Institutional Review Board
for Studies Involving Human Subject Research

POLICY AND PROCEDURES MANUAL

Office of the Vice President for Research

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Introduction

This manual provides faculty, staff and students with a comprehensive over-view of the regulations, procedures, and guidelines for conducting human subjects research at Northeast Ohio Medical University (NEOMED).

What Constitutes Human Subject Research?

The definition of research is provided by the Federal Government in the Code of Federal Regulations, 45 CFR 46.

Definitions Provided in 45 CFR 46

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

Human subject research is research conducted on humans, which is currently defined in 45 CFR 46 as:

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

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

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

(3) Interaction includes communication or interpersonal contact between investigator and subject.

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

(5) Identifiable private information is private information for
which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

(6) An identifiable biospecimen is a biospecimen for which the identify of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Human subjects research has a clearly stated research question or hypothesis. Data collection is both systematic and generalizable. The primary purpose is to expand a body of knowledge via the discovery of new information, facts, or theories. The data collected is ABOUT persons (i.e. human subjects). Participation is voluntary. There may or may not be direct benefits to human subjects. Results apply broadly and not to a specific site, program, or practice making it "generalizable." IRB review is required.

What Does Not Constitutes Human Subject Research?

Activities such as program evaluation, quality improvement, environmental scans, and case reports are not considered regulatory Human Subject Research which require IRB review. Other scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), include the collection and use of information that focus directly on the specific individuals about whom the information is collected, thus do not produce generalize knowledge and are not human subject research.

Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority is not human subject research. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes are not human subject research.

Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions are not human subject research.

As stated prior, program evaluation (PE) and quality improvement (QI) projects are not human subjects research regulated by the IRB. It can be difficult to distinguish among the categories of research, PE and QI, however. If you are uncertain what type of project you are conducting, please complete a Project Determination Form for help in categorizing the project.

Program Evaluation
PE is a systematic collection of information about the merit of a program, its effectiveness, and/or outcomes. Program evaluation informs decisions about future programming. Data is NOT generalizable; it is program specific. Questions are ABOUT the program and NOT about individual persons. Survey questions and information gained align with program objectives

and/or goals. Participation may or may not be voluntary (e.g., student evaluations of courses). Surveys, interviews, focus groups, observations are commonly used to evaluate programs. All data must be de-identified by a third party prior to analysis by the researchers. The data must remain de-identified for presentation or publication. PE may be published but it is advised that the term "program evaluation" is used so as to distinguish from human subjects research. No IRB review is required; this is not regulated human subjects research.

Quality Improvement
QI involves the collection of data for decisions to improve policies, programs, procedures, processes, and outcomes. Quality improvement studies evaluate EXISTING practices, applications of practices, policies, or procedures. The purpose of QI is to manage changes and improve outcomes. Performance measures may be part of QI research. QI data is systematic but not generalizable – it focuses on a particular practice, policy or procedure. It is not necessary to de-identify data prior to analysis by the researchers unless it is student data. It is necessary to de-identify the data prior to presentation or publication of the data. QI studies may be published, but it is advised that manuscripts/documents clearly indicate the parameters in which the work is QI and not human subjects research. No IRB review is required; this is not regulatory human subjects research.

Environmental Scan
An evolving area of study involves the systematic assessment of an organization or external program, process or procedure. This type of research has been called an "environmental scan" and is focused only on a program and not on individual people.

Examples of Studies/Projects that Generally Do Not Require IRB Review

- Data collected for internal departmental or administrative purposes, such as teaching evaluations, student performance data, etc.
- Activities designed solely for quality improvement or evaluation of a program, course, etc.
- Oral histories or biographies (unless data will also be used to contribute to generalizable knowledge)
- Training activities unless the training activity is conducted for research purposes
- Single case studies

Program Evaluation and Quality Improvement Certification Process
NEOMED has designed a process to determine whether a project is research, PE or QI. If the project is determined to be PE or QI, then the investigators will be provided with a Certificate stating the project, as described, does not require IRB review or oversight because it is not human subjects research. The investigator may use the Certificate as documentation that their project does not meet the criteria for human subject research and does not require IRB review when submitting abstracts to meetings or papers to journals. To obtain a Certificate of Not Human Subjects Research, please access the form and instructions on the NEOMED IRB website.

Definition of Clinical Trial

"Clinical trial" means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. The Final Rule's preamble notes that, while not implementing the Notice of Proposed Rulemaking's (NPRM) proposed extension of the Common Rule to all clinical trials, the definition of clinical trial should be used for determining which studies require posting of the IRB-approved consent form used to enroll subjects. The definition is intended to harmonize with the definition of clinical trial in the ClinicalTrials.gov Final Rule (HHS 2016).

Definition of Secondary Research

Secondary research is re-using identifiable information and identifiable biospecimens that are collected for some other ''primary'' or ''initial'' activity (HHS 2017). Examples include medical records, leftover tissue/samples from a hospital's pathology specimen repository, or excess blood drawn for clinical purposes. Secondary research is not surveys, interviews, or collection of samples by the investigator (that would have a primary research purpose).

The Institutional Review Board (IRB)

The ethical conduct of biomedical research assumes that the researcher and the subjects are fellow human beings, equal in dignity and rights. The researcher's quest for knowledge must always be balanced with respect for the person, their rights and welfare. Thus University policy is intended to support the legitimate impulse for scientific inquiry within the context of human values and ethical principles.

Research involving human subjects conducted by faculty, staff, or students on its premises or under its sponsorship, whether supported by outside funds or not, must be reviewed and approved by the NEOMED Institutional Review Board (IRB) for human subject research. NEOMED retains final judgment, to the extent allowed by Federal regulations, as to whether a particular activity is covered by this policy.

Federal Regulations

NEOMED is in full compliance with State and Federal regulations for the protection of human subjects and further extends such policies to include all human research projects, whether sponsored by Federal agencies or not. The manner in which the University will implement the appropriate Federal regulations for the protection of human research subjects is detailed in its Federalwide Assurance of Compliance, filed with the U.S. Department of Health and Human Services Office for Human Research Protections.

Documentation of this compliance is designated by NEOMED's receipt of **Federalwide Assurance No. FWA00000027,** which is on file in the Office of Research and Sponsored Programs and available for review.

IRB Responsibilities
The IRB has the authority to approve, modify, or disapprove proposed studies and to modify, suspend or terminate approval of on-going studies. The decisions of the IRB may only be modified by other institutions, groups, or individuals to be more restrictive, not less so. **No research can be approved in the face of IRB disapproval.**

45 CFR §46.109 IRB review of research:
(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.
(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.
(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.
(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
(e) An IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, not less than once per year, except as described in §46.109(f).

(f)(1) Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §46.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

(2) [Reserved]

(g) An IRB shall have authority to observe or have a third party observe the consent process and the research.

IRB Description and Responsibilities Provided in 45 CFR 46

IRB Staff and Membership

NEOMED assures that its policies regarding the review of research involving human subjects are implemented systematically by distributing the responsibilities at several levels. The Vice President for Research is the Authorized Institutional Official designated by the President of NEOMED to be responsible for the oversight of research and IRB functions. The V.P. for Research assures that the IRB Chair is provided staff support, while the IRB Vice Chair, on request, fulfills the Chair's responsibilities. The Office or Research and Sponsored Programs is responsible for developing and maintaining those systems relating to IRB applications, written procedures, meeting notices, agenda, minutes, approval notices, and on-going review as well as coordinating the functions of the IRB with other activities relating to sponsored research.

In order to ensure complete and adequate review of University research activities, IRB membership is a composition of experience and expertise reflecting the University's research climate. The committee is composed of 10 members and includes one committee chair and one vice-chair, two medical experts from a clinical background, four Rootstown based faculty from various departments, one member not affiliated with NEOMED, and one non-scientific member. There is also one alternate non-scientific member.

Prospective IRB members are nominated by the V.P. for Research, who takes into consideration the range of topics typically reviewed by the Board and what expertise is available and appropriate to participate in such reviews. The V.P. for Research's recommendations are developed in consultation with Office of Research and Sponsored Programs personnel who are familiar with the scope of NEOMED's research community. The President reviews and approves the final list of nominations. Membership is for three years and is renewable. A profile of the IRB's membership is maintained with the U.S. Office of Human Research Protections.

§46.107 IRB membership

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, or individuals with impaired decision making capability , consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(c) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(d) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(e) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Responsibilities of the NEOMED Community and Investigators: Reporting of Noncompliance

Federal regulations require that a process be in place to ensure prompt reporting of serious or continuing noncompliance to the Institutional Review Board (IRB), institutional officials, and Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), or other relevant agencies and sponsors. NEOMED has established a procedure to report allegations of noncompliance and the role of the Institutional Review Board (IRB) to confirm, manage, and resolve issues of noncompliance in accordance with federal, state, or local laws and regulations, institutional policies governing the protection of human subjects, and requirements of Northeast Ohio Medical University Institutional Review Board (NEOMED IRB).

It is the responsibility of all members of the NEOMED community, including investigators, to report concerns of noncompliance with research when NEOMED is considered engaged in the research (as defined by OHRP Guidance on Engagement of Institutions in Human Subjects Research). Intentional or unintentional noncompliance can create undue burden or unnecessary risk for human subjects. This policy does not cover acts of research misconduct including, but not limited to, fabrication, falsification, or plagiarism of research.

Definitions

Noncompliance is defined as minor or serious violations of any institutional, state, and federal regulation or policy that governs human subject research, which may compromise the integrity of scientific research and/or the safety and welfare of human subjects.

