- A full investigator's or sponsor's protocol;
- All proposed informed consent document(s) and/or script as appropriate ;
- All applicable supplemental forms;
- A copy of all forms of recruitment materials, in final form (*e.g.,* TV ads, radio spots, mass e-mail communications);
- A copy of all research related measures (*e.g.,* surveys, questionnaires, tests, interview question outline);
- When applicable, a copy of the grant application;
- When applicable, a copy of other Committee approvals (*e.g.,* SRC, IBC, RDRC);
- All letters of cooperation or IRB approval letters, when appropriate, for performance sites not engaged in research;
- All IRB letters of approval from performance sites engaged in research;
- When applicable, an Investigator's brochure (typically submitted with industry sponsored research);
- When applicable, a copy of the "Statement of the Investigator" (FDA Form #1572);
- When applicable, a copy of the Investigational Device Exemption (FDA Form #2891);
- When applicable, the patient cost template; and

- When appropriate, verification of the approved indemnification language included in the contract.

Please submit all materials including the grant application through DISCOVR-E.

Before an application can be placed on an agenda for IRB review, a RCA from the designated Health Science Team will complete a pre-review of the application. Should there be any additional materials or modifications needed as required by the federal regulations and HRPP policies and procedures, the RCA will contact the Investigator either through DISCOVR-e, by e-mail or by phone. Upon completion of the pre-review changes, the study will be placed on the next available agenda. Each Health Sciences Committee meets on a weekly basis. Materials to be reviewed by the Committee are given to its members at least one week in advance to allow adequate time for review. At times, the reviewers may contact the Investigator to ask for clarification, before the meeting to attempt to avoid deferring the proposal.

Results of Full Committee Review

Following the convened meeting, the IRB Committee will communicate to the Investigator the determinations as voted upon in the meeting. Each Investigator will receive a letter indicating one of the following determinations:

- The study is approved, in which case a copy of all approved working documents, including the consent documents with the approval period date stamped will be sent with the final approval letter and the study may begin.

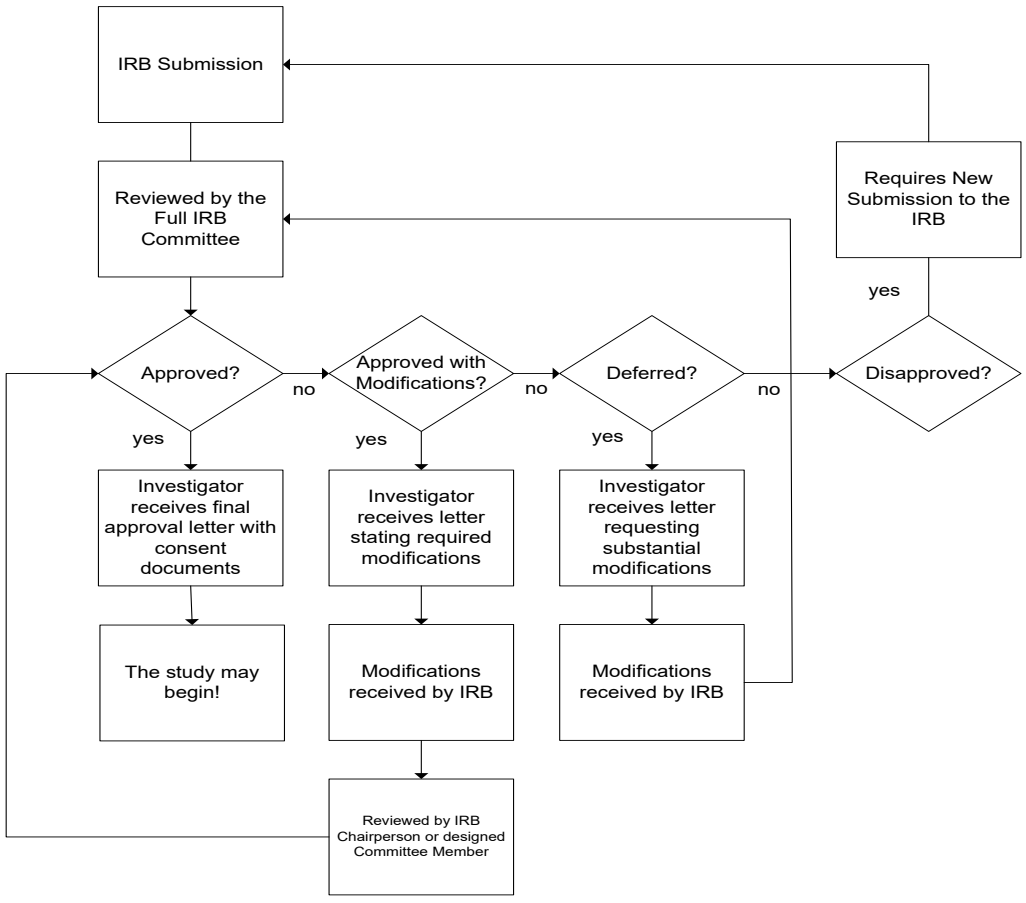
- The study requires specified, non-substantial revisions to secure approval. The Investigator will receive a letter clearly indicating the required modifications. Upon receipt of the changed documents, the Committee Chairperson will verify that the appropriate additions/corrections were made and will approve the study. A link to the final approval letter will be sent to the Investigator along with all approved working documents, including the consent documents stamped with the corresponding approval period.

- The study is deferred, in which case the Investigator will be asked to make substantial modifications and/or provide additional information. A deferral requires that the study along with the additional information/modifications be reviewed by the Committee at a convened meeting. When the study contains multiple issues to clarify, the IRB Committee may invite the Investigator to attend the next available meeting in order to directly address concerns.

The IRB Committee may disapprove the study. Prior to disapproving a study, the IRB may make attempts to resolve the issues of concern, including inviting the Investigator to the Committee meeting and discussing the study at the HRPP Optimization Committee

Optimization Committee (OC) - A representative group of IRB Members, HRPP Staff, and HRPP Administration that work in partnership to assure the protection of human research participants, maintain compliance with federal regulations, and to promote consistency between IRB Committees.

No subject may be enrolled or recruited prior to receipt of written final IRB approval of the research.



Use of the Single IRB (SIRB) Model:

Under the SIRB model, one IRB agrees to provide IRB oversight for **all** participating institutions via an authorization agreement (a.k.a. "reliance" or "collaborative" agreement).

Vanderbilt Serving as a Single IRB:

Vanderbilt utilizes the SMART IRB Master Reliance Agreement along with a separate Letter of Indemnification (LOI) to establish reliance with other institutions. Both of these agreements are completed one time per institution to avoid lengthy negotiations on a study-by study basis. Vanderbilt also uses the IRB Reliance Exchange (IREx) portal to facilitate and support Single IRB documentation and communication with the other participating institutions.

Request Review By Another IRB:

SMART IRB Reliance Agreement: A national master reliance agreement supporting SIRB review.

Letter of Indemnification (LOI): is a separate agreement concerning indemnification and related terms that is required by the Vanderbilt SIRB.

IRB Reliance Exchange (IREx): A single IRB documentation and communication portal.

VUMC may rely on another IRB if the study meets the regulatory requirements under the SIRB mandate. Vanderbilt prefers use of the SMART IRB Master Reliance Agreement when relying on another IRB, as well. The Vanderbilt investigator should submit a "Request Review By Another IRB" application.

Request Review by another IRB

Initial Review:
After the IRB of Record has approved the submission, an abbreviated application to cede review should be submitted in DISCOVRe. Submission documents needed to conduct our local review when relying on another IRB:

- IRB Approval Letter from the IRB of record
- IRB Approved Protocol
- IRB Approved Consent Form with VUMC's required local language included
- Vanderbilt stand alone HIPAA Authorization form (when applicable)
- Local Considerations Surveys, questionnaires, worksheet
- IRB approved study documents from the IRB of Record
    - Protocol
    - Investigational Brochure
    - Study Measure and Materials being used at Vanderbilt
- Any Vanderbilt specific study documents (e.g., advertisement and recruitment materials being used locally**)**

When relying on another IRB's review, the Vanderbilt's Human Research Protection Program (HRPP) is still responsible for assuring any ancillary reviews are completed prior to beginning any study for which the single IRB policy applies.
Ancillary reviews may include but is not limited to:

- Radiation Review
- IBC Review
- COI Review
- Privacy Review

CHAPTER 5 - Informed Consent

The Belmont Report provides Investigators with basic ethical principles for conducting research. The principle of "respect for persons" incorporates two ethical convictions. First, individuals should be treated as autonomous agents; and second, persons with diminished autonomy are entitled to additional protection.

An autonomous individual is capable of establishing personal goals and completing actions toward the goals. Others may respect an individual's autonomy by taking into consideration an individual's opinions and choices while refraining from obstructing their actions unless the actions are harmful to self or others. With respect to research participation, respect for autonomy is addressed by giving an individual a choice to enter research **voluntarily** after being presented with adequate information. This is the premise of informed consent.

For individuals who may have diminished autonomy either through age, maturity, or psychological state (e.g., children, cognitively/decisionally impaired), Investigators must assure that additional protections are in place (*e.g.,* permission from legally authorized representative). The federal regulations provide additional guidance on including participants with diminished autonomy.

The ethical principle of "respect for persons" is met through voluntary, informed consent.

Informed consent is a person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic or experimental procedure. Informed consent is a process and is essential for studies involving humans. Participants need to understand why the research is being pursued, the procedures and time commitments involved, and the potential risks and benefits associated with the research.

It is the responsibility of the Investigator to assure that consent is obtained by personnel knowledgeable about the study who are able to respond to questions by the study participant. Investigators must obtain legally effective informed consent from each participant or from the participant's legally authorized representative prior to his or her participation in the research, unless this requirement has been waived by the IRB. The Investigator is also responsible for assuring that the consent document is signed and dated, at the time consent is given, by the participant or his or her legally authorized representative. Consent must be obtained before commencing any screening activities, including those that are to be done solely for purposes of determining a prospective participant's eligibility to be included in the research. Unless waived by the IRB, participants must document their consent by signing a written consent document.

