Policies and Procedures for the Approval of Research involving Human Subjects

Cary Institute – Institutional Review Board (IRB)

POLICY STATEMENT

Human subjects research at the Cary Institute of Ecosystem Studies (Cary Institute) is guided by the basic ethical principles found in The Belmont Report.

The Belmont Report sets forth three basic ethical principles for the conduct of human subjects research:

1) Respect for persons
    - Respect individual autonomy
    - Protect individuals with reduced autonomy
2) Beneficence
    - Maximize benefits and minimize harm
3) Justice
    - Equitable distribution of research burdens and benefits

Application of these general ethical principles to the conduct of human subjects research leads to the following requirements:

1) Respect for persons
    - Informed consent
    - Protecting privacy and maintaining confidentiality
    - Additional safeguards for protection of subjects likely to be vulnerable to coercion or undue influence
2) Beneficence
    - IRB assessment of risk/benefit analysis including study design
    - Ensure that risks to subjects are minimized
    - Risk justified by benefits of the research
3) Justice
    - Ensure that selection of subjects is equitable

The Food and Drug Administration (FDA) has a separate set of regulations governing human subjects research (21 CFR Part 56 — IRBs and 21 CFR Part 50 — Informed Consent). The basic requirements for IRBs and for informed consent are congruent between the HHS and FDA regulations.

Differences center on differences in applicability:

- HHS regulations at 45 CFR Part 46 apply to research conducted or supported by HHS.
- FDA regulations apply to clinical investigations of FDA regulated products: drugs, devices, or biologics.

Human subjects research at the Cary Institute is guided by the procedures described in 45 CFR, Subtitle A, Part 46 of the Department of Health and Human Services (HHS) regulations. These regulations were updated and amended by the final rule published on January 19, 2017 (82 FR 7149), and effective on January 21, 2019 (referred to as the Revised Common Rule or 2018 requirements).

The HHS regulations contain three basic provisions for the protection of human subjects:

- Institutional assurances of compliance
- IRB review
- Informed consent

Institutional assurance of compliance is documentation of an institutional commitment to comply with HHS regulations for the protection of human subjects. HHS will conduct or support non-exempt research covered by the regulations only if: the institution has an OHRP-approved Assurance, and the institution has certified to the HHS that the research has been reviewed and approved by an IRB.

These procedures are codified in the respective regulations of 15 other federal agencies.[1] These regulations do not permit the commencement of research activities involving human subjects until such activities have received the approval of an Institutional Review Board (IRB), whose function is to review and approve research activities involving human subjects. In this document, all regulatory references will point to 45 CFR Part 46.

While the regulations specifically apply to human subjects research that is conducted, supported, or otherwise subject to regulation by any Federal department or agency that has made the policy applicable to such research, the Cary Institute applies this policy to any human subjects research lead or conducted by its employees, regardless of sponsor.

This document is broken down into the sections described below in the Table of Contents.

[1] These agencies include the Departments of Homeland Security, Agriculture, Energy, Commerce, Housing and Urban Development, Labor, Defense, Education, Veterans Affairs, and Transportation, as well as NASA, Social Security Administration, Agency for International Development, EPA, and NSF.

Cary Institute of Ecosystem Studies

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Applicability of the 2018 Requirements

All human subjects research protocols approved by the Cary Institute IRB after the implementation date of the revised Common Rule (January 21, 2019) will be subject to the 2018 requirements.

All Cary Institute IRB protocols approved prior to the 2018 requirements will continue to be compliant with the pre-2018 requirements, unless a substantial amendment is proposed such that the IRB determines that it is appropriate for the protocol to comply with the 2018 requirements. Such a determination will be discussed with the Principal Investigator (PI) first.

In summary, all IRB actions and research-related activities that occur after January 21, 2019 will be subject to the 2018 requirements. The IRB will not review actions, activities, or approvals that occurred prior to the 2018 requirements to review whether or not these actions, activities, or approvals complied with the 2018 requirements unless a proposed amendment to the protocol makes this necessary.

Definitions

For the purposes of this policy, the definitions follow those found at 45 CFR 46.102. This can be found by visiting the following website: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html.

Some important definitions are included below:

Research: a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Human Subject: a living individual about whom an investigator (whether professional or student) conducting research: (1) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (2) obtains, uses, studies, analyzes, or generates identifiable identifiable private information or identifiable biospecimens.

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 that will not be made public (e.g., a medical record).

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

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

Institutional Review Board (IRB): an institutional review board established in accord with and for the purposes expressed in this [HHS] policy.

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.

Interaction: includes communication or interpersonal contact between investigator and subject.