Minor noncompliance issues or events may include administrative protocol deviations, and/or any event that may pose minimal risk to the safety and welfare of human subjects. Examples of noncompliance include, but are not limited to: conducting human subjects research without IRB approval; modifying or deviating from the originally approved protocol without IRB consent or written documentation; violating IRB approved procedures for informed consent, including lack of proper documentation of informed consent; failing to report unanticipated problems or adverse events; conducting research without IRB approved education and training; failing to maintain data security.

Serious noncompliance issues or events compromise the integrity of scientific research and may include minimal or more than minimal risks to the safety and welfare of human subjects.

Compromising the privacy and confidentiality of human subjects or excluding human subjects from participation based on irrelevant characteristics without justification or prior IRB approval, are examples of serious noncompliance.

Continuing noncompliance is a series of more than one noncompliant issue or event that further prompts the need for (i) the evaluation of the procedures and processes used to protect human subjects, and (ii) yields automatic reporting to (OHRP).

Policy Statement

(1) Any person who suspects or discovers a deviation or incident of noncompliance must report the incident to the IRB Chair or the Human Protections Administrator (HPA), or, alternatively, complete a Noncompliance in Human Subjects Research form and submit the form to the designated IRB coordinator for processing.

(2) The IRB is responsible for investigating and reporting to appropriate institutional officials and federal agencies any deviation or noncompliance event or a series of events that violates any regulation or policy applicable to human subjects research. All reported noncompliance issues or events will be thoroughly investigated and considered *suspected* or *possible* noncompliance until a final determination is made by the IRB Chair or by the convened IRB committee.

(3) The individual reporting noncompliance shall:

(a) Schedule an appointment with the IRB Chair or HPA to discuss the suspected or identified unanticipated problem or incident of noncompliance,

Or

(b) Acquire a Noncompliance Reporting Form from the IRB website to document all suspected deviations or acts of noncompliance.

(c) Submit completed form to designated IRB coordinator with contact information; names are held in confidence unless there are regulatory or legal requirements to disclose.

(4) The individual(s) suspected of noncompliance shall:

(a) Be notified by the IRB Chair or HPA in writing of the suspected incident

(b) Schedule a meeting with the IRB Chair and/or HPA to review the reported incident

(c) Provide the IRB Chair and HPA with any requested information during the investigation.

(5) The IRB Chair and/or HPA shall:

(a) Document the details of the reported unanticipated problem or incident of noncompliance during a scheduled meeting, or review the completed Unanticipated Problem, Adverse Events, and Noncompliance Reporting Form

(b) Notify the individual(s) suspected of noncompliance

(c) Gather additional information for purposes of a thorough investigation

(d) The IRB Chair and HPA will convene to review all collected information and make a determination as to whether a noncompliance event or issue occurred, and the extent to which the noncompliance negatively impacted the integrity of the research and the safety and welfare of the human subjects.

(e) For those noncompliance issues that are serious or continuous, including the failure to report unanticipated problems and adverse events, the IRB committee will be convened.

(f) Determine a course of action

(g) Notify the Institutional Official (IO), either verbally or in writing, of the unanticipated problem or incident of noncompliance

(6) Determinations and Consequences of Noncompliance

(a) If the incident or issue is determined to be ***Minor Noncompliance:***

i. The IRB Chair and/or HPA may determine that the noncompliance is minor, and in such instances, a corrective action plan is required.

ii. The corrective action plan should identify those steps that will be completed to correct the noncompliant incident, as well as steps to prevent future incidents.

iii. Minor noncompliance events that do not include adverse events will be reported to the IRB committee, the investigator, the department chair or supervisor of the investigator, and the IO.

iv. The IO may choose to report the noncompliance event to others whose position and authority may dictate further action beyond the purview of the IRB (e.g., Dean).

v. A hard copy letter detailing the investigative findings of the noncompliance issue or event, and the request for a corrective action plan, will be provided to the investigator, the HPA, the department chair or supervisor of the

investigator, and the IO through the IRB office. Copies may be made by the IO to be distributed confidentiality to others on a need to know basis.

(b) If the incident or issue is determined to be ***Severe or Continuous Non-Compliance:***

i. For noncompliance events or issues that are more severe, including the failure to report unanticipated problems and adverse reactions, or are continuous, the OHRP will be notified in addition to the IRB committee and the IO.

ii. The IO may choose to report the noncompliance event to others whose position and authority may dictate further action beyond the purview of the IRB.

iii. In the event of a severe or continuous noncompliance issue or event, the IRB Chair will immediately bring the issue to the IRB committee at the earliest possible time to determine whether the protocol should be suspended or terminated in whole or in part.

iv. All members of the IRB committee will be provide with a summary of the issue or event prepared by the IRB Chair and HPA, as well as current investigative findings. The IRB committee reserves the right to ask the investigator(s) to attend the committee meeting to further explain the issue or event.

v. Investigator(s) will be required to submit a corrective action plan based on the committee's recommendations, as well as a written report responding to all issues and questions raised by the IRB Chair and/or IRB committee

(7) Final Outcome Notification

(a) Upon *successful* completion of a corrective action plan, the investigator(s) submitting the plan will be notified in writing of the final outcome of the incident.
(b) The reporter may contact the IRB Chair or HPA to discuss the final outcome of the incident.
(c) The final report will be distributed to the IO, and will be maintained in the IRB office.
(d) The IO will report adverse events and any noncompliance issue or event that is serious or continuing to the Office of Human Research Protections (OHRP).
(e) In the event of a reporting a serious or continuing noncompliance issue or event, the OHRP may require additional investigations and sanctions.

Responsibilities of NEOMED Investigators

Only a University faculty member may serve as principal investigator (PI) for research conducted under the auspices of NEOMED. It is the policy of the NEOMED IRB that each approved human subject protocol has a single PI who is responsible for its design and conduct. The designation of multiple PI's or Co-PI's is not recognized by the IRB. The PI must be familiar with the following responsibilities, reviewed in more detail on the NEOMED IRB website:

- Ongoing communication with the IRB
- Conduct of the Project
- Responsibility for Research Staff
- Changes to Research Activities (Amendments)
- Record Retention
- Continuing Review and Study Termination
- Mentoring of Student Researchers
- Reporting Non-compliance and Unanticipated Events

The PI is responsible for implementing the project in accordance with the IRB-approved protocol, ethical and scientific principles, University policies, and all pertinent laws and regulations. The PI is responsible for ensuring that informed consent is obtained in an ethical and legal manner, adverse events are reported to the IRB, and periodic reports are submitted as required by the IRB. The PI also ensures that all participating researchers, staff, and other key personnel are aware of their responsibility to comply with University policies regarding human studies education (see Section: Required Human Subjects Research Education) and the confidentiality and storage of project data (see Section: Record Keeping – Investigators).

All investigators affiliated with a human subject research study are responsible for ensuring approval by the IRB has been obtained prior to the initiation of any activity and then assuring that the research does not continue beyond the period of time approved by the IRB. All research investigators affiliated with an IRB approved study acknowledge and accept their responsibility for protecting the rights, safety, and welfare of human research subjects and for complying with all State, Federal, and University policies.

Student Research Projects

As part of their academic role, faculty members are responsible for teaching students ethical principles relating to human subject research and guiding them through the mechanisms of obtaining IRB approval. As NEOMED policy, students are not permitted to be named as PI of any human subjects research study. Student-initiated research involving human subjects, whether dissertation, Capstone, thesis or other research projects must be submitted on an IRB Application, listing as PI the name of the faculty member designated by the academic department to be responsible for coordinating the student project. This faculty member assumes responsibility for ensuring that the student's research complies with State, Federal and University policies regarding the protection of human research subjects. All records and correspondence with the IRB will be done under the faculty member's name. Thus the faculty advisor, as the PI, must keep the student investigator informed about IRB decisions and communications.

Grant Applications that Include Research
Involving human subjects in research requires a carefully thought-out, detailed plan. Grant applications to federal, state or foundation sponsors require a complete description of such a plan. Well in advance of the grant deadline, schedule a meeting with the Office of Research and Sponsored Programs to discuss the submission of the grant.

Investigators submitting a grant application to a funding agency that accepts "Just in Time" approval for human subjects research must complete a Summary of Human Subjects Questionnaire at the time of grant submission. The questionnaire is available in the ORSP electronic grants management system, Kuhli. Completion of this questionnaire does not constitute IRB approval of the project. No human subjects research may begin until a formal application has been submitted and approval has been granted.

Grant submissions involving research require a conflict of interest (COI) form be on file for every PI, co-investigator, and any other person (e.g. technicians, post-docs, graduate students) who is responsible, in whole or in part, for the design, conduct or reporting of a research study. This form can be obtained by contacting the Office of Research and Sponsored Programs.

Types of IRB Regulated Research Studies

There are three categories of IRB review: Exempt, Expedited and Full Board.

Exempt Status
Exempt status may be granted to studies in the following categories. Exempt status means the project is exempt from 45CFR46 regulations. It DOES NOT mean that the protocol does not need to be reviewed by the NEOMED IRB. Only the NEOMED IRB can determine, through review, that the project is exempt from the regulations. Research within these categories may receive Exempt status by the NEOMED IRB:

Category 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. A condition of this exemption is that the research is not likely to have adverse impacts on students learning required educational content or assessment of educators who provide instruction (HHS 2017). The exemption may only be used for studies about normal educational practices.

Category 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless

One of the three following criteria must be met:
(1) Information obtained is not identifiable
(2) Disclosure outside of the research would not put subjects at risk of harm

(3) Information obtained can be identifiable but the IRB has done a limited IRB review in keeping with 46.111(a)(7), which relates to there being adequate provisions for protecting privacy and maintaining confidentiality.