Legally authorized representative - An individual, judicial, or other body authorized under applicable law to grant permission on behalf of a prospective participant for their participation in research (e.g., a court appointed guardian or conservator, a Durable Power of Attorney for Health Care (DPAHC) or a Health Care Decision Maker.

An Investigator must seek consent only under circumstances that provide the prospective participant, or his or her legally authorized representative, sufficient opportunity to consider whether to participate and to minimize the possibility of coercion or undue influence.

The IRB must approve all consent documents, assent forms, and scripts. If these forms need to be changed for any reason, the changes must be approved by the IRB prior to use of the revised consent document(s).

Requirements for Informed Consent

Informed consent must begin with a concise and focused presentation of key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. In particular, a brief explanation of:

- What will happen during the course of the study and the duration;
- A summary of risks and discomforts;
- Any reasonable benefits; and
- Any alternatives.

The federal regulations provides the specific elements of consent required for obtaining legally effective informed consent (46.116). These are required, unless a waiver or an alteration of the informed consent process is granted by the IRB. In addition, there additional elements that may be required when applicable. Each of the additional elements should be evaluated for applicability to the study information and relevance to the decision by the participant to enroll.

Elements of Informed Consent

The required elements are as follows:

- 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 investigational;
  - This requirement will encompass the bulk of the information to be communicated to the potential participant. It must be clear to the participant that this is research and he or she should know the purpose of the study (*e.g.,* why are they being asked to participate).

- This section of the consent document should also include all of the procedures to be completed and the time commitment expected. For studies in which the commitment is lengthy and multiple procedures are part of a complex research design, it is helpful to include a table or chart clearly outlining the expectations. Describe the study activities in a clear sequence of events and indicate which activities are routine or standard of care versus those that are investigational in nature. Additionally, include a description of any screening activities that will be done solely to determine the participant's eligibility for enrollment into the study. Questionnaires, assessment scales, surveys, interviews, or other study tools should be described, and sample questions provided if possible.
- Audio or Videotaping - If the study involves audio or videotaping, explain what will happen to the tapes after the study is completed or if a participant withdraws before completion.
- If a student is conducting the research, this information should be included in the consent (*e.g.,* thesis, dissertation).

- A description of any reasonably foreseeable risks or discomforts to the subject;
  - It is best to organize this section by those risks that are "common", "uncommon" and "rare" and define the terms (e.g., greater than equal to 10%, less than 10%, etc.). Of these risks, specify which are potentially life-threatening or severe.
  - For studies involving minimal risk procedures or activities, potential risks may include the inconvenience for participation, psychological distress (even after participation), or physical discomfort, (*e.g.,* frequent visits, time commitment, answering questionnaires, uncomfortable procedures). It is also applicable to discuss any risks due to a possible loss of confidentiality.
  - The IRB recognizes that some model consents for multi-center trials will have the risks and discomforts detailed in a format that differs from the preferred format. In these cases, the IRB will make requests for changes that increase readability and understandability for the participant or recommendations based on the expertise of the ex-officio Pharmacist.

- An adequate description of any benefits to the subject or others that may reasonably be expected from the research;
  - This description should include any potential for benefit to the participant, to humankind and/or to the research community for generalizable knowledge.
  - Payments made to participants as compensation for their time may ***not*** be included as a benefit.

- 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;
  - An explanation should be given about who will have access to the data, where the data will be kept, for how long and whether the data, if retained, will be used for further research purposes and/or shared with other researchers for additional studies.
  - If the retained data are to be used for further research and/or data are to be shared with other researchers for additional or other research purposes, participants should also be told whether identifiers will also be used or shared.
  - The consent form must describe the disposition of video and audiotapes taken of the subject. A statement should be included in the consent form as to whether the research data will become part of a permanent record for the participant (*e.g.,* medical record).
  - When applicable, explain any foreseeable circumstances, under which the Investigator will be required to give information about the subject to third parties, (e.g., mandatory reporting of child abuse).
  - The IRB provides Investigators with template language for confidentiality.
  - There are additional requirements for studies involving the use or disclosure of Protected Health Information (PHI). This issue is addressed in Chapter 11 of this handbook.

- For research involving more than minimal risk, an explanation as to whether any compensation and/or whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
  - Typically it is the Investigator or a key study personnel serving as a contact person, who is listed on the consent document for contact concerning questions regarding the research or injuries.
  - The IRB office number and toll-free number should be listed as whom to contact for questions regarding the participant's rights. The informed consent document template includes standard language that will meet this requirement.

- A statement that participation is voluntary, that refusal to participate at anytime will involve no penalty or loss of benefits to which the subject is otherwise entitled.

- The informed consent document template contains language indicating the right to withdraw or refuse to participate without prejudicing the participant's health care.
- Examples of such statements might also include phrases that withdrawal or refusal to participate will not affect the participant's grades and class standing (for students or trainees), status on the team (for athletes), or job standing (for employees or subordinates).

- One of the following statements about research that involves the collection of identifiable private information or identifiable biospecimens:
  - A statement that identifiers may 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 participant or their legally authorized representative, if applicable; or
  - A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future studies.

Additional Elements of Informed Consent - Required When Appropriate

As an Investigator and the IRB considers pertinent study related information that should be shared with the potential participant to aid in the decision to participate, the following additional elements of informed consent should be considered for applicability.

- For women of child-bearing potential, a statement that a particular procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
  - When a study is greater than minimal risk and the effects of the procedure may be uncertain, a statement indicating that there may be risks to the participant which may be unforeseen must be included.
  - Template language is available within the informed consent document template.

- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent;
  - An Investigator may need to withdraw a participant for not following the research procedures or if a participant's safety is involved.
  - There may be other situations in which a participant would be withdrawn by the Investigator. These situations should be described for the potential participant to assist in understanding all that will be expected in order to be enrolled.

- Dissenting behaviors (e.g., refusing to cooperate, crying) should be listed for studies involving children.

- Any additional costs to the subject that may result from participation in the research;
  - Should there be study related procedures that will be the financial responsibility of the participant (*e.g.,* transportation, hotel), this needs to be included.
  - If there are procedures that will be billed to a participant's health insurance, and the participant is responsible for any co-pay, deductible or partial payment, this should also be included.

- Any consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
  - Specific procedures that need to be followed in order for a participant to withdraw (*e.g.,* contacting the PI or key study personnel) should be stated in the informed consent document.

- 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; and
  - As new information is gathered regarding the research, it is sometimes necessary to inform participants of relevant findings that may impact their willingness to participate. When this occurs, it may be necessary to consent the participants again with the new information.
  - The informed consent document template includes language meeting this additional requirement.

- The approximate number of subjects involved in the study.
  - In evaluating the risks, a potential participant may make a different decision as to whether to enroll if they know that they are 1 of 10 participants versus being 1 of 10,000.
  - When this is required, the IRB typically asks that the participants be informed as to how many will be enrolled at Vanderbilt and how many will be enrolled nationwide, if this is a multi-site study.

- When applicable, the following should be included: A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

- A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in this commercial profit.

- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.

- 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).

- Study treatment(s) and the probability of random assignment to placebo or to each treatment.

  · The IRB may require that information, in addition to that required in federal regulations, be given to research participants when in its judgment the information would meaningfully add to the protection of the rights and welfare of participants.

Exculpatory Language Prohibited!

Informed consent documents may not contain any exculpatory language through which the participant is made to waive or appear to waive any of his or her legal rights, or release or appear to release the Investigator, the sponsor, the University, or its agents from liability for negligence. For example, "I waive any possibility of compensation for injuries that I may receive as a result of participation in this research," is an unacceptable statement to include in a consent document.

Posting of Clinical Trial Consent Forms:

For federally funded clinical trials, one IRB approved consent form used to enroll subjects must be posted on www.clinicaltrials.gov, no later than 60 days after the last study visit of any subject.

Clinical Trials are defined as **"**Research studies in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the

effects of the intervention on **biomedical or behavioral** health-related outcomes."

AUTHORIZATION

HIPAA Alert

There are additional requirements to be included in an informed consent document for studies involving the use or disclosure of Protected Health Information (PHI).

Authorization: A customized document, usually as a part of the informed consent document, that gives Vanderbilt University Medical Center (VUMC) permission to use specified protected health information (PHI) for a specific purpose, or to disclose PHI to a third party specified by the individual.

Protected Health Information (PHI): Individually identifiable health information that is or has been collected or maintained by the covered entity, including information that is collected for research purposes only, and can be linked back to the individual participant.

A legally effective authorization must include the following:

- A specific and meaningful description of the information to be used or disclosed;
- The name or identification of the persons or class of persons authorized to make or receive disclosures of PHI and to use the PHI for research-related purposes;
- An expiration date or event, or a statement such as "end of research study" or "none" when appropriate (e.g., for a research database);
- A statement that the individual may revoke the authorization if requested in writing to the Principal Investigator. However, the Investigator may continue to use and disclose, for research integrity and reporting purposes, any PHI collected from the individual, pursuant to such authorization before it was revoked;
- A statement that an individual's clinical treatment may not be conditioned upon whether the individual signs the research authorization;
- A statement that information disclosed under the authorization could potentially be re-disclosed by the recipient and would no longer be protected under HIPAA; and
- The individual's signature (or that of his or her legally authorized representative) and date.

For more information regarding the HIPAA regulations, please see Chapter 11 of this handbook.

Format and Style of Informed Consent Documents

- Standard Consent Document
  The IRB encourages Investigators to use either the standard consent form template, which is available on the HRPP website at http://www.vumc.org/irb, or the sponsor's provided document as long as:
  - All required elements and pertinent additional elements are present; and
  - VU and VUMC's local information is included in the document (i.e., subject injury information, authorization information, and any local context information that is relevant to that study).

- Consent forms/letters should be written in **lay language**, at a level understandable to the participants in the study (6th to 8th grade reading level for adult participants). For non-English speaking participants, see the section on **Oral Presentation using a Short Form** below.

- The use of a 12-point **font** is recommended. A larger type size may be appropriate for some populations, such as, children, the elderly, or the visually impaired.

- Documents must be **typewritten**.

