How Do You Know if Your Project Requires Institutional Review Board (IRB) Approval?

All research that involves human subjects, including some student projects, conducted under the auspices of the Cary Institute of Ecosystem Studies must be reviewed **and approved** by the Cary Institute's Institutional Review Board (IRB) for the Protection of Human Subjects.

In certain instances, a research protocol may be considered exempt from the regulations regarding human subject research. More information is provided below for exempt determinations. In other instances, the IRB will review the protocol and make a determination that it meets the requirements for the appropriate conduct of human subject research.

This document will assist you in determining if your project is a research project that involves human subjects, and if it is what steps you must take to ensure that your research protocol complies with the regulations for the protection of human research subjects. It should be used in conjunction with the Cary Institute's Policies and Procedures for the Approval of Research involving Human Subjects, as well as the Cary Institute IRB Consent Policy. Any questions can be directed to the Cary Institute's IRB Chairperson or Institutional Official.

Topics covered in this document include the following:

Is it considered research?

The Department of Health and Human Services (DHHS) defines *research* as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

Some activities have been deemed not to be research. These activities include (as described in the Protection of Human Subjects section of the Code of Federal Regulations (CFR) Part 46.102(l)):

1) Scholarly and journalistic activities (such as oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of

information, that focus directly on the specific individuals about whom the information is collected.

2) Public health and surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Does your research involve human subjects?

Human subject is defined as "a living individual about whom an investigator (whether professional or student) is 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 private information or identifiable biospecimens."

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."

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

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."

Planning for research projects involving human subjects

Investigators should begin to consider IRB issues during the planning stages of a research project. One should consider issues such as subject selection, the use of deception, and the collection of sensitive information or biospecimens. When possible, the investigator should try to eliminate the need for these higher risk procedures. When it is not possible to eliminate these risks, the investigator must demonstrate the need for such high-risk procedures and take steps to minimize the potential risk to the subject. Risks to subjects posted by participation in research should be justified by the anticipated benefits to the subjects or society.

What level of review will your project require?

Protocols Exempted from IRB Review

These are studies that can be considered exempt from the human subject policy requirements. The application must demonstrate that the research is minimal risk and that it falls within one or more of the exemption categories listed below[1]:

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.

[1] Category 6 (taste and food quality evaluation and consumer acceptance studies) is not included due to relevance.
[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."

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.

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

Note that PIs cannot make their own determination about whether or not a protocol is considered exempt, but can provide justification to support their view if they think it is. The final determination will be made by the IRB Chairperson.

Minimal risk means "that the probability and magnitude of harm or discomfort anticipated in the research setting 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."

Additional protections are afforded to pregnant women, human fetuses and neonates; prisoners; and children involved as research subjects. Exempted research may be applied in all categories to research involving pregnant women, human fetuses and neonates. Exemptions may not be applied to research involving prisoners unless the research involves a broader subject population that only incidentally includes prisoners. 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.

Protocols Subject to Expedited IRB Review

These studies may be reviewed by the Institutional Review Board through expedited review procedures (e.g., the review is carried out by the IRB Chairperson or one or more experienced reviewers that have been designated by the Chair from among the Cary Institute's IRB members).

To qualify for expedited review, the protocol application must demonstrate:

1. **No more than minimal risk to subjects, and**
2. **Involve procedures listed in one or more of the following categories in a list published by the Secretary of Health and Human Services in the Federal Register.** The Secretary will review this list at least every 8 years and amend it as needed after consultation with other federal departments and agencies and through publication in the Federal Register with the opportunity for public comment. The full list of categories is provided in Appendix 1.

Below is an abbreviated list of non-clinical research categories that would likely align with projects being reviewed by the Cary Institute's IRB:

1. 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);
2. Collection of data from voice, video, digital, or image recordings made for research purposes;
3. 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;
4. 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.
5. Continuing review 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.

Protocols Subject to Full IRB Review

These studies involve 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).

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.

Submitting an IRB protocol application – Things to consider

When preparing an IRB protocol application, review the full protocol application and fill in all the required information. This will provide the IRB with the information they need to understand the research project and likely reduce or eliminate the number of questions that may arise during the review. Provide all required supplemental documentation (e.g., consent forms, copies of questionnaires). If the IRB has questions, provide clarification.

Modifications to the regulations involving informed consent were made in 2018 to ensure that prospective research participants receive and fully understand the details regarding their participation in the research. The Cary Institute's Consent Policy document provides details related to the general, basic, and additional elements of informed consent, as well as how researchers can properly document informed consent. The policy also contains information about obtaining broad consent for the storage, maintenance, and secondary research use of private information or identifiable biospecimens.