Also, the Final Rule revised this category to include visual or auditory recording as research methods. Surveys also cannot include collection of biospecimens or interventions, as those additional activities would disqualify the research from this category.
When the research is subject to Subpart D and includes children, Category 2 still does not allow surveys or interviews or the observer participating with children (public behavior observation without intervention is permitted).

Category 3. Benign Behavioral Interventions in Conjunction with the Collection of Information From Adult Subjects

Benign behavioral interventions are defined as "brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing" (HHS 2017). An example provided is having subjects solve puzzles under various noise conditions. Research using deception is not eligible for exemption in this category unless the subjects prospectively agree that they will be unaware of or misled regarding the nature and purpose of the research. As with research in Category 1, exemption is permitted if the data are recorded in such a way that the identities of the subjects cannot be readily ascertained either directly or indirectly or if the identities can be ascertained, a disclosure of the subjects' responses outside the research setting would not reasonably place the subjects at risk of harm. Alternatively, if the subjects' identities can readily be ascertained and if a disclosure of subjects' responses has potential to harm subjects, the exemption is permitted if the IRB conducts a limited review and determines that there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Category 4: Secondary research for which consent is not required.
This category covers secondary research uses of identifiable private information or identifiable biospecimens. The Final Rule revised and clarified the pre-2108 rule category for the use of secondary use of data. Category 4 does not require informed consent if at least one of the criteria listed below is met. There are four available options for use of the exemption:

1. Use of publicly available identifiable private information or identifiable biospecimens.
2. Information recorded by the investigator in such a way that the identity of the subjects cannot be readily ascertained, and the investigator will neither contact the subjects nor re-identify subjects.
3. Research use of identifiable health information when that use is regulated by HIPAA as health care operations, research, or public health activities and purposes as those terms are defined in HIPAA.
4. Analysis of data on behalf of a federal agency or department – as opposed to an investigator-initiated analysis of federally supplied data – if the requirements of certain federal laws are met.

It is important to note that data do not need to be existing ("on the shelf") at the time of the research study, as was previously required by the pre-2018 rule. The data can be collected prospectively and still be used for exempt research under Category 4 in the Final Rule.

Category 5: Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. The category has been revised to allow research supported by a federal agency (not just conducted) to qualify for this exemption; provide examples of the types of public benefit and service programs covered by the exemption; and clarify the federal components for which the exempt research is subject to approval (for example, delegated subordinate agencies).

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

Category 7 and 8 for broad consent have been omitted and are not used as exemption criteria by the NEOMED IRB.

Subpart Applicability
Subpart B- Additional Protections for Pregnant Women, Human Fetuses and Neonates
The Final Rule is consistent with the pre-2018 rule. Each of the exemptions can be applied to research subject to Subpart B.

Subpart C- Biomedical and Behavioral Research Involving Prisoners
The Final Rule changes the pre-2018 rule to allow the exemptions to apply to Subpart C for research involving a broader subject population if the research only incidentally includes prisoners. The Final Rule permits the exempt secondary research of information or biospecimens from subjects who are prisoners, if that research is
not seeking to examine prisoners as a subpopulation. The Final Rule allows subjects to continue in exempt research if they become prisoners during a study.
Subpart D: The Final Rule allows research with children to be exempt for categories 1, 4, 5, 6, 7, and 8. The Final Rule does not permit the exemption of research with children that includes identifiable information and is reviewed under a limited IRB review. Consistent with pre-2018 rule, observation of the public behavior of children under Category 2 is allowed only if the researcher does not participate in the activities being observed. Consistent with pre-2018 rule, surveying and interview procedures with children may not be exempt.

Limited IRB Review as a Condition of Certain Exempt Research
The Final Rule introduced a new concept of limited IRB review as a condition of exemption for four of the exempt categories listed above.

For Categories 2 and 3, it is only sometimes an option.
A limited IRB review is only required if the research involves identifiable information (the regulation states "information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects" [HHS 2017]). Then, the IRB must conduct a limited IRB review to determine if there are adequate provisions in place to protect privacy and confidentiality as defined under 46.111(a)(8).

For Categories 7 and 8, it is always required. These are the broad consent exempt categories. Category 7 requires limited IRB review for secondary research involving storage or maintenance of identifiable private information or identifiable biospecimens to determine if conditions of 46.111(a)(8) are met. This includes if broad consent was obtained and documented (or waiver of documentation was obtained) in accordance with the requirements for broad consent, and if there are any changes made for research purposes to the way information or biospecimens are stored or maintained, there are adequate protections for privacy and confidentiality.

Category 8 is also for secondary research and requires a limited IRB review to determine if broad consent was obtained and documented (or waiver of documentation was obtained) in accordance with the relevant regulatory requirements, and there are adequate provisions in place to protect privacy and confidentiality. Category 8 also stipulates that the researcher does not include returning individual research results to subjects as part of the study plan (except where legally required).

How is limited IRB review applicable to research in the social and behavioral sciences, education, and the humanities?
For research in these areas, a limited review may be required when the research involves benign behavioral interventions in conjunction with the collection of information from adult subjects (Category 3) and when it involves educational tests, surveys, interviews, or observations of public behavior (Category 2). A limited review must be conducted for exempt research in these categories when information is recorded in a manner in which the identity of the subjects can be readily ascertained and a disclosure of the data could pose a risk of harm (limited review does not need to be conducted if the identifiable data would not reasonably place the subjects at risk).

There is only one criterion for limited review for these categories: "When appropriate, there are adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of the data" (46.111(a)(7)).

Who may be a limited IRB reviewer?
An IRB may use the expedited review procedure to review research for which limited IRB review is a condition of exemption. "Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the

chairperson from among members of the IRB" (HHS 2017). The reviewer cannot be a non-IRB member, such as IRB staff.

Expedited Review

Expedited review of research studies are provided for studies that present no more than minimal risk to subjects and fall within one of the following categories. The NEOMED IRB will determine if a submitted research protocol can undergo expedited review.

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

Continuing review for research initially approved using expedited review procedures no longer needs to occur. If an IRB chooses to conduct continuing review when it is not required by the regulation (as described in 46.109(f)(1)), the rationale for doing so must be documented. Although continuing review is no longer a require, institutional policy requires investigators to provide a yearly "check up" of their projects. The yearly checkup will provide brief information to the IRB regarding the general status of the project. Investigators will receive an e-mail from the IRB each year prompting them for check-up information until such time that the project ends and the investigator closes the study.

Continuing review is also no longer required for studies initially reviewed by the full convened IRB, when only certain specified activities are all that remain for the study, including:

- Research eligible for expedited review in accordance with § __.110; or research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    - a) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - b) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Below are the categories of studies that may qualify for expedited review. If the reviewer determines that the study involves more than minimal risk, the reviewer can override that presumption, but the reviewer has to document his/her rationale:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 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:
(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
(b) from other adults and children [2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.
Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); € 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; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject=s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; € moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS

regulations for the protection of human subjects. (45 CFR 46.104). This listing refers only to research that is not exempt.)

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

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.104). This listing refers only to research that is not exempt.)

Full Board IRB Review
All human subjects research that poses more than minimal risk to subjects must be approved by a convened meeting of the full board IRB. Contact the IRB office at 330-325-6364 for information on the next upcoming convened meeting.

IRB Submission

Required Human Subjects Research Education
NEOMED requires that all key personnel involved in human subject research complete its specified program of education. The requirement for training is the CITI human subjects training modules. The link is available at the IRB website and also the CITI website. The CITI training certificate is valid for three years from the date of completion. IRB approval will not be granted until all key personnel have completed required training. Training modules are tailored to the type of research you are conducting and include modules in Human Subject Behavioral Research, Human Subject Biomedical Research, and Research with Data or Specimens Only. To make an account and complete the training, following the link below to CITI's homepage, then click the register button and enter the information requested.

CITI Registration

Only in instances where international investigators may not have access to CITI training will NIH's on-line training be accepted. Should an international investigator not have access to the CITI website, please contact the IRB office to see if the NIH training modules would be acceptable.

Submission Forms and Processes
Application guidelines and forms are available from the NEOMED IRB website. Instructions are provided for completing the IRB application, but please feel free to contact the IRB for clarification. Investigators involved in human subject research for the first time are particularly encouraged to make an appointment with the IRB to discuss their application prior to submission.

Questions? Please Contact:
Regulatory Affairs Coordinator
Office of Research and Sponsored Programs
Phone: 330.325.6364
Email: researchcompliance@neomed.edu

Conflict of Interest
While no specific conflict of interest (COI) form is required as part of an IRB application, a section requiring disclosure of any COI is included within the application.

Informed Consent
Except as discussed below, studies involving human subjects must contained an informed consent document. Information in the informed consent document must be in language that is understandable to the subject or the subject's legal representative. It may not include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

An important regulatory term in the 2018 Final Rule is "Key Information." Key Information must receive priority by appearing at the beginning of the consent form and be presented first in the consent discussion. According to the Final Rule's preamble, a brief description of five elements at the beginning of the consent form, and informed consent process, would encompass the required key information:

- The fact that consent is being sought for research and participation is voluntary.
- The purpose of the research, expected duration of the prospective subject's participation, and procedures to be followed in the research.
- The reasonably foreseeable risks or discomforts to the prospective subject
- The benefits to the prospective subject or others that may reasonably be expected from the research
- Appropriate alternative procedures of courses of treatment, if any, that might be advantageous to the prospective subject.

The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

Basic elements that must be included in the informed consent document are:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to 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
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

New Requirements for Informed Consent

The eight basic informational elements listed above remain.

Research that involves the collection of identifiable private information or identifiable biospecimens must include one of the following statements:

i. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

ii. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional elements of informed consent that may be required include:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- 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
- The approximate number of subjects involved in the study.

Three new requirements were added:

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

Waiver of Documentation of Informed Consent
An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of written informed consent set forth above, or waive the requirement to obtain documentation of informed consent 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: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) 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.