- All consent forms must identify the **subject population**, for which the consent form is intended, (*e.g.,* adults, parents-legal guardians, surrogates).

- The consent forms must be written in **second person** (*e.g.,* you will be asked to. . .) which may help convey that there is a choice to be made by the participant.

- A place for the **participant's signature and date** must appear on the consent document. There may be situations in which a witness' signature is required.

- A place for the **person obtaining consent's signature and date** must appear on the consent document.

- The consent document should include a statement telling the participant that he or she will receive a **copy** of the consent form.

- When applicable, the document should state that the research is being conducted to fulfill a requirement for a **doctoral dissertation**, **master's thesis** or **classroom assignment**.

- The consent form should identify any **external sponsor** or **funding agency**.

Consider the age of the participant and cognitive abilities

Assent is required from children who participate in research. The assent form should take into consideration the age, maturity and psychological state of the child. The IRB recommends that the forms be grouped as follows:

- Assent script for children under 7 years;
- Assent form for children 7 – 12 years; and
- Assent form for children 13 – 17 years.

ASSENT - Agreement by an individual not competent to give legally valid informed consent (*e.g.,* a child or cognitively impaired person) to participate in research.

Children ages 13 – 17 years may sign a form with language similar to that presented to the parents or legal guardians. However, it is preferable for the child's form to be simplified in age appropriate language. Often times the parent consent form will need additional information that may not be pertinent to the child regarding the decision to participate.

IRB Approval and Expiration Dates on Consent Documents

The IRB will affix the approval date and expiration dates (when applicable) on all approved informed consent documents. Copies of the current, dated documents are the only versions that may be used by Investigators in obtaining consent. This procedure helps assure that only the current, IRB-approved informed consent documents are presented to participants and serves as a reminder to the Investigators of the need for continuing review.

Each participant or his or her legally authorized representative must sign and date a copy of the current IRB-approved consent form prior to enrollment or any participation in any phase of the study, unless the requirement is waived by the IRB.

"Deferred Consent" or "Ratification" Not Permitted

Informed consent procedures, which provide for other than legally authorized and prospectively obtained consent, fail to constitute informed consent under federal regulations for the protection of human subjects in research. Therefore, waiving informed consent using a method other than those described in this policy is a violation of HRPP policy and federal regulations and is subject to reporting to the appropriate federal, state, and Institutional Officials.

Waiver or Alterations Regarding Informed Consent

There are two types of "waivers" to consider when making a request to the IRB.

Process waiver – under this approval, the Investigator would not obtain informed consent from the participant. There would not be an informed consent document reviewed and approved by the IRB. However, research must meet certain conditions to be granted the waiver, which is described below.

- ☑ Example: An Investigator wishes to review existing data and record identifiable information from a dataset for the purpose of analysis. However, the information has been collected several years ago and the likelihood of being able to contact the participants is not practicable. The information to be recorded would not place them at risk should there be a breach in confidentiality. This type of research, may meet the acceptable conditions in which a **process** waiver may be granted.

Documentation waiver – under this approval, informed consent is obtained. However, the requirement to obtain a *signature* from the participant is waived. Again, there are specific conditions that must be met which are described below.

- ☑ Example: An Investigator wishes to conduct a phone interview regarding the participant's satisfaction with a newly implemented process in his or her clinic. The Investigator would present the IRB with a script containing all of the required elements of informed consent for review and approval. However, there would be no signature obtained.

Waiver or Alteration of the Consent Process

There are circumstances under which the federal regulations give the IRB the authority to waive or alter the required informed consent **process** (46.116).

☞ Waiver for Research Activities Designed to Study Certain Aspects of Public Benefit or Service Programs

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waive the requirement to obtain informed consent entirely provided the IRB finds and documents that:

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

3. possible changes in or alternatives to those programs or procedures; or
4. possible changes in methods or levels of payment for benefits or services under those programs; AND

- the research could not practicably be carried out without the waiver or alteration.

Waiver for Minimal Risk Studies

Additionally, the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent entirely provided the IRB finds and documents that:

- the research involves no more than minimal risk to the subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; **and**
- whenever appropriate, the subjects will be provided with additional pertinent information after participation. Or, the IRB may waive the documentation of consent for some of all of the participants if the research involves no more than minimal risk and written consent would normally not be required outside of the research context.

HIPAA Alert

When the IRB grants a waiver or alteration to the consent process, they may also waive the requirement to obtain HIPAA authorization for the use and disclosure of protected health information. In these situations, the Investigator must still track any disclosures of PHI shared outside of the covered entity (*See* Chapter 12 for more information).

Documentation of Consent Process

The IRB may waive the requirement for the Investigator to obtain a signed consent form for some or all participants if the IRB finds either:

- That the **only record linking the subject and the research** would be the consent document and the **principal risk would be potential harm resulting from a breach of confidentiality**;

<u>Note</u>: If the IRB waives the requirement for documentation under this condition, each subject must be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

<u>or</u>

- That 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.**

In cases in which the documentation requirement is waived, the IRB may require the Investigator to provide participants with a written statement regarding the research.

Use of Mail or Facsimile to Document Informed Consent

The IRB may approve a process that allows for the informed consent document to be sent by mail or facsimile to the potential participant or his or her legally authorized representative and to conduct the consent interview by telephone when the participant or his or her legally authorized representative can read the consent document as it is discussed. All consent processes, including conditions for a waiver or alteration of documentation of informed consent must be approved prior to the procedure being implemented. Currently, consent documents should not be e-mailed back to the study team. The signed document contains potential PHI and should be provided back to the study team via a secure method (e.g., a secure file sharing system or electronically through an application such as RedCap).

Oral Presentation Using Short Form

This method is sometimes used when recruiting **non-English speaking** participants but may be considered when recruiting participants who may have an extremely low literacy level.

Participants who do not speak English should be presented with a consent document written in their native language. This is preferred. However, the federal regulations have a provision which permits the oral presentation of informed consent information in conjunction with a **short form** written in the participant's native language (46.117(b)(2)). A short form must include all of the elements of consent and state that they have been presented orally. A **written summary** of what is presented orally, which may be a copy of the English informed consent document, must also be given to the participant.

 **A witness to the oral presentation is required.**

When this procedure is used with participants, who do not speak English,

- the **oral presentation** (*e.g.,* information provided through a translator) **and**

the **short form** written document should be in a language understandable to the participant;
- the IRB-approved English language informed consent document may serve as the **summary**; and
- the witness should be fluent in both English and the language of the participant.

At the time of consent,
- the **short form** document should be signed by the participant or his or her legally authorized representative;
- the **summary** (*e.g.,* the English language informed consent document) should be signed by the person obtaining consent as authorized under the research protocol; and
- the **short form** document and the **summary** should be signed by the witness. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

The IRB must review and approve all foreign language versions of the **short form** document prior to implementation. For studies requiring full Committee review, expedited review procedures may be followed for these versions if the research protocol, the full English language informed consent document, and the English version of the **short form** document have already been approved by the IRB Committee at a convened meeting.

The Use of a Healthcare Decision-Maker for Research

Investigators may utilize a healthcare decision-maker to obtain legally effective informed consent if the adult potential participant lacks decision-making capability or is likely throughout the course of the research to become cognitively impaired or incompetent.

Healthcare Decision-Maker – In the case of an incompetent individual, or an individual who lacks decision-making capacity, the individual's healthcare decision-maker is designated in order of preference as one of the following: the individual's court-appointed legal guardian or conservator with healthcare decision-making authority (*e.g.,* durable power of attorney, or DPA); the individual's healthcare agent as specified in an advance directive; or the individual's healthcare decision-maker.

Submission to the IRB

The Investigator must indicate on the IRB application that the protocol will utilize surrogate consent and submit the surrogate consent rider along with the IRB informed consent document. If the Investigator later decides to utilize surrogate consent, an amendment must be submitted to the IRB requesting the use of the surrogate consent along with a revised informed consent document that incorporates the surrogate rider.

Identifying the Appropriate Health Care Decision-Maker (HCDM)

The HCDM identified on behalf of an individual who is deemed by a court to be incompetent or who lacks decision-making capability and does not have a valid durable power of attorney for healthcare or a court appointed guardian or conservator (legally authorized representative), should be an adult who has exhibited special care and concern for the individual, who is familiar with the individual's personal values, and who is reasonably available.

Consideration shall be given to the following in order of descending preference for service as a surrogate:

- The individual's spouse;
- The individual's adult child;
- The individual's parent;
- The individual's adult sibling;
- Any other adult relative of the individual;
- Any other adult who satisfies the description above; or
- If none of the above individuals are eligible, the individual's treating physician.

The IRB Committee may request at its discretion the use of an Ombudsman or participant advocate to provide additional protections, when appropriate.

The individual's physician, when acting as a surrogate healthcare decision-maker, must follow specific requirements and documentation for acting on behalf of an incompetent or decisionally impaired individual including consulting with the Clinical Ethics Consultation Service and/or an independent physician, who must document the appropriateness of the enrollment of the participant in the study.

Additional Considerations for Informed Consent

Certificates of Confidentiality

When additional protections are needed for the collection of sensitive data, the IRB Committee may request, or the Investigator may choose, that a Certificate of Confidentiality be obtained. The presence of such a certificate should be described in the informed consent document. Effective October 1, 2017, any NIH funded research is automatically issued a Certificate of Confidentiality.

Certificates of Confidentiality protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations.

Is my research covered by a Certificate of Confidentiality?

To determine if a Certificate of Confidentiality applies to research conducted or supported by NIH, investigators will need to ask, and answer the following question:

- Is the activity biomedical, behavioral, clinical, or other research?

If the answer to this question is no, then the activity is not issued a Certificate. If the answer is yes, then investigators will need to answer the following questions:

- Does the research involve Human Subjects as defined by 45 CFR Part 46?
- Is the research operating under an exemption from 45 CFR 46?
- Are you collecting or using biospecimens that are identifiable to an individual as part of the research?
- If collecting or using de-identified biospecimens as part of the research, is there 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?
- Does the research involve the generation or use of individual level, human genomic data?
- Does the research involve information about individuals where there is a very small risk (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 the individual?