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

Cary Institute's Institutional Review Board (IRB)

Membership

The Cary Institute's IRB is appointed by the President (or his/her delegate, which can be the Institutional Official) and is commissioned to review all proposals for research which involve human subjects, according to the Cary Institute's Federal Wide Assurance (FWA00013876) with the Department of Health and Human Services. Membership is updated annually. The task of the IRB is to ensure that the approved research is in compliance with ethical standards, Cary Institute policy, and federal regulations for the protection of human subjects. **All human subjects research conducted at, by, or under the auspices of the Cary Institute, whether funded or not and whether conducted by administrators, faculty, staff, or students, must be reviewed and approved before the research begins.**

The IRB must consist of at least five members (including a chairperson) ideally with different backgrounds and diversity with respect to race, gender, and cultural backgrounds, and covering the following areas:

- One with primary concerns in scientific areas;
- One with primary concerns in nonscientific areas; and
- One who is not otherwise affiliated with the institution and not an immediate family member of a person who is affiliated with the institution.

The Cary Institute's IRB Office is located in the Grants and Compliance Office and is staffed by the Institutional Official and IRB Assistant. Together with the IRB Chairperson (Chair), they handle the day-to-day operations of the IRB.

A current list of all Cary Institute IRB members, including contact information, is posted on the Cary Institute's Compliance Intranet webpage.

Management

IRB Institutional Official (IO)
The Institutional Official (IO) and Grants/Compliance Office staff oversee and provide support to the IRB. They receive incoming IRB protocol applications and conduct initial reviews along with the Chair. They maintain a database of individuals who have completed training in the protection of human research participants. They also maintain a database of active IRB protocols and amendments. The current IO is the Grants Manager/Compliance Officer.

The IO appoints new or renews the membership of existing IRB members annually on or before October 1 and provides the current list of members to the Cary Institute's President.

IRB Chairperson (Chair)
The IRB Chair is appointed by the IO and serves as Chair for at least one year. Chairs may be reappointed for additional one-year appointments. The Chair may be removed or replaced by the IO.

The Chair directs the IRB meetings in accordance with Institutional and federal requirements. The Chair works closely with IRB members, the IO's Grants/Compliance Office, and investigators to ensure the rights and welfare of research participants are protected. The Chair has the authority to sign for the IRB and conducts all IRB meetings. The Chair designates the reviewers for expedited and full-board applications and may delegate the ability to assign reviewers to the IO. The Chair, in consultation with the IO, will make determinations of exempted research, and protocols that can be reviewed under expedited review.

IRB Members
All individuals appointed to the IRB will serve on the board for a one-year term, renewable annually, starting on October 1 of each calendar year. Appointments may begin at other times but all appointments will end on September 30 of the final year of the appointment. There is no limit to the number of terms a member may serve on the IRB. IRB members may be removed or replaced by the IO, or choose when they are no longer willing or able to serve.

IRB members are responsible for protecting the rights and welfare of human research subjects by reviewing, approving and monitoring human subjects research in a manner consistent with federal regulations, state and local laws, and Institutional guidelines and policies.

Consultants to the IRB
The IRB is encouraged to use non-member consultants for advice and information in specialized areas as needed. These consultants may be Cary Institute faculty or staff, affiliates, or experts not affiliated with the Cary Institute. The consultants may present their assessments in writing or in person.

Functions, Operations, and Authority

The Cary Institute's IRB has the authority to certify exempt projects, review and approve all non-exempt (expedited and full board) human subject research (prior to and after approval), require amendments to existing protocols, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and Institutional policy. PIs are notified in writing of the IRB's decision to approve or disapprove protocols, as well as any modifications needed to approve research, and provided with explanations for these decisions. PIs have the opportunity to respond to any decision made by the IRB.

The Cary Institute's IRB functions independently of other committees and makes independent determinations to approve or disapprove the human subjects research application based upon whether or not human subjects are adequately protected.

The minutes of any IRB meetings shall provide sufficient detail to show attendance of IRB members, actions taken by the IRB (including a record of how each individual member voted on a particular action – for, against, or abstain), the basis for any required changes to or disapproval of proposed research, and a written summary of the discussion of controversial issues and how they were resolved.

When reviewing proposed research involving human subjects, the IRB shall require that information given to subjects (or their legally authorized representatives) as part of informed consent is in accordance with the provisions found at 46.116 (General requirements for informed consent) and documentation of informed consent is in accordance with the provisions found at 46.117 (Documentation of informed consent). The IRB also has the authority to require that additional information is provided to the subjects if such information will add to the protection of the rights and welfare of the research subjects.

The Cary Institute defines informed consent as the agreement to participate in research that is made voluntarily by an individual with legal and mental competence and the requisite decision-making capacity, after disclosure of all material information about the research. Informed Consent means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion.