The requirement "practicably" should be interpreted to mean that it would be impracticable to perform the research, not impracticable to obtain consent due to financial or administrative burdens, without the waiver or alteration.

Additionally, an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent 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; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Consent Templates
The following templates are available from the IRB forms website:

- Informational Sheet (signature not required for consent)
- Consent for Adults Form- signature required
- Assent for Minors Form- signature required
- Parental Consent Form- signature required
- Consent by Telephone

HIPAA Application
All IRB applications that involve the use of Protected Health Information (PHI) obtained from a covered enitity must include a HIPAA Application and Data Use Agreement. Consent to share personal health information (Authorization to Share Personal Health Information in Research) must be included as part of the informed consent document. The forms are available from the IRB website.

Studies Involving Human Tissue
A power point presentation is available from the IRB website with information concerning studies that involve human tissue. Please review this power point if human tissue will be used in any way in the proposed research study.

Studies Involving Recombinant DNA or Biohazardous Materials
Investigators proposing a study that will use recombinant DNA or biohazardous materials must complete a form that will be reviewed by the Institutional Biosafety Committee (IBC). Please obtain this form from the Biosafety Committee website.

An Application for Exemptions of Pathological Specimens or Tissue Culture is available from the IRB website.

Studies Involving Ionizing Radiation
Studies involving ionizing radiation, including the purchase of all radioactive materials or radiation-generating equipment and Class 3B or Class 4 lasers (and potentially other lasers) will be reviewed by the Radiation and Laser Safety Committee. Contact the OR&SP for more information if the proposed study involve radiation or lasers in any way.

Advertising
The IRB is responsible for ensuring the equitable selection of research subjects. Additionally, direct advertising for study subjects is considered the start of the informed consent and subject selection process. Thus, in fulfilling this responsibility the IRB reviews the materials and methods that investigators use to recruit subjects. Since advertising (classified, display, posters, videos, television/radio commercials, etc.) is a method of recruitment and an extension of the informed consent process, the IRB reviews the information contained in the ad to determine that adequate protection is afforded in recruiting subjects.

In general, advertising to recruit subjects should be limited to:

- The purpose of the research
- Briefly stated eligibility requirements
- Straightforward and truthful description of benefits to subjects (e.g., payment or free treatment)
- Location of the research and how to obtain further information.
- Name and address of the PI.

No claims should be made, either explicitly or implicitly, that the study treatment is safe, effective, or superior. Advertising should not use terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational. Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation.

Remuneration of Research Subjects
Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. Remuneration for participation in research must be described in the

Consent Form/Information Sheet and approved by the IRB. The amount of remuneration should be reasonable and commensurate with the expected contribution of the subject and should not constitute undue pressure to volunteer for the research project. Quantification of the remuneration should include consideration of travel and parking expenses, time commitment, etc. Just as the size of payment can put inappropriate pressure on subjects, so can the schedule of payment. Holding payment until the subject has completed every procedure in a long, multi-week, multi-visit study is inappropriate. For studies with more than two or three visits, payment should be prorated, that is, based on the amount of time subjects have spent participating so far. Any departure from this guideline should be justified to the IRB.

Gift cards or other cash equivalents

Please note that gift cards or any other form of cash or cash equivalent are taxable regardless of the amount. The NEOMED accounting department must track the amounts each research participant receives. Any compensation or combination of compensations that add up to $600 for the calendar will be reported to the IRS by the issue of a 1099 Statement. All research participants receiving gift cards/certificates must be asked to complete an acknowledgement form before receiving the gift card. If your study requires that participant names be kept anonymous, participants must complete the Receipt of Compensation Acknowledgement--Anonymous Form. All participants in studies which are not anonymous must complete the general Gift Card Acknowledge Form. The instructions and processes for uploading these forms to the Accounting office may be found on the Form Instructions. Questions regarding this process may be sent to purchasing@neomed.edu.

Research Conducted by NEOMED Faculty and Students at other Institutions

Due to FWA requirements, the NEOMED IRB must issue approval of human research: regardless of sponsorship, if one or more of the following apply: (1) the conduct or recruitment of the research involves institutional resources (property, facility or funding, including extramural funds administered by the institution), or (2) the research is conducted by or under the direction of any employee, student or agent of this institution in connection with his or her institutional responsibilities or academic requirements, (3) the research involves the use of this institution's non-public information to identify or contact human research subjects or prospective subjects. For research conducted outside of the NEOMED campus, involving research projects in which the NEOMED student is receiving academic credit or which constitute a faculty member's institutional responsibilities, notification of the project is required to the NEOMED IRB. This applies even if all of the research is being conducted off campus and is approved by another institution's IRB. Please forward a copy of all research materials (application, consents, questionnaires, advertisements, etc) approved by the off-campus IRB to the NEOMED IRB office. A decision to accept the primary review or to re-review the study will be made on a case by case basis.

Time Required for IRB Review

Applications for exempt or expedited review are reviewed on an ongoing basis so there are no deadlines. Time to complete the review will depend on the complexity of the study and the clarity with which the study is written but will require a minimum of 10 business days.

The time to review a full board application is partly dependent on the date of the next IRB meeting. Please remember that the IRB meets every other month. All applications requiring full board review must be in the IRB office ten working days prior to the IRB meeting. After the IRB meeting, approval is granted within approximately two business days if the application receives an unconditional approval.

For all submissions to the IRB, the amount of time required to complete the processing of applications receiving "approval pending changes" depends on the investigator's ability to respond to the corrections and clarifications requested in the interim memo. The IRB retains the option of sending their written correspondence by mail, fax, or e-mail.

Incomplete applications can result in significant delays in the review and processing of research protocols. Also, excessive delay in completing an application may result in the study losing its novelty and accuracy from a scientific perspective. In an effort to prevent these dilemmas, the IRB will hold incomplete submission packets for 60 days. If the submission packet is not completed within 60 days, the packet will be returned to the primary investigator unprocessed, unless the primary investigator requests an extension. A single 30-day extension period may be granted by the IRB. If the submission packet is still incomplete after the extension period, the packet will be returned to the primary investigator as "INCOMPLETE-NOT PROCESSED." This process does not preclude the investigator from resubmitting nor does it adversely affect any submissions the investigator may currently have under IRB review.

IRB Review

Role of IRB Chair

The IRB Chair is ultimately responsible for setting the agenda for each meeting, determining what applications will be exempt, expedited, or require full IRB review. The Chair is officially authorized to represent the IRB in communicating with investigators, administrators, legal advisors, and community representatives. It is the IRB Chair who will consider applicant's appeal of an IRB decision as to whether further information warrants the IRB's review of its decision. The IRB Chair may approve applications that qualify for expedited review or exemption; disapproval requires full IRB review. The Chair is also a mentor for the IRB members, IRB staff, and investigators.

Responsibility of IRB Staff

Prior to each meeting, IRB staff receive applications from faculty, review each application for completeness, and distribute the packet of applications to the necessary individuals. In this process, the staff work with the IRB Chair in identifying those applications requiring full IRB review, prepare a written agenda for the meeting, and assign primary reviewers. The staff is responsible for all logistics of the meeting room, preparation of any additional meeting handouts, introducing visitors into the meeting, and assisting the IRB Chair as needed. The IRB staff prepares the official IRB minutes and summary of project reports on behalf of the Chair.

Role of Investigators

At the request of the primary IRB reviewer or Chair, the PI may attend the IRB meeting in which his/her protocol is to be reviewed. At the meeting, investigators are asked to wait in the hall until

the IRB staff member invites them in at the appropriate time. Once the IRB members have acquainted themselves with a specific protocol, the investigator is invited into the room in order to answer questions and clarify concerns. In lieu of attending the meeting, the IRB may ask the investigator to provide supplementary information.

Role of Primary Reviewer

Many IRB members are selected to serve on the IRB because of their technical expertise. In this capacity, they will frequently be asked to serve as a primary reviewer. The responsibility of a primary reviewer is to present at the IRB meeting his/her evaluation of the application with regard to

- the appropriateness of scientific design as it pertains to the involvement of human subjects;
- level of risk to the subjects;
- risk/benefit ratio;
- suitability of the consent form;
- the equitable selection of research subjects;
- provisions for confidentiality;
- qualifications of the investigators;
- suitability of equipment and facilities for management of the subjects' rights and welfare.

This permits the IRB to focus its discussion on the appropriate issues based on the motion on the floor and make its conclusion in a productive manner.

Guidelines for the Primary Reviewer

The primary reviewer may remain anonymous to the investigator unless the reviewer chooses otherwise. Under no circumstance will the name of the primary reviewer be disclosed in the minutes of the IRB's meeting. The primary reviewer will:

- review the protocol early enough to inquire about specific questions with investigator(s). Delays in approval can be avoided if potential conflicts are dealt with prior to decision of the IRB.
- make an organized list of concerns, questions or corrections to be brought up with the board. This helps speed up the time required to review the projects without overlooking significant details.
- briefly review the purpose(s) of the potential ethical problems and how these are dealt with in the proposal.
- differentiate between points of ethics (including science) and style. Concerns regarding ethical issues must be addressed by the investigators, while those of style are more logically handled as suggestions (unless the style interferes with an ethical point).

The primary reviewer may contact the investigator in advance in order to clarify an issue of concern, ask the investigator to provide supplementary information, or invite the investigator to attend the IRB meeting. If the investigator does not adequately address identified concerns, the primary reviewer should consult with the IRB chair as to the advisability of withdrawing the application from the agenda. The primary reviewer will then prepare a brief outline of the substantive questions to be addressed before the investigator can re-submit.