If the answer to any one of these questions is yes, a Certificate of Confidentiality applies to your research.

What does having a Certificate of Confidentiality (CoC) mean?

Researchers with a Certificate of Confidentiality may ONLY disclose identifiable, sensitive information in the following circumstances:

- if required by other Federal, State, or local laws, such as for reporting of communicable diseases (but not in legal proceedings)
- if the subject consents; or
- for the purposes of scientific research that is compliant with human subjects regulations.

AND you must ensure that anyone who is conducting research as a sub-awardee or receives a copy of identifiable sensitive information protected by the policy

understand they are they are also subject to the disclosure restrictions, even if they are not funded directly by NIH.

Identifiable sensitive information means information that identifies an individual or if there is a very small risk that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of the individual.

Any investigator or institution issued a Certificate shall not:

- Disclose or provide identifiable sensitive information, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding; or
- Disclose or provide identifiable sensitive information to any other person not connected with the research.

Surgical or Medical Consent In Lieu of Research Consent

On occasion, the IRB will permit the Investigator to use a standard surgical or medical treatment consent document in lieu of a specific research consent document. However, the standard surgical consent document must include all required elements of consent, including the purpose of the research and must be approved by the IRB. Reliance on such documents for research generally requires formal waiver of consent requirements in accordance with federal regulations and HRPP policy

CHAPTER 6 - Continuing Review

Except for research determined to be exempt from IRB review and most expedited research, the federal regulations require periodic review of all research involving humans at an interval appropriate to the level of risk, **but not less than annually** (46.109(e)).

OHRP has provided IRBs with additional guidance on continuing reviews of research involving humans which is summarized in this chapter.

Substantive and Meaningful

It is important to understand that the IRB must review the study under the same approval criteria as the initial review of the study (46.111).

- Risks to subjects are *minimized* . . .
- Risks to subjects are *reasonable* in relation to anticipated benefits . . .
- Selection of subjects is *equitable*.
- *Informed consent* will be sought . . .
- Informed consent will be appropriately *documented* . . .
- When appropriate . . . adequate provision for *monitoring* the data. . .
- When appropriate . . . adequate provisions to protect the *privacy and confidentiality*. . .

When conducting a review of the research at a convened IRB meeting, each Committee Member must be provided with the following information:

- The **number of participants** accrued;
- A summary of **adverse events** and any **unanticipated problems** involving risks to participants or others and any withdrawal of participants from the research or **complaints** about the research since the last IRB review;
- A summary of any relevant **recent literature**, **interim findings**, and **amendments** or modifications to the research since the last review;
- Any **other relevant information**, especially information about risks associated with the research; and
- A copy of the **current informed consent document**.

Continuing review is necessary to determine whether the risk/benefit ratio has changed, whether there are unanticipated findings involving risks to participants, and whether any new information regarding the risks and benefits should be provided to participants.
Based on its review, the IRB Committee may require that the research be restricted, modified or halted altogether. Alternatively, special precautions or IRB imposed restrictions may be relaxed. The IRB will determine that the frequency and extent of

continuing review for each study is adequate to assure the continued protection of the rights and welfare of research participants.

Continuing Review of Greater Than Minimal Risk Studies Criteria

Continuing review of a study must be reviewed at the same level as the initial review and approval. However, under certain conditions, a study initially reviewed and approved at a convened IRB Committee meeting may subsequently be reviewed through expedited procedures. The Federal regulations provide the specific categories in which these studies may be reviewed using the expedited review procedure (expedited guidance).

Under category 46.110(F)(8), an expedited review procedure may be used for the **continuing review** of research previously approved by the convened IRB as follows:

- ☒ the research is permanently closed to the enrollment of new subjects;

OR

- ☒ no subjects have been enrolled; and
- ☒ no additional risks have been identified.

Under category 46.110(F)(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 expedited categories (2) through (8) do not apply (*See* Chapter 4), 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 Committee. However, the IRB Reviewer may be unable to determine if new risks are present and may refer the study to the full Committee.

Research Closed to Accrual of New Subjects Still Requires Continuing Review

A research protocol for which no new subjects will be enrolled must be periodically reviewed until such time as:

- ☒ all participants have completed research interventions.

The IRB, not the Investigator, must determine that these conditions have been met before continuing review may cease.

Materials to be Submitted at Continuing Review

Investigators must submit at the time of continuing review:

- ☑ A complete continuing review application, signed and dated by the Investigator, to include a summary of the study activities completed since the last continuing review;
- ☑ The most recently approved consent form(s);
- ☑ IRB approvals or letters of cooperation from other sites;
- ☑ Publications describing this research;
- ☑ A narrative summary of all adverse events or unanticipated problems for the past year;
- ☑ If proposing changes to any of the IRB approved documents (e.g., informed consent document, protocol, application, etc.), a *Request for Amendment* should be included with the modified (tracked changes) consent form(s) or study instruments.

Use of the Single IRB (SIRB) Model

Vanderbilt Serving as a Single IRB:

The Lead Study Team or Coordinating Center must submit at the time of continuing review for each relying site:

- ☑ Continuing Review or Study Closure Application completed in DISCOVR-e (Lead Site Information)
- ☑ Currently approved Part 1 ICD in Word format – clean for date stamping (when applicable)
- ☑ Currently approved Part 2 ICDs in Word format – clean for date stamping (when applicable)
- ☑ Currently approved Assent Forms in Word format – clean for date stamping (when applicable)
- ☑ Progress Report

Vanderbilt Relying on Another IRB

VUMC requires reporting of enrollment numbers to document participant accrual for research studies which will be provided via a continuing review submission. Information should be reviewed and approved by the IRB of record (when applicable) before the local submission is provided in DISCOVR-e. The local submission should occur within 30 days of receipt of CR approval from the IRB of Record or per the update notification that is sent to the Investigator from DISCOVR-e.

Submission documents needed to conduct the review:

- IRB approval letter for the Annual review

Documents submitted to the IRB of record for review that are applicable to Vanderbilt

Determining the Continuing Review Date – Full Committee Reviews

For studies that are reviewed and approved at a convened IRB Committee meeting, and the determination is made that the review period will be not less than annually, the date of expiration will be one year from the date of the convened meeting.

Example - Approved: The IRB reviews and approves a protocol without any modifications at its meeting on July 1, 2020. Continuing review must occur within one year minus one day of the date of the meeting and be reviewed and approved by June 30, 2021.

Example - Approved Pending Modifications: The IRB reviews a protocol at a convened meeting on July 1, 2020, and approves the protocol pending review and approval of specific minor modifications to be verified by the IRB Chairperson or designated Committee Member. On August 3, 2020, the IRB Chairperson or designated Committee Member confirms that the required minor changes were made. The approval date is August 3, 2020 and the continuing review date (date of expiration) is June 30, 2021.

Example - Deferred: The IRB reviews a study at a convened meeting on July 1, 2020 and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on July 8, and July 22, 2020. At its July 22, 2020 meeting, the IRB completes its review and approves the study. Continuing review must occur within one year minus one day of the date of the July 22, 2020, convened meeting. The expiration date is July 21, 2021.

Example - More Frequent Reviews Necessary: The IRB reviews and approves a study at its convened meeting on July 1, 2020 but determines that the continuing review must be in 6 months minus one day due to the level of risk. Therefore, the expiration date or date of continuing review would be December 31, 2020.

Determining the Continuing Review Date – "30 Day Rule"

There are no provisions for any grace period for approval beyond the IRB expiration date. However, studies reviewed within 30 days of the expiration, may retain the anniversary date as the date by which the continuing review must occur.

Example: The IRB reviews and approves the study on July 1, 2014. If the Investigator submits the continuing review application in time for it to be reviewed

and approved no greater than 30 days prior to the expiration date, the July 1, 2015 date will serve as the approval date and the expiration date will be July 1, 2016.

- Initial Approval – July 1, 2014
- Received in IRB for continuing review – June 2, 2015 and Approved – June 5, 2015
- Retain anniversary date of approval – July 1, 2015
- Expiration date (date of next continuing review) – July 1, 2016.

Date Stamping of Informed Consent Documents

Upon review and approval of the informed consent documents, the IRB will affix the appropriate approval and expiration dates to the forms and send the originals to the Investigator. As with the initial approval, these date-stamped consent documents must be used when obtaining consent from participants.

Important Information to Consider with Continuing Review

No Grace Period

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. If the IRB does not re-approve the research by the specified expiration date, all activities must cease pending re-approval of the research by the IRB. Only in situations in which there is a possibility of harm to participants, if study related treatment or intervention is halted, is the Investigator allowed to continue the study with the currently enrolled participants, during which time the Investigator must be pursuing IRB renewal and must provide a justification to the IRB for the continuation of treatment.

Deadlines

Compliance with IRB deadlines regarding continuing review are the Investigator's responsibility. However, as a courtesy, Investigators will be notified by the IRB eight (8) weeks and again at four (4) weeks, prior to expiration of their IRB approval. An application for continuing review must be received in the IRB Office allowing adequate time for review and approval prior to the expiration date. The IRB recommends that Investigators submit continuing review applications four (4) weeks prior to the expiration date.

CHAPTER 7 - Amendments

The IRB Must Approve All Modifications to the Research Activities and Applications Prior to Implementation.

The IRB recognizes that research is a continuous process and that changes in the conduct of a study and/or changes to the consent document are necessary. However, any amendment to a research protocol, informed consent document(s), or any aspect of the research must be approved by the IRB prior to implementation.

Investigators must submit the rationale for the changes and the exact text of an amendment or other revision to the application and any proposed changes to the informed consent document to the IRB.

Modifications to the informed consent document must take into account both prospective research participants and, when applicable, the participants currently enrolled in the study. The latter may be addressed by re-consenting currently enrolled participants using the modified informed consent document.

Minor Changes May Be Eligible for Expedited Review

Minor changes proposed for previously approved research may be reviewed using the expedited review procedure. A minor modification is defined as a change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study.