<u>Authority to Suspend or Terminate Approval of a Study</u>
The Cary Institute IRB has the authority to suspend or terminate approval of research not being conducted in accordance with the IRB's requirements, the requirements of 45 CFR Part 46, and/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 PI. The suspension or termination of a protocol will also be reported to any federal funding agency as required by regulations.

Conflicts of Interest

When an investigator involved in research enrolling human subjects has disclosed a potential financial conflict of interest, the IO will review the financial disclosure and consider the potential conflict of interest to decide the appropriate course of action. The IRB will carefully consider specific mechanisms to minimize the potential adverse consequences of the conflict in an effort to optimally protect the interests of the research subjects. In general, if there are any financial conflict of interest issues on the part of the researcher, he or she should not be directly engaged in aspects of the research that could be influenced inappropriately by that conflict. The IRB will also consider if the source of funding and funding arrangements should be included in the consent form. In all cases good judgment, openness of process and reliance upon objective, third party oversight can effectively minimize the potential for harm to subjects and safeguard the integrity of the research.

Investigators are not able to select which IRB member will review their application. Additionally, any IRB member must recuse themselves from a review if they have any potential conflicts.

Review of applications will be conducted with objectivity and in a manner to ensure the exercise of independent judgment of each member. Members may not participate in a vote by the IRB on actions concerning research in which they have an active role or conflict of interest related to any person or entity connected with the application. Failure to abide by these provisions may be cause for removal of a member from the IRB.

The member is not required to identify the exact nature of the conflict of interest. They may simply inform the Chair or IO that one exists. The member may be asked to participate in the discussion or deliberation to answer committee questions regarding the application under review to the same extent as any investigator when attending an IRB meeting. If there are no questions for the conflicted member, or after the conflicted member has answered any questions, he or she will be recused for committee deliberation and vote.

Education of IRB Members, Investigators, and Other Relevant Personnel

All members of the Cary Institute's IRB, the IO, Grants/Compliance Office staff, and all investigators and research personnel listed on protocols involving human subjects research will complete, or have documentation of, appropriate training in the protection of human research participants. The Cary Institute's Compliance Intranet page provides information for online training opportunities. Some sponsors of projects involving human subjects research may require formal in-person training, which should be discussed with the IRB Chair and IO as appropriate.

The Grants/Compliance Office maintains a database of individuals who have completed training in the protection of human research participants. The Cary Institute requires refresher training to occur at least once every 3 years for all IRB members, the IO and Grants and Compliance Office staff, and any researchers and staff listed on active IRB protocols involving human subjects.

The Cary Institute offers human research subjects training through an institutional subscription to CITI Program. Instructions for completing human subjects training can be found on the Cary Intranet Compliance site, or by contacting the IRB Chair, IO, or Grants/Compliance Office.

Procedures for Review of Proposals for Human Subjects Research

The Cary Institute IRB accepts applications for projects involving human subjects research at any time. Submissions are typically sent to the IO but sometimes they are submitted to the IRB Chair. The IRB protocol application is found on the Cary Institute Intranet site under "Compliance," or by contacting the Grants/Compliance Office or IRB Chair.

Upon submission of a protocol application, the IO and IRB Chair perform an initial review of the protocol submission to determine what level of review it will require. If the submission requires a full IRB review, the Grants/Compliance Office staff initiates contact with the IRB via e-mail to begin the review process. If a submission appears to be exempt or eligible for expedited review, the IO and Chair will review and discuss the submission prior to approval and notification to the PI.

When grant proposals include the potential for human subjects research, the Grants/Compliance Office is notified through submission of a Proposal Review Form (PRF) by the proposing scientist. Upon grant proposal submission, the PRF is shared with the IRB Chair to provide advanced notification of a possible protocol submission in the future should funds be awarded.

If funds are awarded for research that includes a human subjects component, no research involving human subjects may begin until an IRB protocol has been submitted to and approved by the IRB. Similarly, if research initially is not intended to involve human subjects, but later proposes to include human subjects, a protocol must be submitted to and approved by the IRB before human subjects research can proceed and proper notification is provided to the funding agency as appropriate.

The federal regulations under which IRBs operate do not clearly call for IRB review of the scientific validity of an investigator's research design. However, the federal regulations do require that IRBs determine whether "*risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.*"

In general, if an investigator is seeking funding from an external agency for a study, the IRB leaves thorough scrutiny of the research design to the peer review process. The proposals of investigators who are not submitting to external agencies may be examined more closely for research design flaws, and they may be required to correct these flaws before IRB approval is granted.

Exempt Research

A determination of research activities that are exempt from the IRB requirements will be made by the IRB Chair in consultation with the IO after reviewing the IRB submitted by the investigator (a PI cannot make his/her own determination about whether a protocol is considered exempt but can provide justification to support their view). This determination will generally be made within 2 weeks of submission of the research for approval. A letter with the IRB's determination of exemption will be provided to the PI and the appropriate category for exemption will be cited.