After review of the project, the reviewer will make a motion whether to approve or disapprove, including suggested risk assignment and any requests for clarification or changes to be made. Most changes deal with the consent form. The reviewer should pencil in minor modifications and corrections on the consent form and provide them to the IRB staff.

Role of IRB Members
All IRB members are provided a set of resource materials plus access to a variety of supplementary resources and tools on-line at many websites. Members are expected to reference these materials when evaluating applications and participating in IRB discussions at meetings.

The IRB's role is best served when each individual feels free to speak to any observations or concerns on all protocols under review. Each member is expected to have reviewed the agenda material provided in advance, with particular attention to the rights and best interests of subjects, potential for risk, and the quality of informed consent.

Because the IRB cannot function without certain representation present, in addition to having a quorum, a substantial commitment falls on individual members to attend all IRB meetings. If an IRB member is unable to attend a specific meeting, it is that individual's responsibility to notify the IRB staff.

If a committee member has a conflict of interest in a given application, such as serving as investigator or consultant, the member must make this known at the outset of the discussion and must be absent during the final discussion and vote on the application.

IRB members are reminded of the confidential nature of information discussed during the evaluation of applications, especially those sponsored by commercial organizations. At the conclusion of each meeting, IRB members are to take care to personally shred or delete all application materials or provide them to the IRB secretary for confidential disposal.

Role of Institution
NEOMED is committed to complying with ethical standards, as well as state and federal regulations as needed to support its research community. The College will provide resources such as staff support, facilities, faculty/staff training, publications and supplies, as needed to implement such standards and regulations.

The College may impose more restrictive sanctions on the IRB's approval of a given research project but will not override negative or restrictive IRB decisions.

Record Keeping – IRB Meetings
Minutes will be recorded and maintained for each meeting and will contain the following information:

- Date of meeting
- List of members present or absent
- List of guests attending the meeting
- Approval of minutes

- Report of proposals reviewed administratively
- Report of addenda/corrections/adverse events for on-going projects
- New Research Proposals Reviewed: review of new proposals, including the following information:
    title of proposal;
    name of all investigators;
    a brief, administrative introduction to the project;
    a summary of key issues discussed;
    questions, changes, corrections needing attention by applicant;
    vote to approve, disapprove, or table;
    level of risk assigned;
    length of approval period (up to one year maximum)
- On-going review: as needed, to review amendments requiring full board consideration, and follow up on discussion of proposals previously tabled or other business relating to proposals submitted or approved.

The IRB staff member is responsible for preparing and maintaining adequate documentation of IRB activities, including the following:

- Copies of all research proposals reviewed, scientific evaluations (if any), approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
- Minutes of IRB meetings.
- Records of continuing review activities.
- Copies of all correspondence between the IRB and investigators.
- A list of IRB members.
- Written procedures for the IRB.
- Statements of significant new findings provided to subjects.

The IRB's official files of all reviewed projects are retained for at least three years after completion of the research. Such records will be accessible for inspection and copying by authorized representatives of NEOMED, DHHS, and OHRP. In addition, the IRB maintains a computerized database profiling on-going research approved by the IRB, which supports administrative activities of the research community relating to human subjects research.

Risk/Benefit Analysis

Risks to research subjects who participate in research must be justified by the expected benefits to the subjects or to society. One of the major responsibilities of the IRB is to assess the risks and benefits of the proposed research. "Risk" is defined as probability of harm or injury, whether physical, psychological, social, or economic, occurring as a result of participation in a research study. Both the probability and magnitude of possible harm vary from minimal to significant.

Federal regulations define a "minimal risk" as one where 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. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of

routine physical examination. Once the risks have been identified, the IRB must assess whether the research presents greater than minimal risk.

"Benefit" is defined as a valued or desired outcome to the research participant or society. Payment for participation is not considered a benefit but rather a recruitment incentive.

The IRB must:

- identify the risks associated with the research as distinguished from the risks of therapies the subjects would receive even if not participating in research;
- determine that the risks will be minimized to the extent possible;
- identify the probably benefits to be derived from the research;
- determine that the risks are reasonable in relation to the benefits to the subjects, if any, and the importance of the knowledge to be gained;
- assure the selection of subjects is equitable;
- assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits; and
- determine intervals of periodic review, and where appropriate, determine that adequate provisions are in place for monitoring the data collected, and where the subjects are likely to be members of a vulnerable population, determine that appropriate additional safeguards are in place to protect the rights and welfare of these subjects.

The Final Rule's preamble states that the possibility of coercion or undue influence could affect the ability to make an informed decision about participating in research. Therefore, the vulnerability of the subjects in research studies should be considered as a function of the possibility of coercion or undue influence.

The preamble states that this type of vulnerability alone should be the IRB focus of concern in determinations about vulnerable populations. The preamble also notes that the assessment of the equitable selection of subjects (46.111[a][3]) should include factors like societal marginalization or discrimination. Likewise, the preamble discusses that the criterion at 46.111(a)(1) includes risks that some might term "vulnerabilities," which are not covered by the regulatory term.

<u>2018 Preamble to Federal Policy for the Protection of Human Subjects</u>

Deception in Research

There are times, especially in behavioral research, when investigators plan to withhold information about the real purpose of the study or purposely give subjects false information about some aspect of the research. "Authorized deception would be prospective agreement by the subject to participate in research where the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research."

Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results, can be acceptable, provided the subject is fully debriefed after participation. Risks stemming from major deception, such as leading a subject to believe that they have committed a crime or have a disease, must be clearly counterbalanced by the benefits of the research.

Federal regulations do not allow the IRB to waive some or all of the elements of informed consent, including a fair and comprehensive description of all elements of the research, if the study is more than minimal risk.

In addition, the waiver of the elements of consent must not adversely affect the rights and welfare of subjects, and must be essential to the ability to carry out the research. The IRB will consider whether the withheld information would influence the decision of potential subjects to participate in the research. The IRB will NOT approve a study that presents more than minimal risk where subjects are deceived or not given complete information that they would consider material to the decision to participate.

Investigators should justify, in detail, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of: a) the necessity for deceiving subjects; b) how the potential benefits of the research justify the use of deception; and c) how the investigators will conduct the debriefing. In addition, investigators should include a debriefing script or statement that indicates the information subjects will receive regarding their participation in the research.

The IRB in collaboration with the investigator will determine whether subjects should be debriefed either after unwittingly participating in research or after knowingly participating in research that involved deception. The IRB may require debriefing when it contributes to the subject's welfare, i.e., when it corrects painful or stressful misperceptions, or when it reduces pain, stress, or anxiety concerning the subject's performance. For example, if a subject is lead to believe through participation in deceptive research that s/he has committed a crime or has a disease, a debriefing session may correct the induced stress, pain, anxiety, etc.

IRB Authority/Decisions

The IRB reviews, and has the authority to approve, require modification of, or disapprove all human subject research activities, including proposed changes in previously approved projects. The following describes the most common classes of review and decisions made by the IRB:

Categories of IRB Actions. Following review of the application, the IRB will take one of the following actions:

- Approved. The protocol is approved as submitted.
- Conditionally Approved: The problems regarding the protocol are not of a serious nature and consist of minor changes needed in the consent document or clarification regarding an item in the protocol that needs to the documented in the application or protocol. Generally the IRB Chair is authorized by the IRB to review and approve the investigators' resolution of these problems. If more significant problems are identified, the IRB may stipulate how such issues will be resolved. If the investigator does not accept such amendments, he/she must resubmit a justification to the full IRB for review and approval.
- Tabled. The changes proposed or the questions asked by the IRB are significant enough to warrant additional review and clarification.
- Disapproved. The protocol is deemed so lacking in scientific merit or raises such serious ethical questions as to be totally unacceptable.

Special Categories

FDA Regulated Research

The NEOMED IRB currently is authorized by the Institution and the Federal regulations to operate under the Office of Human Research Protections (OHRP) regulations. For studies falling under the FDA regulation, the use of a commercial IRB for drug, medical device, and biologic studies should be considered an option. For this reason, NEOMED has partnered with a commercial IRB, Advarra, to provide review and approval of FDA regulated research. Since the use of a commercial IRB does come at a cost, investigators are encourage to incorporate the expense of review into the budget of the grant supporting the research.

Patients Unable to Provide Informed Consent

Research involving people who may not be able to provide informed consent (trauma, stroke, critically ill, etc) should be addressed with the NEOMED IRB prior to submission of an application.

Genetic Research

Guidance on the Genetic Information Nondiscrimination Act (GINA): Implications for Investigators and IRBs is available at this site:
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-genetic-information-nondiscrimination-act/index.html

GINA is a Federal law that prohibits discrimination in health coverage and employment based on genetic information. GINA defines *genetic information* as information about:

- An individual's genetic tests (including genetic tests done as part of a research study);
- Genetic tests of an individual's family members (defined as dependents and up to and including 4th degree relatives);
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.
- Genetic information does not include information about the sex or age of any individual.

GINA defines a genetic test as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detect genotypes, mutations, or chromosomal changes. Routine tests that do not detect genotypes, mutations, or chromosomal changes, such as complete blood counts, cholesterol tests, and liver enzyme tests, are not considered genetic tests under GINA. Also, under GINA, genetic tests do not include analyses of proteins or metabolites that are directly related to a manifested disease, disorder, or pathological condition that could reasonably be detected by a health care professional with appropriate training and expertise in the field of medicine involved.