Examples of minor modifications may include:

- ☑ The addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol;
- ☑ An increase or decrease in proposed human research subject enrollment as long as the change does not affect the overall design of the study;
- ☑ Narrowing the range of **inclusion** criteria;
- ☑ Broadening the range of **exclusion** criteria;
- ☑ An increase in the number of study visits for the purpose of increased protection of participants;
- ☑ A decrease in the number of study visits, provided that such a decrease does not affect the collection of information related to the assessment of participant protections;
- ☑ Alterations in participant payment or liberalization of the payment schedule with proper justification;

- ☑ Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement;
- ☑ The addition or deletion of qualified Investigators;
- ☑ The addition of study sites or the deletion of study sites; or
- ☑ Minor changes specifically requested by other Institutional Committees with jurisdiction over the research.

Changes That Are More Than Minor are Reviewed by the IRB Committee

When a proposed change in a greater than minimal risk research study is not minor, the IRB Committee must review and approve changes at a convened meeting before implementation. A major modification is defined as any change which materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study.

Examples of major modifications may include:

- ☑ Broadening the range of **inclusion** criteria;
- ☑ Narrowing the range of **exclusion** criteria;
- ☑ Extending substantially the duration of intervention;
- ☑ The deletion of monitoring procedures or study visits directed at the collection of information for participant protection evaluations;
- ☑ The addition of serious unexpected adverse events or other significant risks to the informed consent document; or
- ☑ Changes which, in the opinion of the IRB Chairperson or designed Committee Member, do not meet the criteria or intent of a minor modification.

Use of the Single IRB Model:

Vanderbilt Serving as the single IRB:

Amendments to Single IRB studies are considered either study-wide (global) or site-specific.

Global amendments affect the study in its entirety, such as changes to the protocol, and apply to all participating sites. This amendment type should be submitted as a single submission for all sites.

Site-specific amendments are changes made at an individual site (or sites), such as a PI or study coordinator change. Site-specific amendments are submitted as single submissions for each site unless the change is exactly the same for all sites in which case, a single submission for multiple sites is preferred.

Study-wide (Global) Amendments: modifications to documents that may pertain to the conduct of the study at all sites

Site-Specific Amendments: modifications to documents that pertain to specific site(s) and not the overall study.

Vanderbilt relying on Another IRB:

Modifications that impact Vanderbilt should be submitted for local record-keeping and appropriate documentation via an amendment submission. Affected IRB-approved study documents are reviewed and approved by the IRB of Record BEFORE local submission in DISCOVRe.

Submission documents needed to conduct the review, when applicable:

- IRB approval letter for the modifications
- Affected documents that were reviewed and approved by the IRB of record

Amendments to Exempt Research

Any changes that are made to the approved *Request for Exemption* within the first year of approval must be submitted for review by the IRB prior to implementation. Amendments will be accepted up to one year from the date of approval. Modifications made after the first year of approval require a new application. Some modifications to the research may change the review status and require the Investigator to submit an application for expedited or full Committee review.

Materials to be Submitted for Review

Investigators should submit a *Request for Amendment* with all documents affected by the modifications (*e.g.,* informed consent documents, research protocol, etc.). The changes should be tracked and a "clean copy" of all revised documents must be provided for review.

Chapter 8 – Site Additions

Site Additions

A Site Addition is a submission type specifically designed for Single IRB studies to add relying sites after initial approval has been extended to the lead site. Site Additions are submitted after initial SIRB approval, and should include the following information PER RELYING SITE:

- Institutional Profile
- Human Research Protection (HRP) Survey
- Principal Investigator (PI) Survey
- Study-Specific Reliance Plan (SSRP)
- Part 2 ICD (when applicable)
- Site-specific Assent Form (when applicable)
- Stand-alone HIPAA forms (when applicable): these are accepted with the site's information, but are not approved/stamped by the
- VUMC SIRB

Site Additions are limited to 5 relying sites per submission.

Chapter 9 - Adverse Events or Unanticipated Problems, and Research Plan Deviations or Violations (Non-Compliance)

Investigator Responsibility Regarding Adverse Event/Unanticipated Problem Reporting

Prior to and at the time of IRB continuing review of an approved research study, it is the Investigator's responsibility to keep the IRB informed of any events or problems that were serious, unanticipated and resulted in a change to the risk/benefit ratio that may possibly be or are known to be related to the research activity. This includes events or problems occurring at a location for which the VUMC IRB is not the IRB of record.

Included in the IRB application, the Investigator must describe the research plan for monitoring the data to assure protection of participants, including the procedures for the reporting of adverse events and unanticipated problems to the IRB and other involved parties (*e.g.,* governmental officials, sponsor, funding agency), as appropriate. For studies determined to be greater than minimal risk, consideration should be given to having an independent data and safety monitor to periodically review the data for safety concerns.

Unanticipated Problem Involving Risk to Participants or Others

Any event that is unanticipated, serious and related to the research (*e.g.,* newly identified risk, loss of confidentiality, research protocol deviation possibly affecting the risk to the participant) constitutes an unanticipated problem which should be reported to the IRB. An undesirable or unintended risk to someone other than the participant as a result of the research intervention (*e.g.* family member upset about consent of participant) should also be reported to the IRB. Occasionally, research participants may become very upset because of the nature of the research questions or activities (*e.g.* sexual history, viewing of violent photographs) resulting in an unanticipated problem involving risk to the participants.

Serious Adverse Event or Problem

Investigators must report to the IRB any experience that suggests a significant hazard, contraindication, side effect or precaution and includes any experience that is a death, life-threatening occurrence, persistent or significant disability/incapacity, inpatient hospitalization or prolongation of existing hospitalization, a congenital anomaly/birth defect and/or any other experience that suggests a significant hazard, contraindication,

side effect or precaution that may require medical or surgical intervention to prevent one of these outcomes.

Materials to be Submitted for Review

When a reportable adverse event or unanticipated problem occurs, the Investigator should submit a *Report of Unanticipated Problems Involving Risk to Participants or Others* with any additional documentation. If this event requires a modification to the informed consent document, an amendment should also be submitted, which contains a copy of the revised consent form with the changes tracked and a "clean copy" for date stamping.

Research Plan (Protocol) Deviation or Violation (Non-Compliance)

Deviation: An incident involving noncompliance with the protocol, but one that typically does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the resultant data. Deviations may result from the action of the participant, Investigator, or staff.

Violation: Accidental or unintentional changes to the IRB approved protocol procedures without prior sponsor and IRB approval. Violations generally affect the subject's rights, safety, welfare, and/or the integrity of the resultant data.

It is the responsibility of the Investigator to follow the IRB approved research protocol. When modifications are necessary, an **amendment** should be submitted to the IRB for review and approval prior to implementation. As defined above, deviations need to be reported to the IRB in summary at the time of continuing review unless required by the study funding agency or sponsor. In such a case, the Investigator should submit a *Non-Compliance with the Protocol* submission. The deviation (non-compliance) will be reviewed using the expedited review procedure.

Non-compliances with the Protocol that increase risk or decrease benefit, affect the participant's rights, safety, welfare, and/or affect the integrity of the resultant data are to be reported to the IRB as a Report of Adverse Events and Unanticipated Problems Involving Risk to Participants or Others.

Authority to Terminate or Suspend Approval

The IRB has the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to participants or others. When an IRB Committee takes such action, it is required to provide a statement of reasons for the action and to promptly report this action to the Investigator, the HRPP Director, the

appropriate VU and/or VUMC officials, Office of Sponsored Programs and other appropriate regulatory authorities.

Use of the Single IRB Model:

Vanderbilt Serving as the single IRB:
As the SIRB, VUMC will be responsible for reviewing all Adverse Events and Protocol Deviations at all relying sites. Investigators should specify which site the event or deviation occurred at when submitting the sIRB for review.

Vanderbilt Relying on Another IRB:
Unanticipated problems/protocol deviations are reviewed and approved by the IRB of Record BEFORE local submission in DISCOVR-e. Please note that the IRB of Record may have differing reporting timelines and requirements for documentation.

Submission documents needed to conduct the review:

- IRB approval letter for the event/deviation.
- Any applicable documents that were reviewed and approved by the IRB of record.

CHAPTER 10 - Vulnerable Populations as Participants of Research

The Belmont Report addresses the concern of diminished autonomy and ethical consideration of the need for additional protections. This led to the inclusion of three subparts for vulnerable populations in the federal regulations that must be considered for research involving children; prisoners; and pregnant women, fetuses, and neonates. These are not to be considered as the only vulnerable populations. Cognitively and decisionally impaired individuals, the elderly, students, employees, etc., may all be considered vulnerable to coercion or undue influence. Investigators must include additional safeguards in the consent process and the study activities to protect the potential participant's rights and welfare.

Children (Subpart D)

Children - persons who have not attained the legal age for consent to treatments or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. In Tennessee, the legal age for consent is 18 years of age.

The special vulnerability of children makes consideration of involving them as research participants particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations apply for reviewing research involving children. The IRB may approve research involving children only if special provisions are met. The IRB must classify research involving children into one of four categories and document their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by the IRB Committee are based on degree of risk and benefit to individual subjects.

Most social and behavioral research falls within the approval category **#1** described below.

Four Categories of Research Involving Children

1 *Research not involving greater than minimal risk (45 CFR 46.404).*

When the IRB finds that no greater than minimal risk to children is presented, the IRB may approve the proposal only if the IRB finds that adequate provisions are made for soliciting the **assent** of the children and the **permission** of their parents or guardians.

2 *Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405).*

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the

individual child, or by a monitoring procedure that is likely to contribute to the child's well-being, the IRB may approve the research only if the IRB finds that:

- ☒ the risk is justified by the anticipated benefit to the children;
- ☒ the relation of the anticipated benefit to the risk is at least as favorable to the children as that presented by available alternative approaches; and
- ☒ adequate provisions are made for soliciting the **assent** of the children and **permission** of their parents or guardians, as set forth below.

3 *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 (45 CFR 46.406).*

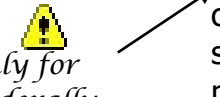
If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual child, or by a monitoring procedure which is not likely to contribute to the well-being of the child, the IRB may approve the research only if the IRB finds that:

- ☒ the risk represents a minor increase over minimal risk;
- ☒ intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- ☒ the intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition; and
- ☒ adequate provisions are made for soliciting **assent** of the children and **permission** of their parents or guardians, as set forth below (see 45 CFR 46.408).