What are a researcher's responsibilities for projects that involve human subjects?

- Investigators have the primary responsibility for protecting the rights and welfare of human research subjects and are responsible for complying with all applicable provisions of their institution's IRB policies.
- Investigators are expected to be knowledgeable about the requirements of the HHS regulations, applicable state law, and institutional policies and procedures for the protection of human subjects.

Investigators are responsible for:

- Conducting their research according to the IRB-approved protocol and complying with all IRB determinations.
- Recruiting subjects only after notification that a protocol has been approved.
- Obtaining and documenting the informed consent of each subject or each subject's legally authorized representative, unless the IRB has waived these requirements.
- Ensuring that each potential subject understands the nature of the research and participation.
- Providing a copy of the IRB-approved informed consent document to each subject or the subject's legally authorized representative at the time of consent, unless the IRB has specifically waived this requirement. All signed consent documents are to be retained for at least 3 years after the completion of the research and according to institutional policy.

Investigators are responsible for:

- Monitoring the research and informing the IRB of findings or developments in the literature that may affect risks and benefits to subjects.
- Promptly reporting proposed changes in previously approved human subject research activities to the IRB, including changes in research procedures. The proposed changes may not be initiated without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
- Reporting progress of approved research to the IRB as often as, and in the manner, prescribed by the IRB and in accordance with the policies of the Cary Institute's IRB.
- Promptly reporting to the IRB any unanticipated problems involving risks to subjects (e.g., serious adverse events (SAEs) or adverse events (AEs)) or others or any serious or continuing non-compliance with the HHS regulations or determination of the IRB.

Privacy and Other Considerations

Privacy

Privacy refers to a person's interest in controlling the access of others to himself or herself. Confidentiality, an extension of privacy, refers to the way in which personal information is handled by a second party who controls access to that information by others. Anonymity refers to the separation of personal identifiers from any information about an individual. The procedures for protecting confidentiality and anonymity and the limitations to confidentiality and anonymity must be discussed in the informed consent document.

IRBs must decide to what extent privacy, confidentiality, and anonymity apply to each project to protect participants adequately. These concepts can be thought of as existing independently in the abstract. However, within IRB approval each serves to counterbalance subjects' ultimate protection from risk, relative to the degree of risk involved in a project. An essential concern of the IRB is how any proposed invasion of privacy could harm an individual. IRBs must assess the

potential repercussion to an individual that results from private information becoming known to others, such as past criminal activity becoming known to an employer. The investigator can regulate the degree of risk that occurs in a project by varying one of these three variables:

1. Do not collect any sensitive personal data: Complete respect for privacy, low risk.
2. Increase the safeguards in maintaining sensitive data: Respect for confidentiality, mild risk.
3. Do not collect information which could link data to subject: Provide complete anonymity, mild risk.

Varying the level of each of these factors in accordance with the level of risk will allow investigators to collect the needed data. It is important to remember that limitations to confidentiality and anonymity must be addressed in the informed consent document. For example, data may be subject to subpoena by court authorities, in which case researchers cannot guarantee confidentiality. However, IRB staff members may be able to provide advice on ways to limit the risks to confidentiality, such as means for delinking subject identifiers from data, and construction of informed consent forms.

Selection of Research Subjects

Several principles guide the selection of subjects for research:

- The burdens of research should be distributed equally among the persons who will benefit from it; therefore, overinclusion or underinclusion of any class of subjects must be justified;
- Convenience alone does not justify using a particular class of subjects; the nature of the research should require or justify the use of a particular class of subjects;
- As a matter of social justice, there should be an order in the selection of classes of subjects: in brief, the least vulnerable classes of subjects should always be selected;
- Participation in research is voluntary; therefore, researchers are heavily discouraged from using subjects who may have restricted freedom to refuse to participate (e.g., family members, employees, or mentored students); and
- In order to ensure voluntary participation, subjects should be recruited through general announcements or advertisements rather than through personal solicitation.

Informed Consent

Informed consent is an integral component of research to ensure that participants are aware of and understand fully the consequences of participation. Informed consent is the process by which participants are provided the information necessary to make a decision about participation. Current Federal regulations (45 CFR 46.116) describe general, basic, and additional elements of informed consent that are necessary to provide an individual with adequate information for making such a decision. More information about obtaining and documenting informed consent (found at 45 CFR 46.117) can be found in the Cary Institute's Informed Consent Policy document.