GINA includes a "research exception" to the general prohibition against health insurers or group health plans requesting that an individual undergo a genetic test. This exception allows health insurers and group health plans engaged in research to request (but not require) that an individual undergo a genetic test. This exception permits the request to be made but imposes the following requirements:

- The request must be made pursuant to research that complies with HHS regulations at 45 CFR part 46, or equivalent Federal regulations, and any applicable state or local laws for the protection of human subjects in research;
- There must be clear indication that participation is voluntary and that non-compliance has no effect on enrollment or premiums or contribution amounts;
- No genetic information collected or acquired as part of the research may be used for underwriting purposes;
- The health insurer or group health plan must notify the Federal government in writing that it is conducting activities pursuant to this research exception and provide a description of the activities conducted; and
- The health insurer or group health plan must comply with any future conditions that the Federal government may require for activities conducted under this research exception.

Given that GINA has implications regarding the actual or perceived risks of genetic research and an individual's willingness to participate in such research, investigators and IRBs should be aware of the protections provided by GINA as well as the limitations in the law's scope and effect. IRBs should consider the provisions of GINA when assessing whether genetic research satisfies the criteria required for IRB approval of research, particularly whether the risks are minimized and reasonable in relation to anticipated benefits and whether there are adequate provisions in place to protect the privacy of subjects and maintain the confidentiality of their data. GINA is also relevant to informed consent. When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider whether and how the protections provided by GINA should be reflected in the consent document's description of risks and provisions for assuring the confidentiality of the data.

GINA and the Criteria for IRB Approval of Research

When reviewing proposed or ongoing genetic research, IRBs should consider the protections provided by GINA when determining whether the research satisfies the following criteria required for IRB approval of research:

- Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures which are already being performed on the subjects for diagnostic or treatment purposes (45 CFR 46.111(a)(1));

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)); and

- When appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data (45 CFR 46.111(a)(7)).

Among the risks typically associated with genetic research, investigators, IRBs, and research subject advocates, among others, have identified the potential adverse impact on insurability or employability if genetic information about the subject obtained as part of the research was disclosed to, or sought by, insurers or employers. When the provisions of GINA take effect, the risk of such harms will be decreased with respect to health coverage and most employment. Since a decrease in risk should favorably affect the risk-benefit assessment for genetic research, the protections provided by GINA have direct relevance for IRBs that are assessing whether genetic research satisfies the criteria under 45 CFR 46.111(a)(1), (2), and (7).

Even though the provisions of GINA related to health coverage generally will take effect between May 22, 2009, and May 21, 2010, and those related to employment will take effect on November 21, 2009, investigators and IRBs should be aware that the protections provided by GINA are pertinent to genetic research that is conducted prior to these effective dates because these protections eventually will extend to genetic information obtained as part of any research study regardless of when the research was conducted. Therefore, IRBs conducting initial or continuing review of genetic research prior to GINA's stipulated effective dates should take into account the protections to be provided by GINA when assessing whether such research satisfies the criteria required for IRB approval of research referenced above.

When making the above determinations required under 45 CFR 46.111(a), IRBs also need to be cognizant that (1) GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance; and (2) GINA's provisions prohibiting discrimination by employers based on genetic information generally do not apply to employers with fewer than 15 employees.

<u>GINA and the Requirements for Informed Consent</u>
When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider the protections provided by GINA, particularly with respect to the following elements of informed consent that must be provided to subjects (unless an IRB has approved an alteration or waiver of these requirements in accordance with the requirements of HHS regulations at 45 CFR 46.116(c) or (d)):

- A description of any reasonably foreseeable risks or discomforts to the subjects (45 CFR 46.116(a)(2)); and
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (45 CFR 46.116(a)(5)).
- Investigators and IRBs must ensure that descriptions of the reasonably foreseeable risks of genetic research and any statements describing the extent to which confidentiality of records identifying the subject will be maintained do not overstate the protections provided by GINA (45 CFR 46.116(a)). Key points for investigators and IRBs to consider when describing these protections include the following:

- The provisions of GINA related to health coverage generally will take effect between May 22, 2009, and May 21, 2010, and those related to employment will take effect on November 21, 2009.
- The discrimination protections provided by GINA address health coverage and employment only.
- GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance. Therefore, to the extent that the risks of genetic research include potential adverse impact on a subject's ability to obtain life insurance, disability insurance, or long-term care insurance if genetic information about the subject obtained as part of the research was disclosed to or sought by such insurers, GINA has no effect on these risks.
- GINA generally does not apply to employers with fewer than 15 employees. Therefore, subjects who are or will be employed by such employers receive none of the GINA protections that prohibit discrimination in employment on the basis of genetic information.

OHRP recommends that for genetic research undergoing initial or continuing review investigators and IRBs consider whether consent processes and documents should include language regarding the protections provided by GINA, and if so, ensure that such language accurately describes the impact of GINA on the risks and confidentiality protections for such research.

Human Stem Cell Research
The IRB supports the American Society for Reproductive Medicine (ASRM) guidelines on the use of gametes and embryos for research and the NIH guidelines on the use of stem cells for research purposes. The IRB also supports the report and recommendations of the National Bioethics Advisory Committee (NBAC) regarding human stem cell research. Research utilizing human pluripotent stem cells for both basic knowledge and for clinical applications is subject to IRB review and current Federal regulations.

Specific guidance from OHRP regarding human embryonic stem cells, germ cells and cell derived test articles is available at this site:
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-research-involving-stem-cells/index.html

Children
Additional protections for children involved as subjects in research is covered in sections 45 CFR 46.401 – 409. Categories covered include
- Definitions
- Research not involving more than minimal risk
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- 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
- Requirements for permission by parents or guardians and for assent by children, and wards.

Additional information is provided in a FAQ section at this Research with Children- FAQ

Employees of NEOMED and its Affiliates
Employees, such as office staff, lab technicians, and post-doctoral fellows, are similar to students in that they are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor's work. Accordingly, many of the same procedures employed to reduce the likelihood of coercion in recruiting student volunteers apply equally to employees. The IRB will not approve recruitment procedures that include employees from the investigator's own lab or office as research subjects.

NEOMED Students
Students traditionally have served as subjects for biomedical research and behavioral research. The obvious concern is that their participation may not be truly voluntary because of a desire to appear particularly cooperative or highly motivated, or because participation in research is a course requirement. The IRB suggests several procedures to reduce the possibility of unintended coercion, while still permitting students to participate as subjects in research. These include:
(a) Design study advertisements so that they recruit subjects from a broad base of students;
(b) Avoid personal solicitations of students by faculty, graduate assistants, or fellow students;
(c) Provide a number of research projects from which to chose, if participating as a subject in research can be used as a course requirement;
(d) Provide alternative and equal methods for meeting course credit (or extra credit) requirements, such as attending a series of research presentations by faculty, writing a brief paper, conducting one's own research.

Minorities
Federal regulations require the equitable selection of minorities as research subjects [45 CFR 46.111.(a)(3)].

The inclusion of minorities in research is important both to ensure that they are eligible for an equal share of the benefits of research, and to ensure that they do not bear a disproportionate burden. Sometimes minorities are subject to different clinical conditions compared to other populations. For example, sickle cell anemia and Tay Sachs disease only affect a few minority groups. Other research focuses on characteristics of diseases or effectiveness of therapies in particular populations (e.g., HIV transmission, treatment for hypertension), and may also concern conditions or disorders that disproportionately affect a certain racial or ethnic group. Exclusion or inappropriate representation of these groups, by design or inadvertence is unjust. Considering that participation in research could potentially offer direct benefits to the subjects (e.g. HIV/AIDS research), under-representation of minorities denies them, in a systematic fashion, the opportunity for direct benefit. A discussion of this determination can be found in the guideline: Inclusion of Women and Minorities in Research.

Prisoners
Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for voluntary choices, earning wages, interaction with the community, and obtaining medical care. Studies have shown that prisoners often volunteer for medical research as a means of access to a competent medical examination, because health care

may be woefully inadequate in prison. Protections pertaining to biomedical and behavioral research involving prisoners as subjects is covered in section 45 CFR 46.301 – 306. Because a prisoner's autonomy is limited, they may participate only in certain categories of research, and special precautions are needed to assure that their consent to participate in the research is both knowing and voluntary [45 CFR 46.302].

The IRB will only allow research studies involving prisoners when the research involves the following methods and goals:

- Studies of the possible causes, effects, and process of incarceration and criminal behavior, if these studies present no more than minimal risk or inconvenience to the subjects;
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects;
- Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the Secretary of Health and Human Services has consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register; and
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects. However, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by the Secretary of Health and Human Services, after consultation with appropriate experts, as described above.

Additionally, the IRB will review each submitted protocol to verify that:

- Any advantages that prisoners will realize as a result of participating in the research, when compared to the general living conditions within the prison, are not so great as to impair prisoners' ability to weigh the risks and benefits of participation and freely choose whether or not to participate;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (usually demonstrated by enrolling non-prisoner subjects from the community, as well);
- Procedures for selecting subjects within the prison are fair, and free from arbitrary manipulation by prison authorities or prisoners;
- Control subjects will be selected randomly from among the group of eligible volunteers, unless the PI justifies a different procedure;
- The information presented during recruitment and consent procedures is in a language, and level of complexity, understandable to the subject population;
- The IRB must be assured that the parole board will not take research participation into account in making decisions about parole, and each prisoner is informed in advance that participation will have no effect on the possibility of parole;
- If medical follow-up is necessary to protect the health and welfare of the subjects, adequate provision is made for such care, taking into account the varying length of prisoners' sentences.
- The IRB that reviews research involving prisoners is required to have at least one member who is either a prisoner, or a prisoner representative. The majority of the IRB members cannot be in any way associated with the prison(s) involved.