4 *Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407).*

If the IRB does not believe the research proposal meets any of the requirements set forth above, it may still approve the application but only 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 children; and
- ☒ the Secretary of the Department of Health and Human Services, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  - that the research in fact satisfies one of the conditions set forth above, or
  - the following:



- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance 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 below.

Requirements for Permission by Parents or Legal Guardians (45 CFR 46.408)

The federal regulations have specific requirements for obtaining permission from parents or guardians that are based upon the category of approval. The Investigator must make adequate provisions for soliciting the permission of each child's parent(s) or legal guardian.

1 *Research not involving greater than minimal risk (45 CFR 46.404).*

Where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research not involving greater than minimal risk.

2 *Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405).*

Where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants.

3 *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 (45 CFR 46.406).*

Research approved under this category requires that permission be obtained from **both parents**, 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.

4 *Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407).*

Research approved under this category requires that permission be obtained from **both parents** 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.

Waiver of Parental or Legal Guardian Permission

If the research protocol is designed for conditions or for a participant population for which parent or legal guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), an Investigator may request that the IRB waive the consent requirements described above, provided that both conditions are met:

- ☑ an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and
- ☑ the waiver is not inconsistent with federal, state, or local law.

Note: The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the research plan, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Documentation

Permission by parents or guardians shall be documented in the same manner as required for other participants. When the IRB determines that assent of a child is required, it shall also determine whether documentation is required.

Assent by Children

Adequate Provisions for Child's Assent

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

The Investigator must make adequate provisions for soliciting the assent of a child participant when the children are capable of providing assent. In determining whether children are capable of assenting, the Investigator should take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular research protocol, or for each child. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition.

Waiver of Assent

The assent of children is not a necessary condition for proceeding with the research, if the IRB determines either of the following to be true:

- ☒ The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- ☒ The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

Child's Dissent

It is often appropriate to include a description of behaviors that will be indications to the Investigator that the child does not wish to participate (*e.g.,* crying, moving away from the Investigator, unwilling to complete tasks), therefore, not relying solely on the absence of objection.

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that a child's dissent, which should normally be respected, may be overruled by the child's parents or legal guardians.

Finally, even where the IRB determines that the children are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults (see 45 CFR 46.116 of Subpart A).

It is important to remember that under the conditions in which the child does not have a choice regarding participation, the Investigator should not speak with the child in such a manner to imply that they may choose not to participate (*e.g.,* we want you to . . ., is that OK?).

Children as Wards of the State or Other Agency

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under categories 45 CFR 46.404 and 405. However, they can only be included in research approved under categories 45 CFR 46.406 and 407, if it falls into one (1) of the two (2) categories below. Additionally, the research must be either:

- ☑ 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.

1 ***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.***

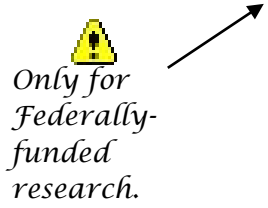
The IRB may approve research under this category only if the IRB finds that:

- ☒ the risk represents a minor increase over minimal risk;
- ☒ the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- ☒ 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
- ☒ adequate provisions are made for soliciting assent of the children and permission of their legal guardians.

2 ***Research which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of wards.***

The IRB may approve research under this category 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 wards; and
- ☒ the Secretary of the Department of Health and Human Services, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  - that the research in fact satisfies the condition set forth above, 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 wards;
    - the research will be conducted in accordance with sound ethical principles; and
    - adequate provisions are made for soliciting the assent of children and the permission of their guardians.



If the research is approved under this authority, the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the Investigator(s), or the guardian organization.

Pregnant Women, Fetuses and Neonates (Subpart B)

The six categories for research meeting exemption under 45 CFR 46.101 are applicable to Subpart B.

Research involving women who are or may become pregnant should receive special attention from Investigators because of a woman's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. Further, in the case of a pregnant woman, the Investigator must consider when the informed consent of the father is required. Special attention is justified because of the involvement of a third party (the fetus) who may be affected but cannot give consent and because of the need to prevent harm or injury to future members of society. Procedural protections beyond the basic requirements for protecting human research participants are prescribed in the federal regulations for research involving pregnant women.

Activities typically approved in most social and behavioral research do not involve interventions or procedures that have the potential to impact the fetus. When such potential exists, the research proposal should be submitted to a Health Sciences Committee to assure that special precautions are in place.

For more information, see Subpart B of the federal regulations.

Prisoners (Subpart C)

The special vulnerability of prisoners makes consideration of involving them as research participants particularly important. Prisoners may be under constraints because of their incarceration that could affect their ability to make a truly voluntary and un-coerced decision whether or not to participate as subjects in research. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations apply for reviewing research involving prisoners. The IRB may approve research involving prisoners only if these special provisions are met.

Prisoner – 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 which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing. Probation and parole are treated the same and are usually NOT considered as incarceration. Ankle bracelets/in home restrictions are considered as incarceration. Mental and substance abuse facilities are considered incarceration if someone is mandated to attend in lieu of jail or prison; however, an individual is such a facility is NOT considered if they voluntarily commit themselves.

For research involving prisoners, the definition of "minimal risk" differs from the definition of "minimal risk" in Subpart A of the federal regulations. The definition for

prisoners requires reference to physical or psychological harm, as opposed to harm or discomfort, to risks normally encountered in the daily lives, or routine medical, dental or psychological examination of healthy persons.

Minimal risk – (prisoners only) is defined as 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 examinations of healthy persons.

When a Participant Becomes a Prisoner During a Research Study

If a participant becomes a prisoner after enrollment in research, the Investigator is responsible for reporting in writing this situation to the IRB immediately. If the study was not previously reviewed and approved by the IRB in accordance with the requirements of Subpart C, all research interactions and interventions with, and obtaining identifiable private information must cease until the requirements of Subpart C are satisfied. This is necessary because it is unlikely that review of the research and the informed consent document contemplated the constraints imposed by the possible future incarceration of the participant. Upon its review, the IRB can either approve the continued involvement of the prisoner in the research in accordance with the federal regulations or determine that the participant must be withdrawn.

Specific Findings of IRB Required to Approve Research

When the IRB is reviewing a research project targeting the prison population or in which there is a high likelihood that a participant may become a prisoner (*e.g.,* study involving drug use/abuse), the IRB Committee must make **seven** findings as follows:

- *Research falls into certain category.*
  The research under review represents one of the following categories of research:
  - A 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 participants;
  - A 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 participants;
  - Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults); or
  - Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of

the subject.

- Research on epidemiologic studies and the sole purpose of the study is (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.

➢ *Any advantage of participation does not impact the prisoner's ability to weigh risks.*

- 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 Investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

➢ *The information is presented in language which is understandable to the subject population.*

➢ *Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole*; and

➢ *Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact*.

Permitted Research Involving Prisoners

For research conducted or supported by HHS to involve prisoners, two actions must occur:

- ✓ the IRB must certify to OHRP that it has reviewed and approved the research under the federal regulations; and

- ✓ OHRP must determine that the proposed research falls within one of the categories of permissible research described above. If an Investigator wishes to engage in non-HHS-supported research such certification is not required. However, the IRB will apply the standards of the federal regulations in reviewing the research.

Full Committee Review Required

The IRB Committee must review research involving prisoners as participants with a "prisoner representative" present at the meeting. Research that would otherwise be exempt from the requirement that it receive IRB approval is not exempt when the research involves prisoners.

Prisoners Who Are Minors

When a prisoner is also a minor (*e.g.,* an adolescent detained in a juvenile detention facility as a prisoner) the special protections regarding children in research will also apply.

Chapter 10 - Recruitment and Selection of Participants

General Guidelines

Recruitment and selection of participants must be **equitable** within the confines of the study. The Investigator may not arbitrarily exclude participants on the basis of gender, race, national origin, religion, creed, education, or socioeconomic status.

Equitable - fair or just; used in the context of selection of participants to indicate that the benefits and burdens of research are fairly distributed.

Economically Disadvantaged Participants

Investigators should consider added costs related to the research that might prevent participation by the economically disadvantaged. Justification for such cost must be fully explained in the IRB application.

Financial remuneration, reward, reimbursement for expenses, or other inducement for participation should not be so great as to be coercive to potential participants and should constitute reasonable compensation for the inconvenience of participating.

Recruitment Scripts

Prospective participants often have their first contact with a research coordinator or third party who follows a script to determine basic eligibility for the specific study. The IRB must review these procedures to assure that they adequately protect the rights and welfare of the prospective participants. The IRB must have assurance that any information collected about prospective participants will be appropriately handled.

Internet Recruitment

All advertisements and recruitment methods must be reviewed and approved by the IRB prior to implementation to assure that the information does not promise or imply a certainty of benefit beyond what is contained in the protocol and the informed consent document.

Students as Participants

The Investigator should exercise particular discretion when recruiting students as research participants. Specifically, the Investigator should assure that consent for

participation is sought only under circumstances that minimize the possibility of coercion or undue influence, and that genuinely equivalent alternatives to participation are available (*e.g.,* alternate research activities, appropriate length term papers).

Advertisements

Advertising and Recruitment Are Part of the Informed Consent Process!

Direct recruiting advertisements are viewed as part of the informed consent and subject selection process. When direct advertising is to be used, the IRB reviews the information contained in the advertisement and the mode of its communication to determine that the procedure for recruiting participants is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. This is especially critical when a study may involve participants who are likely to be vulnerable to undue influence.

The IRB must approve the final copy of all advertisements to include flyers that will be posted on bulletin boards or used as handouts, and broadcast on radio, television or through other venues (*e.g.,* mass email).

Content of Advertisements

Generally, advertisements to recruit participants should be limited to the information that prospective participants need to determine their eligibility and interest. When appropriately worded, the following items should be included in advertisements:

- name and address of the Investigator;
- purpose of the research;
- criteria to be used to determine eligibility in a summary form;
- location of the research (*e.g.,* Vanderbilt);
- a brief description of the study activities, when appropriate;
- potential benefits, if any; and
- name and phone number of the person to contact for further information.