Special Subject Groups

A special issue in consent arises when participants are unable to give consent for themselves, as with children or cognitively impaired individuals. In such cases consent is generally given by "proxy." However, this proxy consent is not the same as true consent, and thus raises other ethical questions. In the event proxy consent is obtained, the subject should be given veto power whenever feasible. Such is often the case with children involved in research activities. While they are unable to give legal consent, they may still be able to grasp at least basic aspects of the research project. When this is the case, assent of the subject is necessary. While there is no clear rule regarding the age at which children can adequately give assent to participate, the rule of thumb is that assent should be obtained from children seven years and older. In general, if the participants have the cognitive ability to understand what they will be asked to do in a project, they should be asked if they would like to participate. Again, this issue must be assessed on a case by case basis, and the IRB will make a final determination as to whether both assent from participants and consent from guardians are necessary.

Certain groups of persons may be considered vulnerable research subjects. They include:

- children and minors;
- pregnant women, human fetuses and neonates;
- prisoners;
- individuals with impaired decision-making capacity;
- economically or educationally disadvantaged persons;
- members of minority groups;
- elderly persons; and
- persons who are in a subordinate relationship to researchers (such as students, employees, or patients).

In general, when an IRB is considering research with vulnerable subjects, the IRB can approve research that is of minimal risk or will benefit subjects directly. If the IRB determines that the research involves more than minimal risk and does not benefit the subjects directly, the study may be subject to approval by the Secretary of Health and Human Services.

Children and minors are defined as persons who have not attained the legal age for consent to treatment or procedures involved in the research. In the State of New York the age of consent is 17. When children or minors are research subjects, researchers must obtain both the **permission** of the parents (i.e., parental informed consent) and the **assent** of the child (i.e., the child's affirmative agreement to participate). Mere failure to object is not assent. The IRB has the authority to waive the requirement of assent. Special DHHS regulations applying to children may be found in 45 CFR 46, Subpart D.

Individuals with impaired decision-making capacity are those persons having a psychiatric or developmental disorder that affects cognitive or emotional functions to the extent that the capacity for judgment and reason is significantly diminished. Other persons, including those under the influence of or dependent on alcohol or drugs, those affected by degenerative brain diseases, those who are terminally ill, and those who have severe physically disabling handicaps, may be compromised in their ability to make decisions in their best interests. Persons with impaired decision-making capacity may not be able to give legally valid informed consent.

However, researchers have a responsibility in these cases (1) to inform subjects with impairments about the procedures, risks, and benefits of the research to the extent that the subject can understand, and (2) to obtain affirmative assent in so far as the subject is able to do so.

Selection of subjects is a particularly important issue as it relates to persons with impaired decision-making capacity. Research involving persons whose autonomy is compromised by disability or restraints on personal freedom should bear some direct relationship to their condition or circumstances. Persons who are institutionalized should not be chosen as subjects simply because it is convenient to the researcher. Nevertheless, persons do not become incompetent the moment they enter a mental institution, and their right and considered judgment to participate in research should be respected.

Economically or educationally disadvantaged persons are those persons placed at special risk by socioeconomic and educational background. Economically disadvantaged persons include those persons who struggle to provide basic necessities for themselves and their families or communities. Therefore, the use of financial incentives for research participation is a special issue with economically disadvantaged persons. Psychological care, remedial education, and financial remuneration are common incentives in research. To a person who is economically disadvantaged, seemingly nominal inducements may be powerfully coercive. Incentives cannot be so strong that they take away a person's voluntary choice to participate in research. Educationally disadvantaged persons may have educational deficits, learning disabilities, or cultural backgrounds that limit communication with a researcher. It is the responsibility of the researcher to ensure that a subject is fully informed. This includes presenting material at an appropriate level, in an appropriate language, and via an appropriate medium (e.g., verbal or visual).

Members of racial and ethnic minority groups are vulnerable research subjects in two respects: overrepresentation and underrepresentation. On the one hand, members of minority groups should not be over-included in research out of mere convenience or availability. No group of persons should be asked to bear the risks of research when many groups will share the benefits of that research. On the other hand, members of minority groups should not be excluded from research out of mere convenience or availability. For generalizability of research findings, investigators must include the widest possible range of population groups. Therefore, investigators must provide a *"clear compelling rationale for their exclusion or under representation"* of minority group members from research.

Persons who are in a subordinate relationship to researchers may experience a loss of autonomy because of that relationship. Students, employees, and family members may fear a loss of grades, work benefits, or adverse treatment when they are asked to be research subjects. This means that they are subject to undue coercion, even if researchers do not intend to be coercive. Therefore, the IRB scrutinizes proposed research using any subjects who are in direct subordinate relationships to investigators. The researcher is obligated to inform the subject clearly that the subject's participation is voluntary, that the subject may withdraw from participation at any time, and that grades, employment, health care, or any other benefits to which the subject is otherwise entitled will not be affected by their choice to participate or not to participate.