Women
The primary aim of clinical trials is to provide scientific evidence leading to a change in health policy or a standard of care, therefore it is imperative to determine if the intervention or therapy being studied affects men and women differently. NIH has concluded that the inclusion of women in research is sufficiently important that the only justifiable reason to exclude non-pregnant women of child-bearing potential from research is compelling evidence that the proposed project would be inappropriate with respect to the health of the subject or the purpose of the research. A discussion of this determination can be found in the guideline:
Inclusion of Women and Minorities as Participants in Research Involving Human Subjects - Policy Implementation Page

Pregnant Women, Human Fetuses and Neonates Involved in Research
Protections for pregnant women, human fetuses and neonates involved in research are covered in sections 45 CFR 46.201 – 207 at this site
Subpart B- Protections for Pregnant Women, Human Fetuses and Neonates

International Research
Research in foreign countries conducted by NEOMED faculty, staff or students poses unique and complex ethical challenges. This is because of the different cultures and values found in each country. It is crucial in conducing ethical research to understand the local context of the human participants enrolled in the research project. As the PI of an international research study, you are required to display the knowledge and meet the expectations listed below:

- **You must obtain IRB approval before your study can begin.** Whether you are a faculty member, staff or student, your research study must be approved by the NEOMED IRB before it can begin. Make sure you have the IRB's approval before you leave for the host country and allow adequate time for reviews before your departure.
- **Demonstrate cultural understanding and sensitivity.** Your IRB application/protocol should describe any anticipated cultural sensitivities of conducting your research and how you intent to overcome those barriers. The researcher should be familiar with local customs, culture and religious norms in the country where the study will be conducted. Is the typical process of signing an informed consent document culturally acceptable for your study? How should recruitment be done? Are there other cultural barriers you might encounter once you arrive? The IRB will consider alternative consent form formats or methods if culturally appropriate.
- **Understand the research ethics guidelines of the host country.** Investigators will be required to obtain IRB approval for research done internationally from the NEOMED IRB and also from the local IRB/Ethics Committee within the country in which they will be doing their research. This approval must be on file with the IRB prior to IRB approval being granted. *The IRB strongly recommends you clearly understand the host country's requirements for reviewing and approving human subject research.* Some countries have clear ethical guidelines that must be met for conducting domestic and/or international research. Other countries will not have a formal process but might rely on other

neighboring countries to assist with the review. Where there is no equivalent board or group, researchers must rely on local experts or community leaders to provide approval. Resources to help determine a countries ethical guidelines are listed below:

- The Office of Human Research Protections (OHRP) publishes the International Compilation of Human Research Standards, a listing of over 1,000 laws, regulations, and guidelines on human subjects protections in over 100 countries and several international organizations. Researchers should check this document to determine the countries applicable laws, regulations and guidelines on Human Subjects Researcher.
- The Office of Human Research Protection (OHRP) has issued a List of 27 Social-Behavioral Research Standards. This includes laws, guidelines, and regulations applicable to social-behavioral research around the world.
- **Know the data laws.**While not specifically under the IRB's domain, you should know that there are some restrictions on bringing identifiable data into/out of some countries. The EU, for example, has laws surrounding what kind of identifiable information can be taken out of Europe and brought to the US (this applies to electronic data that will be housed on a US server as well). Data export laws may also affect your research in countries with which the US has embargoes or trade restrictions, such as Iran.
- **Please contact the IRB while abroad if you encounter any problems or need to change your IRB-approved protocol.** If you find that upon arrival in the host country, some aspects of your research study must be modified for whatever reason, *please notify the IRB office immediately*. The IRB will do its best to quickly respond to your notification with further instructions and guidance. Please wait to hear back from the IRB before making any changes to your protocol!

Writing your IRB Application for International Research: What Information Must Be Included:

In your IRB submission, it is important that you tell us what you know about the country where the study is being conducted. The IRB relies on the information you provide to help assess whether the rights protections are in place for subjects. In addition to the usually required information submitted for review to the IRB, the following points should be addressed in your submission.

- Your IRB protocol should describe relevant local context information, any anticipated cultural sensitivities of conducting your research and how you intent to overcome those barriers. This should include, but not limited to the following:
    1. Cities, regions countries where research will be conducted
    2. Scientific/ethical justification for conducting the research in an international setting
    3. Economic status of the country/community
    4. Current events or socio-political environment in the country that may impact research conduct or alter the risks or benefits to subjects
    5. Societal and cultural beliefs in the country that may impact research conduct or alter the risks or benefits to subjects
    6. The role of women and children in the society, including their autonomy and legal capacity to make decisions
    7. Literacy rate of the potential subject population

8. Languages and dialects of the potential subject population
9. Involvement of organizations, community leaders, or experts in engaging the subject population or conducting the research
10. Description of the research team's knowledge of or experience in the host country
11. Relevance of the research to the area's health, economic, educational, or other needs
12. Distribution of risks and current and future benefits
13. Detail any proposed remuneration (payment, gifts, incentives, etc.) for subjects including:
    - Specific description of the remuneration (payment, gifts, incentives, etc.)
    - Value both in US and local currency
    - Local household income information (e.g. how much an average household earns in a month or a year in US and local currency)
    - When remuneration will be given during the study (the payment schedule)
    - To whom remuneration will be given
    - Whether the remuneration could pose undue influence on the subject's decision to participate.

- Approval letter from the local IRB/Ethics Committee within the country where research will be conducted. equivalent board or group, researchers should provide an explanation of such and should consult with local experts or community leaders to provide an approval letter that the research as proposed meets local standards.
- The consent form should be submitted in both the local language of the host country and in English. Please clearly label each form for the IRB. The application should also indicate who conducted the translation of the forms and provide a letter certifying the translations are correct.
- Local contact information for participants to contact about research related questions.
- Recruitment materials to be used in both the local language of the host country and in English.
- Describe how you will keep your data secure at all stages: while you are collecting it in the host country, while you are traveling back to the US and once you arrive here.

Study Implementation, Event Reporting and Completion

A study involving human subjects research may not begin until the IRB has reviewed and approved the research. Continuing annual review, which is an IRB function, needs to be differentiated from monitoring or surveillance. **The IRB or IRB Chair may audit a human study at any time without advance notice**.

Role of Investigators

All University investigators, including students, are responsible for abiding by the protocol approved by the IRB, coordinating any communications regarding IRB approval through the PI (including reporting of adverse events), and implementing the authorized informed consent process exactly as described in the approved IRB protocol. The latter includes not only the

consent form but also recruitment materials and the manner in which prospective subjects are approached and consent is obtained.

Research investigators will promptly report proposed changes in previously approved human subject research activities to the IRB by submitting an IRB Amendment Form found of the IRB website with the IRB office. The proposed changes may not be initiated without IRB review and approval, except where necessary to eliminate immediate hazards to the subjects.

Investigators are expected to report adverse events and other problems to the IRB and possibly sponsors, designated institutional representatives, and OHRP. (See section on Adverse and Serious Adverse Event Reporting, below).

The PI is also responsible for assuring that any required closure or continuation forms are completed as requested by the IRB office and filed in a timely manner. While the IRB office tracks the review period of all approved projects requiring annual review, it is the responsibility of the PI to submit a continuation application before the expiration of his/her current approval.

Complete instructions for requesting extension approval appear on the Continuation Review Report Form. **The continuation of research after expiration of IRB approval is a violation of Federal regulations** 45 CFR 46.103(d)**.** If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities should stop. No new subjects may be enrolled in the study. However, if the investigator is actively pursuing renewal with the IRB and the IRB believes that an over-riding safety concern or ethical issue is involved, the IRB may permit the study to continue for the brief time required to complete the review process.

If a research study has been formally completed or terminated, the PI must notify the IRB in writing by filing a Study Completion Form. The investigator is responsible for reporting data in a completely accurate manner when publishing final results of a study.

Obtaining Informed Consent

The new definition of ‘‘written or in writing’’ is included in the Final Rule to clarify that these terms include electronic formats, which aligns the Common Rule with U.S. Food and Drug Administration (FDA) and the International Council for Harmonization (ICH) initiatives to promote electronic consent. The Final Rule’s preamble notes that the definition does not preclude the possibility that consent forms could be in media other than paper or electronic formats and still meet the requirements of the Common Rule.

While electronic consent is allowed, participants must be provided with a written copy.

Informed consent is an educational process, not just a form to sign.
The procedures used to obtain informed consent should be designed to educate the subject population and ensure they fully understand the study and the voluntariness of their participation.

- Informed consent must be prospectively obtained from subjects or their legally authorized representatives (guardian, parent, proxy).

- Subjects should fully understand the study and their role as participants.
- Subjects must be given sufficient opportunity to consider whether they want to participate.
- Consent must be given without coercion, manipulation or undue influence.
- Subjects do not give up any of their legal rights or be given the impression that they are being asked to do so.
- The consent document is to be used as a guide for the verbal explanation of the study.
- The consent document should be the basis for a meaningful exchange between the researcher and the participant.
- Each element of the consent form should be read to the subject for studies that have face-to-face interactions and require a signature to confirm subject understanding and voluntary participation.
- The subject's signature and the investigator's signature (or person obtaining consent) provides documentation of mutual understanding and the subject's agreement to participate in a study, but is only one part of the consent process.
- The consent document must not serve as a substitute for discussion.
- A copy of the consent document must be provided to subjects.
- Contact information – including the PI's and HPA's contact information – should be provided. If someone is obtaining consent other than the PI, their contact information should also be given to the subject in the event they need to clarify elements of the study, especially when a trusting relationship has been established.

Documentation of Informed Consent

In most cases, informed consent is documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. The subject or their representative must be given ample time to read the form and contemplate its contents before signing. A copy should be given to the person signing the form, another kept in the investigator's research records, and (if medical research) one in the patient medical record.

The consent form must be written in language considered appropriate at the eighth grade reading level regardless of the subject population. Novel tools to assist the informed consent process include videos, question and answer workbooks, photos, sketches and diagrams. The use of bold face font, underlined font, and simple paragraph structures are highly recommended as an aid to calibrate informed consent to a participant's level of educational sophistication.