Advertisements to be Taped for Broadcast

When advertisements are to be taped for broadcast, the IRB must review the final audio/video tape. The IRB can review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate content. The review of a taped message prepared from IRB approved text may be accomplished through expedited review procedures.

New Advertisements Introduced After IRB Approval

If an Investigator decides to begin advertising for participants after the study has received IRB approval, the advertising will be considered as an **amendment** to the ongoing study. When such advertisements are easily compared to the consent form, the Committee Chairperson can choose to review and approve the advertisement using expedited procedures. When the comparison is not obvious or other complicating issues are involved, the advertisement may receive Committee review.

Payments to Participants

Payment to research participants for participation in studies is not considered a benefit. Rather, it should be considered compensation for time and inconvenience or a recruitment incentive. The amount and schedule of all payments should be described in the IRB application at the time of initial review, including a summary of both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. Procedures for prorating payment should the participant withdraw should be considered when submitting the IRB application and informed consent documents.

Timing of Payments

Credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be paid at the time the study would have been completed had they not withdrawn. For example, in a study lasting only a few days, it may be permissible to allow a single payment date at the end of the study, even to participants who withdraw before completion.

Completion Bonus

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion is acceptable, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

Disclosure of Payments

All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document. Before using gift cards, please

check with your department concerning whether the institution deems them an acceptable method of payment. Also, if subjects are to be financially compensated, they need to be informed their social security number and address may be requested.

For a research study that involves compensation insert the following language:

"We may ask for your social security number and address before you are compensated for taking part in this study."

Advertisement of Payments

Advertisements may state that participants will be paid but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Alterations in Payments

Any alterations in human research participant payment or liberalization of the payment schedule must be reported to the IRB prior to implementation as an **amendment**.

Reporting Payments to the IRS

The Internal Revenue Service (the IRS) requires that VU or VUMC (or whomever is paying the participants for their participation) report payments in excess of $600 per calendar year on Form 1099-Misc. The filing of these forms necessitates the name and social security number of the participant be collected on a Form W-9 and released to the Office of Accounting to process the Form 1099-Misc. The collection and release of this information must be addressed thoroughly in the informed consent document so that it is clear to the participant that his or her identity will be released for the purpose of payment and reporting.

For a research study that involves a reimbursement amount of $600 or greater in a year, insert the following language:

"This reimbursement may be considered taxable and may be reported to the Internal Revenue Service."

Chapter 12 - Additional Considerations

Umbrella Reviews

Investigators may receive a grant to begin a large research project that will involve multiple sub-studies or a training grant, both of which are expected to involve human participants. The IRB has a *Request for Umbrella* to grant an administrative approval to allow for the overall concept of the research to be approved and therefore, release the funds to establish the sub-studies. This approval does not extend to the sub-studies involved, each of which must be submitted as a separate IRB application under the appropriate level of review (*e.g.,* exempt, expedited, full Committee). Umbrella reviews require continuing review no less than annually.

Repositories

The IRB has established a mechanism in which an Investigator may create a specimen/data repository for the purpose of storing large banks of specimens/data for future research. An Investigator may have specimens/data that was previously collected for non-research purposes in which he or she would like to analyze for research. This is a separate application process for review and requires ongoing continuing review by the IRB. An Investigator should submit the *Standard/Expedited Application*. Most repository applications may be reviewed following expedited procedures. However, should the storage of such data present a risk to participants (*e.g.,* breach of confidentiality of extremely sensitive data) the IRB may choose to review such a repository at a convened Committee meeting.

Conflicts of Interest

According the HRPP Policy VI.B/Investigator Conflict of Interest, all Investigators and key study personnel must identify in the IRB application, whether they or any other person responsible for the design, conduct, or reporting of the research has an economic interest in, or acts as an officer or a director of any outside entity whose financial interests would reasonably appear to be affected by the research. An Investigator is considered to have a financial conflict of interest if he or she, his or her spouse, domestic partner and dependent children own together $5,000 worth of equities in a sponsor. The combined ownership of all Investigators is not considered.

HIPAA

The Health Insurance Portability and Accountability Act (HIPAA) was passed in 1996 and is known as the "Privacy Rule." This rule requires VUMC to adopt standards to protect a patient's individually identifiable health information. Although the rule was not written with research in mind, it greatly impacts the manner in which VUMC researchers may use or disclose a participant's protected health information (PHI) for research purposes.

The following are identifiers as defined by the HIPAA regulations.

Names	Account Numbers
Addresses	Certificate/License Numbers
Dates	VIN/License Plate Numbers
Phone Numbers	Device Identifiers
Fax Numbers	Web URLs
Email Address	IP Addresses
Social Security Numbers	Biometric Identifiers
Medical Record Numbers	Photographs and comparable images
Health Plan Numbers	Any other unique identifying number, characteristic, or code.

Because much of the social and behavioral research does not include the use or disclosure of PHI, the HIPAA regulations may not apply. Many of the Vanderbilt University departments are not included under the "covered entity" and are therefore not bound by the regulations.

For studies involving the use or disclosure of PHI (*e.g.,* studies involving fMRI procedures), the participant must provide authorization. This is incorporated in to the informed consent process and specific template language is provided. When the research involves children, the authorization language must be included in the parent informed consent document.

HIPAA and Decedents

The Privacy Rule permits individually identifiable information (PHI) on decedents to be used and disclosed without authorization (from decedent's family/legally authorized individual) if the following criteria are met.

1. the use is solely for research on the PHI of a decedent;
2. the PHI sought is necessary for the purposes of the research; and
3. the Investigator has documentation of the death of the individual about whom information is being sought.

Deception

When an Investigator plans to withhold information about the real purpose of the research or give participants false information about some aspect of the research, the participant may not be fully informed and therefore cannot provide informed consent.

The IRB must first consider whether the information to be withheld would influence the decision of the prospective participant to consent to the research. In addition, the request to use deception must meet the regulations to waive or alter informed consent. The research activities cannot be greater than minimal risk and the exclusion of the information may not adversely affect the rights and welfare of the participants. The use of deception must be imperative to the completion of the research project. All other possible research designs should be considered.

Whenever appropriate, participants will be given additional pertinent information after they have participated in such a study through a debriefing process. The IRB may decide that such a debriefing could itself produce pain, stress, or anxiety and may therefore determine that it is not required.

MRI Studies

When Investigators use MRI or fMRI procedures in research, the following template language should be included in the informed consent document:

"The MRI (or fMRI if being performed) scan will take about ____ minutes. An MRI (fMRI) scan is taken in a large machine that is shaped like a tunnel. This scan does not use x-rays. Instead, they use a strong magnet and radio waves, like those used in an AM/FM radio to make pictures of your body.
You may not be able to have this scan if you have a device in your body, such as aneurysm clips in the brain, heart pacemakers or defibrillators, and cochlear (inner ear) implants. Also, you may not be able to have this scan if you have iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye).
Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the part of the body being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.
You will hear "hammering", clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.
During the scan, the MRI (fMRI) staff is able to hear and talk to you. You will also be able to hear the staff. They will be talking to you during your scan and may ask you to hold your breath, not move, or other simple tasks. You may be asked to lie very still throughout the scan."

Add if appropriate:
In this study, the MRI (fMRI) scan is for research only. But, if we see something that is not normal, you will be told and asked to consult your doctor.

At some point during your scan, the staff will stop the scan in order to give a contrast agent (dye). The dye is given through a needle placed (an IV) in your arm. If you have one, we will use your IV.

If you do not have one, we will place an IV in your arm using standard practice.

Insert the following language in the consent document if using the B-160 MRI facility:
"This MRI (fMRI) scanner has been used with research animals. For your safety, we clean the scanner with bleach before and after your scan as we do with scanners used only for patients."

MRI (fMRI) Risks Add to the risk section of the consent form:
"There are no known major risks with an MRI (fMRI) scan. But, it is possible that harmful effects could be found out in the future. Even though the tunnel is open, it may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and/or move slightly during the scan. It may be hard to lie on the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissues or organs.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an MRI scan and cause skin burns in the immediate area of the patch. Tell the study doctor that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an MRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the health history questions you are asked when you arrive for your appointment."

Add if using a contrast dye other than Gadolinium:
"The contrast dye you will receive is the standard dye used in these scans. Getting the dye through the IV does not cause pain, but you may feel discomfort, tingling or warmth in the lips, metal taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. Very rarely, there may be an allergic reaction, which may be severe. This may cause you to have a rash, swelling, tightness in the throat, trouble breathing, low blood pressure, and very rarely death. Placing the needle in your vein may also cause minor pain, bruising and/or infection where it goes into your arm. There will be trained health workers and supplies on hand to treat you and keep you safe if you have any of these symptoms. Also, a doctor will be on hand during the scan to provide any needed care if side effects do occur, and to decide when or if we should stop giving you the dye.

There are no known risks of having MRI scans without contrast while pregnant. However, there may be risks that are unknown."

If the study will use Gadolinium, please use the Gadolinium specific risk language available in our Template Language for Consents.

7 Tesla MRI Studies Add to the risk section of the consent form:
"The MRI used in this study has been used in human research for several years and no risks have been identified. However, some people may experience discomforts such as nausea, dizziness, flashing lights in the eyes, and a metal taste in the mouth. These discomforts are most likely to occur as a result of rapid head movement in or near the MRI machine. For this reason, you should try not to move, especially your head, while you are inside the MRI."

Research in the Public Schools

Research within a public or private school system requires not only review and approval from the IRB, but also from the school system. The Davidson County Metro Schools has a research committee to review each project and will provide an Investigator with a letter of cooperation. For other schools, the IRB requires a letter of cooperation from the appropriate institutional official.

In addition, Investigators must take into account the **Family Educational Rights and Privacy Act** (FERPA) regulations when requesting to obtain private identifiable school records.

The requirements of informed consent may be more difficult when recruiting students from a school system. It is imperative that the Investigator obtain parent permission, prior to obtaining assent from the children. This may be done by sending letters home to parents through the students. However, assent may not be obtained without a signed informed consent document from the parents.

Guidance for Situations Involving Suicidal Ideation.