If a request for exempted research does not meet one or more of the exemption category requirements, the IRB Chair and/or IO will discuss with the PI and require modification of the protocol application as needed.

Additional protections are afforded to pregnant women, human fetuses and neonates (45 CFR Part 46, Subpart B); prisoners (45 CFR Part 46, Subpart C); and children (45 CFR Part 46 Subpart D) involved as research subjects such that the pre-2018 requirements never allowed any research involving these groups to be exempted. However, these protections as they relate to exempted research have been amended with the 2018 requirements in the following ways:

1) Exempted research may be applied in all categories to research involving pregnant women, human fetuses and neonates as long as the conditions of the exemption are met.
2) Exemptions may not be applied to research involving prisoners unless the research involves a broader subject population that only incidentally includes prisoners.
3) Exemptions may be applied to research involving children in items 1, 4, 5, 6, 7, and 8 above. The exemptions described in item 2 may apply to children for subitems "a" and "b" if the investigator does not participate in the activities being observed. However, the exemption described in subitem "c" cannot be applied to research involving children.

Types of research that are exempted from the IRB requirements include (see 45 CFR Part 46.104 for a more complete listing):

1. Research on instructional strategies that is conducted in established or commonly accepted educational settings, that specifically involves normal educational practices, that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction;
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior as long as one of the three below criteria is met (this category can apply to research with children for subitems "a" and "b" below, so long as the investigator does not take part in the activities being observed):
    a. information obtained is recorded in such a manner that human subjects cannot readily be identified, directly or through identifiers linked to the subjects;
    b. any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; **OR**

   c. information obtained can be identifiable but the IRB has conducted a **limited IRB review** and determines that there are adequate provisions in place to protect the subjects' privacy and maintain confidentiality of the data. *This criterion cannot be applied to research that involves children.*
3. Research involving benign behavioral interventions[2] in conjunction with the collection of information from adult subjects where responses are verbal or written, including data entry, or via audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the below criteria are met:
   a. information obtained is recorded in such a manner that human subjects cannot readily be identified, directly or through identifiers linked to the subjects;
   b. any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; **OR**
   c. information obtained can be identifiable but the IRB has conducted a **limited IRB review** and determines that there are adequate provisions in place to protect the subjects' privacy and maintain confidentiality of the data.
4. Secondary research where consent is not required. This is research involving the prospective collection or use of existing identifiable private information or identifiable biospecimens if these are publicly available, or recorded by an investigator in such a manner that subjects cannot be identified (this category can also include the use of health information when that use is regulated by HIPPA, as well as the analysis of data on behalf of a federal agency or department if the requirements of certain federal laws are met);
5. Research and demonstration projects, which are conducted or supported by, or are otherwise subject to the approval of, a Federal department or Agency heads. These projects seek to examine public benefit or service programs.
6. Taste and food quality evaluation and consumer acceptance studies (not applicable to the research being conducted by the Cary Institute).
7. Storage or maintenance for secondary use* for which broad consent is required, as long as a **limited IRB review** determines that there are adequate provisions in place to protect the subjects' privacy and maintain confidentiality of the data.
8. Secondary research for which broad consent is required. This allows the use of identifiable private information or identifiable biospecimens for secondary research as long as the following conditions are met: a) broad consent for storage and maintenance of the identifiable private information or identifiable biospecimens was obtained; b) informed consent documentation or a waiver of documentation of consent was obtained; c) the IRB conducted a **limited IRB review** and determined that the research falls within the scope of broad consent and adequate provisions are in place to protect the privacy of the subjects and maintain confidentiality; and d) the investigator does not return individual research results to subjects so long as this is not required by law.

[2] Benign behavioral interventions are defined as being "brief in duration, harmless, painless, not physically invasive, not likely to have significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing."

*Secondary research is "re-using identifiable information and identifiable biospecimens that are collected for some other "primary" or "initial" activity."

Limited IRB Review

In the 2018 requirements, this new provision was included as a condition to allow the exemption of certain research activities from the requirements. Limited IRB review is intended to ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens. In the Exempt Research section above, those exemptions for which limited IRB review is required as a condition of exemption show the text "**limited IRB review**" in bold. More information on how limited IRB review is applied can be found in the below section, General Criteria for IRB Approval of Research Protocols.

The IRB will document all determinations of limited IRB reviews in letters sent to the PI.

Expedited Review

It is expected that almost all research at Cary Institute that is not exempted from review may qualify for expedited review. As described in the Exempt Research section above, there are two scenarios in which a limited IRB review is required as a condition for exemption.