The IRB recognizes that certain populations may require additional protections because they are economically or educationally disadvantaged. Every subject's rights and welfare should be safeguarded by making sure that any possible coercion or undue influence is eliminated (e.g., compensation that is not commensurate with risk, discomfort, or inconvenience involved; recruiting in settings where voluntary participation might be compromised). Investigators should address these issues specifically when submitting their protocol to the IRB.

Federal regulations require the translation of consent documents into the language that is most easily understood by research subjects. The possibility of illiteracy should be accounted for, as should the need for communicating in non-English languages. Non-English speaking subjects must have informed consent documentation presented in a written language that they understand

(45 CFR 46.116 (a)(3)). The inability to read or to read English is not an appropriate basis for exclusion from most research.

If the research protocol proposes to use non-English language consent documents, quality assurance procedures should be developed such as translation of the consent document from English to the second language and then back to English, by a certified translator, to ensure that the information is correctly conveyed. The IRB is required to review and approve all non-English consent forms and recruitment tools. The role of cultural values and norms of subjects should also be addressed. This information should be provided in a clearly identifiable form to the IRB for review.

Record Keeping – Investigators
Investigators are notified in writing of the IRB's decisions, including results of exemption and expedited review. This notice includes the approval date, risk classification, and approved project period, and is accompanied by the authorized version of the consent form (indicated by a stamp on behalf of the IRB). A 5-digit reference number is assigned to each application and provided to the investigator at the time of IRB review. This number must appear on all communications between the investigator and the IRB to assure that all related documents are correctly associated with a given project.

Investigators will maintain documentation and record-keeping in accord with good academic process and as required by applicable University policy. Research investigators are responsible for retaining the records of all IRB-approved projects in a specified location for at least three years after the study has been closed with the IRB. If the project is funded, it is three years after the end of the funding period. This responsibility includes storage of confidential data in a secure manner that assures only authorized personnel will have access. While this timeline applies to Federal requirements, investigators are advised to ascertain the retention requirements of their certification, licensing, and/or professional bodies, as appropriate.

What are Unanticipated Problems?
NEOMED considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given:
    (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
    (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized**.**

The common features of events that are considered unanticipated problems is that all potentially place subjects at risk of harm. Even when no actual harm occurs, if the event meets the definition of an unanticipated problem, it must be reported to the IRB. When the event goes beyond simply potential harm to where actual harm befalls a subject, then the event would be considered an adverse event. Adverse events make up the most frequently reported unanticipated problem reported to the IRB.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

What are Adverse Events?
In general, NEOMED recognizes the term *adverse event* to include any event meeting the following definition:
Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events are defined as undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention. Adverse events do not necessarily have to have a causal relationship with the research project. An adverse event may or may not be serious and may or may not be expected.

Investigators are responsible for reporting two types of adverse events (AE): 1. Any subject injuries or adverse reactions associated with the study procedures, and/or problems involving the conduct of the study that may occur during the course of the research project; and 2. Any possible breach of human subject protection in other research activities of which the investigator may become aware. The IRB Chair is responsible for the appropriate and timely presenting of such events to the full IRB for the purpose of evaluating risk assignment, consent information, and approval period.

Failure to report an AE is a breach of the conditions in which the IRB granted protocol approval. This breach can result in the suspension or termination of the research study. Unreported AE's can affect the safety and welfare of current and future research participants thus it is essential that these events/incidents be reported in a thorough and timely manner.

What are Serious Adverse Events?
An adverse event is considered a "Serious Adverse Event" when any adverse event temporally associated with the subject's participation in research meets any of the following criteria:

- results in death;

- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Requirements and Procedures for Unanticipated Problems and Adverse Events
Serious adverse events, as defined above, must be reported to the IRB within 24 hours of the PI's becoming aware of the event by completing a "Unanticipated Problem/Adverse Event" form on the IRB website and forwarding to the IRB Chair. All other non-serious adverse events and unanticipated problems or should be reported to the IRB within 5 working days of the first awareness of the problem by the Protocol PI, another researcher, or a member of the IRB by completing and submitting an Adverse Event/Unanticipated Problem" form. Prompt reporting is important, as unanticipated problems often require some modification of study procedures, protocols, and/or informed consent processes. Such modifications require the review and approval of the IRB.

After confirming the described event meets the qualifications of an adverse event or unanticipated problem, the IRB Chair will meet with the Human Protections Administrator to discuss the event.

All unanticipated problems/adverse events will be reported to appropriate institutional officials, the supporting agency head (or designee), and OHRP if required within one month of the IRB's receipt of the report of the problem from the investigator. The V.P. for Research is responsible for reporting qualifying events to OHRP as required, and for reporting to other appropriate Institutional Officials (IO).

IRB Actions to Problem and Event Reporting
Initial review of unanticipated problems/adverse events will be conducted by the IRB Chair (or his or her designee). The IRB Chair is authorized to take the following actions in response to the receipt of an Adverse Event/Unanticipated Problem Form :

- Assess whether the incident constitutes an unanticipated problem/adverse event and by whom it should be reviewed (e.g., the Chair only, another IRB member, a subcommittee of the IRB, or the convened/full committee IRB).
- If full committee review is needed, assign the incident report for review at the next available regularly scheduled IRB meeting.
- If warranted, convene an emergency meeting of the full committee IRB to review the report.
- If warranted, temporarily suspend research if the rights, safety, and welfare of subjects are jeopardized until such time that the full committee IRB can convene to review the report.

In order to protect the ongoing safety of research subjects due to the nature or frequency of reported problems/events, the IRB may require the following actions:

- Modification of subject inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Modification of informed consent documents to include a description of newly recognized risks;
- Provision of additional information about newly recognized risks to previously enrolled subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;
- Suspension of the entire study; or
- Termination of approval for the entire study.

If the unanticipated problem/adverse event results in an amendment of the research protocol and/or informed consent documents, an amendment application must also be submitted to the IRB. If the changes are minor they may be reviewed by expedited procedures. If the changes are more than minor, they must be reviewed and approved by the convened committee. Any such proposed changes in response to an unanticipated problem/adverse event must be reviewed and approved by the IRB before being implemented, except when implementation is necessary to eliminate apparent immediate hazards to subjects.

Further guidance is provided by OHRP:

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007)

The following form is available from the IRB website:

- Adverse Event/Unanticipated Problem Form

Amendment/Addendum to an Approved IRB Protocol

Section 45 CFR 46.103(b)(4) states the IRB must be notified of all proposed changes in an IRB approved research activity and that no changes may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

IRB approval must be obtained prior to any changes in an IRB approved protocol by submitting and amendment/addendum request form. This requirement includes protocols granted exempt status.

The following form is available from the IRB website:

- Amendment/Addendum Request Form

Annual Check Point – For Studies Approved by Expedited Review

The 2018 Federal Regulations for the review of research state that continuing review of research reviewed by expedited review is no longer a requirement. In place of a continuation review, researchers will be asked to provide an annual "check point" for their research. The yearly check

point will provide brief information to the IRB regarding the general status of the project. Investigators will receive an e-mail from the IRB each year prompting them for check point information until such time that the project ends and the investigator closes the study for filing a study closure form.

Continuation Requests – For Studies Approved by Full Board
An annual continuation review is required of all studies approved at a convened meeting of the full IRB (unless the study now meets the requirements for expedited research.) The investigator will be sent a reminder approximately 6 weeks prior to the IRB meeting along with the Continuation Review Form found on the IRBs website. Continuation Review Forms and all associated materials are must be received in the IRB office 10 working days before the IRB meeting date. The IRB will assign one primary reviewer and place the continuation request on the next available agenda of a convened IRB meeting. At that meeting, the primary reviewer will lead the discussion of the renewal request. Material accompanying the Annual Continuation Form include a summary of the study, an outline of all amendments and adverse effects occurring during the approval period, the most recently used informed consent, and any reports of other findings relating to subject safety. During this review, the IRB will make a determination whether any new findings, new knowledge, or adverse effects should be communicated to subjects. Discussion will focus on any substantive issue resulting from this review. Final approval will include stipulated changes to the informed consent document(s), whether the risk classification is altered, and the length of the new approval period, not to exceed one year.

The following forms are available from the IRB website:

- IRB Continuation Request Form
- IRB Study Completion Form

Noncompliance
Failure to obtain IRB approval prior to the involvement of human subjects constitutes violation of University policy, which is subject to disciplinary action and/or legal action by the University in accord with standard academic practice.

Suspension/Termination: 45 CFR 46.113
An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

The IRB may suspend or terminate approval for any of the following reasons:

The investigator fails to:

- obtain informed consent
- retain completed consent form(s)
- make required revisions prior to starting the study
- made requested changes in the study
- provide accurate progress reports regarding the conduct of the study, i.e., number of subjects, adverse reactions, etc.

- inform the IRB that the sponsoring agency has discontinued the study for reasons of safety

The investigator shows lack of propriety or deceit through:

- evidence the original study has been altered
- unauthorized modification of the study or consent form
- scientific misconduct involving risks to human subject or others
- evidence that the rights of subjects have been violated
- Careful review of reports of adverse events show that unexpected or serious harm occurred to subjects.
- Significant new findings developed during the course of the research which alter the feasibility of the study.

Protocol Close-Out

All IRB non exempt studies that are completed must undergo a formal close-out procedure by completing a "Study Closure Form" available at the IRB website. Failure to complete a study closure/study continuation form and return to the IRB Office may result in administrative closure of the study. No additional studies will be accepted by the IRB for review until the required form is received. The Study Completion Form is available on the IRB website.