It should be noted that the regulations state that nothing in its policy is intended to limit the authority of a physician to provide emergency medical care to a patient without prior IRB review and approval, to the extent permitted by applicable federal, state, or local law.

Deception

Many research questions cannot be adequately addressed when full informed consent is required. In many cases incomplete disclosure or deception is necessary to obtain essential information. This presents a "Catch 22" in the informed consent process. The first solution should be to attempt to design a study which can answer the research question without any form of deception. The IRB will expect an explanation as to the necessity of deception in any project. When it is not possible to answer the research question without deception, the IRB will assess the risks to participants and make a decision as to what is necessary to protect them. With any research utilizing deception, a thorough debriefing procedure is necessary. The debriefing allows the investigator to explain tactfully what happened and why deception was necessary. At times deception may generate ill feelings among research subjects. It is the responsibility of the investigator to address the ill will and attempt to restore subjects to the pre-testing state of feeling and mind that was disrupted by deceptive methodology.

By its very nature, deception in research violates the principles of voluntary and informed consent to participate in research. Therefore, deception is an extraordinary measure that is not normally permitted in research. In all cases proposed research involving deception must meet the following criteria:

1. Risks to subjects are minimal.
2. The rights and welfare of the subjects must not be adversely affected.
3. Particularly vulnerable subjects (e.g., children, individuals with impaired decision-making capacity, or prisoners) are excluded from research involving deception.
4. A reasonable person would be willing to participate in the research if he or she knew the nature and procedures of the study.
5. At the earliest possible time, subjects must be informed of the nature of the deception, and given a reasonable opportunity to withdraw from participation.
6. Any data collected during the deception may be used only with a subject's explicit approval, obtained after the subject has received full disclosure regarding the study.
7. The proposed research is sound in theory and methodology.
8. Anticipated findings will contribute significantly to the general body of knowledge.
9. Deception is essential to the ability to carry out the research.
10. Deception must be minimized to the greatest extent possible.

Language Used in Consent Forms

Many special circumstances can arise when developing an adequate informed consent procedure. One of the most important factors to consider is the language of the document. While investigators have complete control over the language contained in the document, they have limited control over the prospective participants' comprehension levels. It is crucial that investigators consider the possible variation in comprehension levels of subjects in their sample

and write informed consent documents that reflect the subjects' reading abilities. While this is a difficult task to accomplish, there are several rules of thumb to follow:

1. Avoid technical jargon; rephrase in lay terms.
2. Do not include any language that implies that subjects may waive any rights based on their participation in the research.
3. Do attempt to write documents at a sixth grade level.

Many consent forms contain extensive amounts of technical information and are written at a college/graduate level. Reducing the reading level and complexity of the document does not guarantee comprehension, but it does provide a better opportunity for participants to understand their involvement in the research project.

Although the IRB has a standard consent form format, there are situations when this format may be counterproductive for a given group of subjects. Researchers are encouraged to contact the IRB if they believe an alternate format would be more appropriate.

Remuneration/Use of Incentives

Subjects may receive remuneration or incentives for participating in research, e.g., money, gift cards, or course credit. Modest incentives or reimbursements for expenses incurred by subjects are appropriate. However, if incentives are so strong that prospective subjects do not think that they can refuse them, then the incentives become essentially coercive (i.e., “undue”). Undue inducements are troublesome because: (1) offers that are too attractive may blind prospective subjects to the risks of a study or impair their ability to exercise proper judgment, and (2) they may prompt subjects to lie or conceal information that, if known, would prevent them from enrolling or continuing as participants in research projects. IRB standards for judging whether incentives constitute undue influence must vary according to research procedures and subject populations, but the following questions form the general basis for determining whether incentives are appropriate:

1. Are all research conditions in keeping with standards for voluntary and informed consent?
2. Are the incentives offered reasonable, based on the complexities and inconveniences of the study and the particular subject population?

Additional considerations on the use of incentives in research can be found as part of the Cary Institute protocol application document.

Monitoring of IRB-Approved Research

Continuing monitoring and observation of research is the responsibility of both the researcher and the IRB. Monitoring of the research by the researcher is important because preliminary data may signal the need to (a) change the research design, (b) change the information presented to the subjects, or even (c) terminate the project before the scheduled date. Concurrent monitoring

by the IRB helps ensure the protection of subjects and continued compliance with federal regulations. IRB monitoring is related to the degree of risk posed by the research and the history of compliance demonstrated by researchers. When risk to subjects is minimal, the IRB usually will ask for an annual progress report for a given study. However, when risks are more than minimal or when researchers have a history of noncompliance with IRB guidelines, the IRB may ask for detailed progress reports at intervals specified by the IRB. The IRB has the authority to observe all research procedures first hand or to assign monitoring of research to another individual or group of individuals (45 CFR 46.109).