Expedited review procedures may be used for research that presents no more than a minimal risk and for the following cases:

1. Some or all of the research listed in one or more of the categories defined by the Secretary of Health and Human Services, unless the reviewer determined that the study involves more than minimal risk. If a reviewer makes this determination, there must be written documentation of the rationale. The Secretary of HHS has published this list in the Federal Register and will evaluate the list at least every 8 years. The HHS Secretary will amend the list as needed after consultation with other federal departments and agencies, publication in the Federal Register, and opportunity for public comment.
2. Minor changes in previously approved research during the period for which approval is authorized; or
3. Research for which limited IRB review is a condition of exemption (see above).

Minimal risk "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." There are currently 9 research categories included on the HHS Secretary's list as eligible for review by expedited procedures. However, the activities in these categories should not be considered minimal risk just because they are included on this list. Inclusion on the list means that the activity is eligible for review through expedited procedures when the circumstances of the proposed research involve no more than minimal risk to human subjects.

<u>Research Categories Eligible for Review by Expedited Procedures</u>

Below, the 9 categories of research that are eligible for review by expedited procedures are provided. Those that are in italics are considered to be representative of those most likely to be submitted for review and approval by the Cary Institute IRB based on the nature of research activities at this institution. The list can be found on the following HHS OHRP website: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html):

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

5. *Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).*
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 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)*
8. *Continuing review of research previously approved by the convened IRB (e.g., full IRB review) as follows:*
    a) *where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or*
    b) *where no subjects have been enrolled and no additional risks have been identified; or*
    c) *where the remaining research activities are limited to data analysis.*
9. *Continuing review of research that was previously approved by the IRB, not conducted under an investigational new drug application or investigational device exemption, where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting (e.g., full IRB review) that the research involves no greater than minimal risk and no additional risks have been identified.*

Expedited review may not be used for research protocols 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.

Expedited reviews consist of a review by the IRB Chair or by one or more experienced reviewers designated by the Chair from among members of the IRB. Many times the other reviewer is the IO. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. Only the full IRB committee can disapprove a research protocol. An expedited review is usually accomplished within two weeks of receipt of an application.

After approval of a protocol by expedited review, an e-mail is sent to members of the full IRB informing them of the protocol and its approval, with copies of these documents attached.

Full IRB Review

Full IRB Review is required when the study involves more than minimal risk and/or may be conducted on human subjects that may be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons in certain cases (see the exceptions above).

Full IRB review (convening of the full IRB) is necessary when the research involves any of the following:

1. **More than minimal risk to subjects, and/or**
2. **Certain types of research conducted with certain vulnerable populations**

Examples:

a. Certain types of research with vulnerable subjects and/or populations
b. Research involving prisoners (except in studies where prisoners are incidentally included in a broader study population)
c. Research that involves experimental drugs or devices
d. Research that involves invasive procedures
e. Survey research that involves sensitive questions or is likely to be stressful for the subject.

In accordance with HHS regulations at 45 CFR 46.108(b), except when an expedited review procedure is used (as described in 46.110), an IRB review in the Full Review category must be conducted at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting. If the proposed research protocol involves expertise beyond the expertise of the IRB, the Board may call for external consultants to assist but they would not be voting members. The IRB may approve the protocol, disapprove the protocol, or request revisions and/or more information.

If the research is approved, written verification of the approval will be sent to the researcher, who will keep this approval on file for at least three years after completion of the research. Any other outcome of the review process will also be given in writing to the researcher.

Considerations During Research Protocol Review

Regardless of the review method involved (expedited or full IRB), IRB members must consider a variety of factors when determining whether to approve the proposed research. This includes, but is not limited to, the following:

1. Involvement of vulnerable research subjects (e.g., vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged people);

2. Whether or not incentives are proposed to be used (an Appendix to the research protocol application incorporates a section to more fully describe the use of incentives if they are proposed for use during the research);
3. The methods of data collection that will be used and whether adequate justification was provided to support the methods;
4. Proper consent procedures have been followed and documentation provided, or a waiver of consent is being sought, proper explanation is provided;
5. How will the study subjects be recruited;
6. Description of benefits and/or risks is provided and justified;
7. Description of how data confidentiality will be maintained and how data will be stored.

General Criteria for IRB Approval of Research Protocols

The IRB is responsible for the review of all research involving human subjects conducted under the auspices of the Cary Institute, regardless of funding source.
The IRB will consider the below criteria (45 CFR 46.111, Criteria for IRB approval of research) when reviewing protocol applications that involve human participants in research. All must be satisfied for the IRB to approve the research.