When a study involves subjects with possible suicidal ideation, the investigator has an obligation to review the data and implement a protocol to protect the safety of the participant. This document provides guidance for screening for suicidal ideation and suicide risk; the appropriate actions to take to protect the subjects; the choice of appropriate study personnel and training; and consent form language.

Chapter 13 -Investigational Drugs, Agents, Biologics and Devices

(*Social/Behavioral investigators should note that development of software and mobile applications fall under the jurisdiction of the FDA and may have additional regulatory requirements)*

The Food and Drug Administration (FDA) regulates clinical investigations that involve drugs, agents, biologics and devices to assure that such test articles being introduced to markets are safe and effective for its claimed indication. Research activities that involve FDA regulated test articles are subject to FDA and DHHS regulations. The Investigator is also expected to abide by ICH Section E.6 "Good Clinical Practice" Guidelines

Medical Products Support Services (MPSS) assists engineers, physicians, scientists, and other faculty investigators who are working to bring innovative medical products out of their laboratories, and progress them toward the marketplace. MPSS is part of Vanderbilt's Center for Technology Transfer and Commercialization (CTTC). The MPSS team provides free assistance to Vanderbilt investigators in two areas: Medical Device Regulatory Affairs Program (MDRAP), and the Medical Products Development and Commercialization Program (MPDCP). MDRAP focuses only on medical device regulatory affairs assistance. **We encourage a consultation early in your medical product research process, prior to submission to the IRB**.

Investigational Medical Devices

Unless exempt by the IDE regulations, all medical devices utilized in human research activities must be classified as a Significant Risk (SR) or a Non-Significant Risk (NSR) device.

Significant Risk (SR) device: A device that presents potential for serious risk to the health, safety, or welfare of a participant and is intended as an implant; or is used in supporting or sustaining human life; or is of substantial importance in diagnosing, curing, mitigating or treating disease, otherwise prevents impairment of human health; or otherwise presents a potential for serious risk to the health, safety, or welfare of participants.

Initial Determination of Non-Significant or Significant Risk Device

The sponsor or manufacturer of the medical device **initially** makes a determination that the device will be categorized as a Non-Significant Risk (NSR) or a Significant Risk Device (SR). If it is determined that the device is a **SR** device, the sponsor or manufacturer must submit a request for an IDE from the FDA. Research involving the use of a SR device must be conducted in accordance with the full requirements of the FDA and must have an IDE.

When the sponsor or manufacturer determines that the device is a NSR device, an IDE is not required and research must be conducted in accordance with the "abbreviated" requirements of the FDA as described in federal regulations 21 CFR 812.2(b).

Once received, the IRB will determine if it is in agreement with the rendering of the decision by the sponsor of a NSR device. If the IRB is in **agreement** with the sponsor's NSR determination, the IRB review and approval process may be completed. If the IRB **disagrees** with the sponsor's NSR ruling, the Investigator must report the IRB's determination to the sponsor. The sponsor will then decide if they wish to pursue approval through the FDA and obtain an IDE or cease attempts at seeking IRB approval at this institution.

The IRB's determination of approval will be based on local context and its responsibilities to protect participants in research. The IRB has the authority to disapprove research activities even when the FDA has granted approval of the device.

Exemptions from IDE Requirements

It is the responsibility of the sponsor to provide sufficient justification to support the exemption from IDE requirements based on the seven (7) exemption categories provided by the FDA. These exemptions can be located at 21 CFR 812.2(c). An exemption from the IDE requirement is not an exemption from the requirement for prospective IRB review and informed consent requirements.

Submission to the IRB of an IDE or an Exemption from IDE Requirements

The convened IRB Committee must review all studies involving investigational medical device uses and therefore, the Investigator must prepare the initial IRB submission for such by completing the *Standard/Expedited Application* and all required supporting documents. In addition, the Investigator must obtain the following: :

- ☒ For SR devices, a copy of the IDE number;
- ☒ For NSR devices, supporting documentation of this determination from the sponsor;
- ☒ For devices that have been granted an exemption, supporting documentation from the sponsor of the specific category of exemption under FDA regulations.

Use of an Investigational Device

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

- ☒ The investigational device must be used only by the Investigator or under his or her direct supervision;
- ☒ The investigational device must be used only as approved by the FDA and as described in the currently approved IRB documents;
- ☒ The Investigator must not supply the investigational devices to any persons not authorized under the IDE; and
- ☒ Informed consent from the participant or the participant's legally authorized representative must be prospectively obtained, unless waived by the IRB.

Continuing Review Requirements

The Investigator is responsible for fulfilling continuing review requirements at the IRB determined intervals (*See* Chapter 6). However, at the time of continuing review, if the Investigator is the HDE-holder, they must report the HUD activities for the previous 6 months for all non-VU or VUMC performance sites. In addition, the following information must be provided to the IRB in summary form for each HUD at VU, VUMC, or affiliated sites. This report must include the following:

- ✓ The clinical indications for the use of the HUD in each patient;
- ✓ Adverse events or unanticipated problems to participants or others that are possibly related to the use of the HUD; and
- ✓ Clinical outcomes of each participant, if known.

Definitions

ADVERSE EVENT - An untoward or undesirable experience or any undesirable experience associated with the use of a medical product in a patient.

ASSENT - An individual's affirmative agreement to participate in research obtained in conjunction with permission from the individual's parents or legally authorized representative. Mere failure to object should not, absent affirmative agreement, be construed as assent.

ASSURANCE - A contract or agreement that establishes standards for human subjects research as approved by the Office for Human Research Protections (OHRP) also known as a Federalwide Assurance (FWA).

AUTONOMY - Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

CHILDREN - Persons who have not attained the legal age for consent to treatments or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. According to Tennessee State law, the legal age for consent is 18 years of age.

CLINICAL TRIAL - 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.

COGNITIVELY/DECISIONALLY IMPAIRED - Having either a psychiatric disorder (*e.g.,* acute episode pf psychosis or bipolar disorder, or autism spectrum disorder), an organic impairment (e.g., delirium or dementia) or a developmental disorder (*e.g.,* intellectual disability) that affects cognitive or emotional functions to the extent that decisional capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interest.

CONFIDENTIALITY - Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

DEBRIEFING - Giving participants previously undisclosed information about the research project following completion of their participation in research.

DISCOVR-E (**D**ata **I**ntegrated **S**tudy **C**onsole **o**f **V**anderbilt's **R**esearch **E**nterprise) - The Human Research Protections Program's electronic submission system.

EQUITABLE - Fair or just; used in the context of selection of participants to indicate that the benefits and burdens of research are fairly distributed.

EXPEDITED REVIEW - Review of proposed research by the IRB chair or a designated voting member rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

FULL BOARD REVIEW - Review of proposed research at a convened meeting at which a majority of the membership of the IRB is present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

HUMAN SUBJECTS - A living individual about whom an Investigator (whether professional or student) conducting research obtains:

- information or biospecimens through intervention or interaction with an individual and uses, studies, or analyzes the information or biospecimen;
- obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens; or
- identifies a subject as either a recipient of a 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. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

INFORMED CONSENT – An individual's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, participants may not waive or appear to waive any of their legal rights, or release or appear to release the Investigator, the sponsor, the institution or agents thereof from liability for negligence.

INSTITUTIONAL REVIEW BOARD - A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral/social science research.

INVESTIGATOR - The scientist or scholar with primary responsibility for the design and conduct of a research project.

KEY STUDY PERSONNEL - Anyone who is responsible for the design or conduct of the study. This list may include sub-investigators, research assistants, research coordinators, research nurses, etc.

LEGALLY AUTHORIZED REPRESENTATIVE - A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, 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.

MINIMAL RISK - The probability and magnitude of harm or discomfort anticipated in the proposed 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.

PRISONER – 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 which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing. Probation and parole are treated the same and are usually NOT considered as incarceration. Ankle bracelets/in home restrictions are considered as incarceration. Mental and substance abuse facilities are considered incarceration if someone is mandated to attend in lieu of jail or prison; however, an individual in such a facility is NOT considered incarcerated if they voluntarily commit themselves.

RESEARCH - A systematic investigation (*i.e.,* the gathering and analysis of information) designed to develop or contribute to generalizable knowledge.

UNANTICIPATED PROBLEM INVOLVING RISK TO PARTICIPANTS OR OTHERS - Any event that was (1) unanticipated, (2) serious, and (3) related to (or possibly caused by) the research procedures or an

event that places the participant at a greater risk than previously known.

Resources

Vanderbilt University Medical Center Resources:

Human Research Protections Program
Home Page:
https://www.vumc.org/irb/

Education and Training, including links to additional training resources:
https://www.vumc.org/irb/education-and-training-0

Applications and Consents:
https://www.vumc.org/irb/applications-and-consents

Template Language and General Guidance:
https://www.vumc.org/irb/template-language-and-general-guidance

Policies and Procedures:
https://www.vumc.org/irb/policies-and-procedures

Single IRB Help:
https://www.vumc.org/irb/node/28

IMPACTT:
An IMPACTT is requested via Research Support Services at Research.Support.Services@vumc.org or by contacting the RSS Hotline at 615-322-7343. Additional information about IMPACTT can be found on StarBRITE here: https://starbrite.app.vumc.org/research/regulatory/impactt.html

Privacy Office website:
https://www.vumc.org/infoprivacysecurity/

Federal Resources:

Office of Human Research Protections (OHRP):
Home Page: https://www.hhs.gov/ohrp/
Regulations, Policy and Guidance: https://www.hhs.gov/ohrp/regulations-and-policy/index.html

Department of Health and Human Services (HHS):
Home Page: https://www.hhs.gov/
Laws and Regulations: https://www.hhs.gov/regulations/index.html

Food and Drug Administration (FDA):
Hope Page: https://www.fda.gov/
Rules and Regulations: https://www.fda.gov/regulatory-information/fda-rules-and-regulations

Research in Public Schools:

US Department of Education
Home Page: https://www2.ed.gov/policy/elsec/leg/esea02/index.html
Family Educational Rights and Privacy Act (FERPA):
http://www.ed.gov/policy/gen/guid/fpco/ferpa/index.html