Protocols approved under the Expedited Review (pre-2018 requirements) or Full Review procedure require a continuing review. The IRB establishes the intervals of review at the time of approval. The intervals between reviews are commensurate with the level of risk involved to participants. However, continuing review must occur at a minimum of every 12 months from the original approval date. OPRR mandates that all continuing reviews must be substantive and meaningful. Continuing reviews are submitted to the Grants Office's IO using the Cary Institute's Human Subject Protocol Continuing Review Form. Proposed amendments may also be submitted during this annual process.

For protocols approved under Expedited Review procedures after the 2018 requirements, continuing review will only occur if the IRB has a documented reason or concern with the protocol such that continuing review is necessary. For all other protocols approved by Expedited Procedures after the 2018 requirements, each April the IRB will conduct an annual check of all active protocols and reach out to the PIs to request pertinent updates or notice of status changes (e.g., if the protocol is no longer active). However, it is the PI's responsibility to ensure that the IRB is kept up-to-date on all requested changes to active protocols.

Continuing reviews will include the following:

- The number of subjects accrued;
- A description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
- A summary of any recent literature, findings, or other relevant information, especially information about risks associated with the research; and
- A copy of the current informed consent document, if different from the originally approved document and/or if changes were made or are being requested.

In addition to IRB-initiated reviews, investigators are required to submit any changes to the original protocol for IRB approval prior to enacting these changes. Again, it is important to consider the IRB approval as a process rather than an isolated event at the beginning of a research project involving human subjects.

Frequently, staff, visiting scientists and graduate students conduct their research at sites other than at the Cary Institute of Ecosystem Studies. As always, researchers have a primary responsibility to protect human subjects from undue research risks. In research performed away from the Cary Institute campus, researchers incur additional obligations including obtaining the permission of institutions to conduct the research in their locations and with subjects for whom they have some responsibility, and possibly approval by a different IRB.

The Cary Institute IRB requires that researchers provide documentation from the off-campus institution that the researcher has been given permission to conduct research at locations administered by the institution. The type of permission depends on the location and the nature of the research.

IRB Approval: When the off-campus institution has an Institutional Review Board, the Cary Institute IRB expects the researcher to provide an approval letter from the off-campus IRB stating its permission for research to be conducted at that location. Examples of institutions with IRBs include another comprehensive university or research institute. In some cases, an inter-institutional agreement may be formed between the Cary Institute and the collaborating institution to formalize the IRB of record in a collaborative project situation.

A Letter of Permission: When the off-campus institution does not have an IRB, the Cary Institute IRB requires a letter of permission from an official of the institution, on institutional letterhead. Examples of institutions without IRBs include public and private elementary schools, small colleges, and small research institutions.

The Proposal Review Form is the official Cary Institute form for the documentation of the concurrence of Cary Institute officials with plans and commitments contained in proposals for externally funded programs. One of its purposes is to document other institutional reviews that may be necessary because of the specific nature of the program, e.g., use of human subjects. The second page of the Proposal Review Form contains a check-off for use of human subjects.
It is important to check with the external agency to whom you are applying to determine if IRB approval is required at the time the proposal is submitted. If not, you have a choice of submitting a protocol before or after a funding decision is made by the agency. Note that if you wait, you run the risk of either having to return the funds, or experiencing a delay in being allowed to spend funds related to the human subjects research, should the proposal be funded and the protocol not be approved by the IRB. However, preparing a protocol for a project which will not be funded may not be the best use of your time. Often, it is wise to consult with IRB staff before submitting a proposal to determine if there may be problems with IRB approval.
In cases where a grant is awarded for the purpose of developing and administering a questionnaire, IRB approval will be granted in two stages. A conditional approval will allow the Principal Investigator to proceed only with the instrument development phase of the project. The IRB must review the completed instrument before full approval can be granted and human subject contact initiated. Please be aware that the IRB must be satisfied that the instrument meets IRB regulations or approval will be suspended. In this event, depending on the granting agency and the project, you may be responsible for returning all or part of the original award.

APPENDIX I

OHRP Expedited Review Categories (1998)

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure[1]

Applicability

A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. 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.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    a. (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); (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 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 46.101(b)(4). This listing refers only to research that is not exempt.)

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

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the 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 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, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

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[1] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.
[2] Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).