- Risks to subjects are minimized:
  - By using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risks, and
  - Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (BENEFICENCE).
  - In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research.
  - The IRB should not consider possible long-range effects of applying knowledge gained in the research (such as possible effects on public policy) as among those research risks that fall within its purview.
- Selection of subjects is equitable (JUSTICE).
  - In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
- Informed consent will be sought from each subject or the subject's legally authorized representative (RESPECT FOR PERSONS).
- Informed consent will be appropriately documented or waived, in accordance with, and to the extent required by the HHS regulations.

Additional criteria for IRB approval, as appropriate:

- The research plan makes adequate provision for monitoring the data collected to ensure subject safety.
- There are adequate provisions to protect the privacy of the subjects and confidentiality of data.
- For purposes of conducting the limited IRB review as required by 46.104(d)(7) [which exempts from the regulations the storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary use for which broad consent is required so long as the IRB conducts a limited IRB review and makes the determinations described below], the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, but rather, shall make the following determinations:
    - Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of 46.116(a)(1) through (4), (a)(6), and (d);
    - Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with 46.117; and
    - If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included to protect the rights and welfare of these subjects.

Limited IRB Review as a Condition of Exemption

The IRB must conduct a limited IRB review as a condition of exemption in the following four exemption cases:

1. 46.104(d)(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
    (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a **limited IRB review** to

make the determination required by §46.111(a)(7) (that there are adequate provisions in place to protect the subjects' privacy and data confidentiality).

2. 46.104(d)(3)(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
   (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a **limited IRB review** to make the determination required by §46.111(a)(7) (that there are adequate provisions in place to protect the subjects' privacy and data confidentiality).

3. 46.104(d)(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a **limited IRB review** and makes the determinations required by §46.111(a)(8).

4. 46.104(d)(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
   (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
   (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
   (iii) An IRB conducts a **limited IRB review** and makes the determination required by §46.111(a)(7) (that there are adequate provisions in place to protect the subjects' privacy and data confidentiality) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Outcomes of the Review Process

For proposals reviewed by the IRB, three outcomes are possible**:**

Approved:

A protocol which has been approved by the IRB requires no further action from the investigator prior to initiating the study. A letter from the IRB Chair will be sent to the PI, notifying him/her of approval of the protocol and any necessary details or conditions of approval. Electronic notification and documentation of electronic signatures is allowed, as well as record-keeping in electronic files.

Revise and Resubmit:

A protocol that has been deferred by the IRB usually requires that additional information be submitted to the IRB prior to approval. A revised application should be submitted to the IRB clarifying the issues involved or providing the requested documentation. The IRB will review the revised application at its next meeting.

Denied:

An investigator cannot conduct research involving human subjects under a protocol that has been denied approval by the IRB. The reasons for the denial are provided in writing. The investigator will be given the opportunity to respond either in writing or in person at the next meeting of the IRB.

If the research protocol is granted IRB approval, written verification of the approval will be sent to the PI and maintained in the Grants/Compliance Office files. The IO will keep this approval, and any other documents associated with the protocol, on file for at least three years following the completion of the study. Any other outcome of the review process will also be given in writing to the investigator.

Procedures for Continuing Oversight of Ongoing Research

Ensuring prompt reporting to the IRB of changes in research activities

Amendments and modifications to currently approved research must have IRB review and approval prior to implementation. In general, amendments will be reviewed at the original application review level (expedited or full board). Minor changes that do not increase the risk to research subjects may receive review and approval at a lower review level. Minor administrative changes (adding personnel, updating phone numbers, incorporating minor editorial changes to consent documents and cover letters, etc.) may be reviewed and approved by the IRB Chair.

Amendments to approved protocols that may affect the risks and/or benefits to research subjects may be forwarded to the full IRB for review. Reviewers will receive the request for amendment and any modified documents such as revised or new consent forms (should re-consenting of subjects be required), applications, investigator brochures, study instruments, recruitment tools, etc. For reference, the originally approved protocol may also be provided.

Changes in approved research prior to IRB review and approval where necessary to eliminate apparent immediate risks to subjects

There are situations where a serious unanticipated event or adverse event requires an immediate change to a protocol in order to relieve an apparent immediate risk or hazard to research subjects. In these situations, the PI may implement the change necessary to protect the welfare of the research subjects. If possible, investigators are encouraged to contact the IRB Chair or Institutional Official if this type of situation arises prior to implementation of the protocol change.

Investigators are required to notify the IRB in writing of the change, within one week, and include a written description of the change and events which necessitated immediate implementation.

Prompt unanticipated events and adverse events reporting

Any unanticipated or adverse events encountered that pose actual or potential risks to subjects must be reported to the IRB Chair, Cary Compliance Officer/Institutional Official or other compliance staff immediately but not later than seven days following the event. Such events should be reported in writing. The Cary Compliance Officer/Institutional Official will collect all relevant information and work with the Chair as necessary. The CO/IO will contact any relevant Department or Agency Head (sponsor), any applicable regulatory body and OHRP, any report of adverse events as mandated in the Federal Regulations.

- Unanticipated events are generally situations where events which were not articulated in the IRB application or consent form occur in the course of the approved research. Unanticipated events may fall into two categories:
    - Not-serious: those unanticipated events that do not increase the risk to the human participant.
    - Serious: those unanticipated events that increased the risks to the human participants.
- Adverse events are generally considered events that, even if considered in the application review, still increased the risks to the human participants.
- Serious unanticipated events and adverse events will generally be reported to OHRP (based upon the federal regulations, and discussions with the Chair and Institutional Official). Non-serious adverse events may be reported to OHRP as a courtesy (based upon the discussions with the Chair and IO) as OHRP has generally communicated expectations to IRBs to receive such information.

Continuing review and protocol monitoring

The IO and supporting staff maintain an IRB database of approved non-exempt human subjects research protocols. Monthly, this database is reviewed for continuing review and monitoring purposes.

<u>Protocols Following the Pre-2018 Requirements</u>

For protocols approved by expedited or full IRB review methods prior to the 2018 requirements that continue to follow the pre-2018 requirements, PIs are notified approximately one month

before the protocol expiration date that an annual review through submission of the annual renewal form is required before the protocol expirees. The PI indicates on the form whether the research will be renewed for another year, and has the opportunity to explain any proposed amendments they wish to make. Annual renewal forms are typically sent to the IO/Grants and Compliance Office, who then shared the form with the IRB Chair. The IRB Chair reviews the renewal form and discusses any proposed amendments with the IO.

If the proposed amendments do not warrant review by the full IRB, the IRB Chair will approve the annual renewal form and amendment by signing the form. The form is then returned to the PI and the protocol is extended for another year. This can be done through written or electronic signatures.

Amendments that are substantial enough to warrant review by the full IRB will be shared with the IRB and a meeting or conference call to discuss will be arranged prior to approval.

Any protocols that were exempted from the human subjects requirements prior to the 2018 requirements do not require continuing review.

Protocols Following the 2018 Requirements

Continuing review of research is not required for the following:

a) Exempted research;
b) Research reviewed by the IRB in accordance with limited IRB review
c) Research eligible for expedited review (no more than minimal risk);
d) For greater than minimal risk studies initially reviewed by the full IRB, 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.

If the IRB requires continuing review of a protocol, it must document its rationale for requiring this when it otherwise would not be required. This rationale is also provided to the PI.

In the case of active protocols approved by expedited review procedures, the IRB requests an annual update from PIs. On or about April 1 of each year, the IO sends an e-mail to PIs with active expedited protocols to request pertinent updates or notice of status changes (e.g., the protocol is no longer active). This gives PIs an opportunity to think about the upcoming field season and submit a request for the addition of new staff to existing protocols, if needed, or any other amendments that may be required.

The IO/Grants Office updates its database annually based on responses from the PIs. Any protocol amendments that occur are recorded in this database.

For protocols approved by full IRB review, continuing annual review remains a requirement. PIs are notified approximately one month before their protocol expiration date requesting the submission of a signed annual renewal form. This form can also be used to request amendments to the existing protocol. Annual review by expedited procedures will be completed as long as there are no substantial changes requested to the protocol during the renewal. If such changes are requested, the full IRB may be notified to conduct the annual review. Approval of the annual review results in the extension of the expiration date by one year and signature of the renewal form by the IRB Chair, which is sent to the PI.

Any unanticipated problems involving risks to subjects or others should be reported to the IRB Chair and/IO as soon as these problems occur. Serious or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB will be reported by the IRB Chair to the IO (Compliance Officer). In the extreme, penalties imposed by the federal Office for Human Research Protections (OHRP) could include the suspension of all human subject research at the institution for a period, and a sanction that requires all future investigators to apply directly to the U.S. Department of Health and Human Services (HHS) for review and approval of each proposal.

Continuing Review with Verification from Other Sources

For some protocols, it may be appropriate to require verification from sources other than the investigators during continuing review that no material changes have occurred since the previous review. The results of the discussion of this determination will be recorded in the minutes of the IRB for full-board procedures or formal written documentation if the protocol was reviewed by expedited review procedures.

Criteria to consider when determining whether outside verification is needed include the following:

1. Protocols that involve collaborations or partnerships;
2. Studies involving more than minimal risk to participants;
3. Studies that report adverse events, unanticipated risks, or protocol changes;
4. Studies managed by new investigators or investigators whose previous protocol(s) received an audit finding or report of noncompliance with requirements or determinations of the IRB.

Determining Which Protocols Require Review More Often Than Annually

For protocols that require the approval of the full board, the IRB may determine that certain types of protocols require full-board review or expedited review more than once a year. The results of discussion of this determination will be recorded in the minutes and conveyed to the PI in the protocol approval letter. Criteria to consider for this decision include the following:

1) Studies involving more than minimal risk to participants;

2) Studies that report adverse events, unanticipated risks, or protocol changes;

3) Studies managed by new investigators or investigators whose previous protocol(s) received an audit finding or report of noncompliance with requirements or determinations of the IRB.

IRB Record-Keeping and Records Retention

The Grants and Compliance Office will maintain adequate documentation of IRB activities, including the following:

- Copies of all research protocols reviewed and approved for human subjects research, including, but not limited to, the following associated documents:
  - Scientific evaluations, if any, that accompany the proposals;
  - Approved sample consent documents;
  - Progress or annual update reports, if any, submitted by investigators;
  - Reports of injuries to subjects;
  - Continuing/annual review documentation, if required;
  - Rationale for the decision to require continuing review of research that otherwise would not require continuing review; and
  - Correspondences with the PI, including approval letters.
- Minutes of full IRB meetings.
- All correspondence between the IRB and investigators.
- A current list of IRB members.
- Written policies and procedures for the Cary Institute's IRB.
- Statements of significant new findings provided to subjects.
- Documentation related to the reliance on another IRB or where the Cary Institute is the IRB of Record for another institution.

All IRB records described above, including protocols reviewed, consent documents, amendments, IRB documents, and other related materials, will remain on file (in hard copy and/or electronically) with the Cary Institute's Grant Management and Compliance Office for the duration required by the federal requirements (e.g., a minimum of three years after completion of the research). Policy guidance and forms will be disseminated from and stored at the Grant Management and Compliance Office until replaced by new and/or revised documents.

IRB Meetings and Minutes

Convened meetings of the IRB must include the presence of a majority of IRB members, including at least one member whose primary concerns are in non-scientific areas. If the required number and type of members is lost during a meeting, no action may be taken until a quorum is restored. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

Convened meetings may be conducted by telephone conference call, provided that each participating IRB member has received all pertinent material prior to the meeting and can actively and equally participate in the discussion of all protocols.

Minutes of IRB meetings must include the following:

- A list of attendees at the meeting (in person and/or via conference call);
- Actions taken by the IRB;
- The vote on these actions, including the number of members voting for, against, and abstaining;
- The basis for requiring changes in or disapproving research; and
- A written summary of the discussion of disputed issues and their resolution.

Procedures for Reporting by the Institutional Compliance Officer

The Institutional Compliance Officer is responsible for reporting any unanticipated problems involving risks to subjects or others; any serious or continuing non-compliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval to the IRB, appropriate institutional officials (e.g., Cary Institute President), OHRP and/or the sponsor of the research. Such reporting will take place no more than five business days after a determination has been made that one of the events described above has occurred.

Cooperative Agreements/Reliance on Another IRB

The Cary Institute's IRB may enter into written cooperative agreements with other IRBs for specific research protocols when such agreements facilitate and streamline the IRB process while ensuring that the rights and welfare of human participants are fully protected.

In some cases, Cary Institute PIs work on projects involving human subjects with collaborators at other institutions that have their own separate IRBs. It is possible to enter into an agreement with another institution regarding the review of human subjects research protocols, which will designate which institution's IRB will be conducting the review and maintaining oversight of the research once it is approved (IRB of record).

In general, the cooperative agreements allow Cary Institute researchers to complete the review forms for the other IRB and submit the form to the Cary Institute IRB, or allow themselves to be added to the other institution's forms as other personnel working on the project. The Cary Institute IO, in consultation with the IRB Chair, will review the documentation to ensure the other institution's policies align with those of the Cary Institute. Any agreement signed by both institutions will note the IRB of record.

Non-compliance and Complaints/Concerns

Allegations of Non-compliance

The IRB will investigate any allegations of non-compliance (based upon the federal regulations). Any allegation will be discussed with the PI of the IRB application in question. Any investigation of alleged noncompliance will require close cooperation and coordination with the PI of the research.

If there appears to be credible evidence of non-compliance the situation will be presented to the IO. Any non-compliance (based upon the federal regulations) will be reported to federal agencies and funding agencies as required by the federal regulations.

Complaints/Concerns

Anyone may communicate complaints or concerns surrounding any human subject research to either the IRB Chair or the Cary Compliance Officer/ Institutional Official. Following the initial complaint/concern, the Chair and CO/IO in consultation with one another, will decide whether more information is needed. Once their preliminary inquiry is complete, a full IRB meeting will be called to discuss the issue(s). The results of the meeting will be transmitted to the PI in writing. The process will be performed in all due haste, and upon initial review of the complaint or concern, the CO/IO may place a hold the investigator's research in order to protect the human subjects from further risk or harm.