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Guidance for Human Subjects Research in the National Exposure Research Laboratory

SCIENCE

Office of Research and Development
National Exposure Research Laboratory

GUIDANCE FOR HUMAN SUBJECTS RESEARCH IN THE NATIONAL EXPOSURE RESEARCH LABORATORY

NATIONAL EXPOSURE RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY

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DISCLAIMER

This document has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document.

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1.0 INTRODUCTION

1.1 Purpose

This document provides guidance to investigators and managers associated with the U.S. Environmental Protection Agency (EPA) Office of Research and Development (ORD)'s National Exposure Research Laboratory (NERL) on the ethical conduct, regulatory review, and approval of all human research activities. The focus of this document is twofold: first, on the methods for ensuring the safety and rights of human research subjects, and, second, on how to conduct such research in a manner consistent with EPA and NERL policy.

Principal investigators (PIs) are responsible for obtaining approval for human subjects research. If a PI does not have significant experience in the approval process for human subjects research, he or she should rely on an experienced colleague or co-investigator (Co-I) or contact the Office of the Director of the Human Research Protocol Office (HRPO) located at the National Health and Environmental Effects Research Laboratory Human Studies Facility in Chapel Hill, NC. The mission of the HRPO is to assist investigators in all aspects of the ethical and regulatory review of human subjects research. PIs with questions about the process are encouraged to contact the office early in protocol development. The phone number of the HRPO is (919)966-6217.

1.2 HRPO

The Office of the Director of the HRPO will be responsible for the ethical oversight and coordination of the process by which human subjects research activities are developed, reviewed, and approved in NERL, in addition to all intramural research within ORD. Some specific duties include

- ensuring the safety and rights of all human research subjects are respected and protected;
- assisting investigators in the preparation of human subjects research protocols that are consistent with EPA policy;
- maintaining records, including approved protocols, amendments, renewals, adverse events, and protocol deviations (The office of the HRPO should be provided copies of all Institutional Review Board (IRB) correspondence and approvals for the duration of a human subjects research project or protocol.); and
- ensuring that human subjects research in NERL is consistent with principles set forth in the *Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES)* document (EPA 600/R-08/062, available at www.epa.gov/nerl/sots).

The HRPO welcomes any questions regarding the ethics or regulatory compliance of any human subjects research protocol. Past experience has shown that involvement of the HRPO early in protocol development saves time and reduces confusion in the EPA approval process.

2.0
HISTORICAL OVERVIEW OF POLICIES REGULATING HUMAN SUBJECTS RESEARCH

The conduct of human research carries special responsibilities with regard to ethical, medical, and scientific issues. Society, although generally accepting research on humans as necessary to advance scientific knowledge, has imposed special requirements on investigators because of concern of potential maltreatment of human research subjects, based in part, on the historical legacy of improper human studies.

The following sections summarize key documents tracing the changes in human research ethics that took place beginning immediately after World War II and continuing to the present. This is followed by a description of the additional policy documents that currently govern the conduct of human subjects research within EPA. These are covered in more depth in the following chapters.

2.1 Nuremburg Code (1947)

The Nuremburg Code was a direct result of the proceedings of the military tribunal trials after World War II of Nazi physicians who committed atrocities on prisoners of war under the guise of medical research. The code contains 10 principles; among them are the need for voluntary consent, that research yield fruitful results for the good of society, and the degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

2.2 The World Medical Association Declaration of Helsinki (1964)

The World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects initially was adopted in 1964 and has been amended and clarified eight times, most recently in 2008 in Seoul. That document represents the first significant effort of the medical community to regulate medical research and combined the Nuremburg Code with the Declaration of Geneva (1948), a statement of the ethical duties of physicians.

In the case of EPA involvement in foreign countries, adherence to the Declaration of Helsinki is the strongest assurance that investigators will accept the international norm for protection of human research subjects.

2.3 The Belmont Report (1979)

The Belmont Report is the foundation of research ethics in the United States and was the basis for the "Common Rule." The report was a result of the 1974 National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission's charge was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines that should be followed to ensure that such research is conducted in accordance with those principles. The report was the product of a 4-day conference held in 1976 at the Smithsonian Institute's Belmont Conference Center and monthly discussions over 4 years by the commission's 11 members.

The report promoted three principles:

(1) respect for persons,

(2) beneficence, and

(3) justice.

2.4 The Federal Policy for the Protection of Human Subjects or the "Common Rule"

Since 1991, 14 Federal agencies have agreed to adopt an identical basic set of regulations governing human subjects research. The name "Common Rule" refers to these basic regulations being identical in all 14 agencies. Specifically, the Common Rule pertains to subpart A of 45 Code of Federal Regulations (CFR) 46. The Common Rule has brought uniformity to a patchwork of existing Federal research protections and embodies the principles of the Belmont Report. It establishes standards for the conduct of human subjects research funded by the Federal government.

Some agencies, including EPA and Department of Health and Human Services (DHHS), have adopted subparts that provide additional protections to special populations. EPA codified the Common Rule at 40 CFR 26 in 1991, and redesignated it as 40 CFR 26 subpart A when additional subparts were added in 2006.

2.5 EPA Order 1000.17 Change A1 (1999)

This order superseded the 1977 EPA Order 1000.17, Policy and Procedures on Protection of Human Subjects. The order applies to all research covered by 40 CFR 26, including exemptions from the Common Rule. The policy establishes that all human subjects research studies supported by the EPA must either be approved or be determined to be exempt research by the EPA Human Subjects Research Review Official (HSRRO) before any contract, grant, cooperative agreement, Cooperative Research and Development Agreement (CRADA), interagency agreement, or any formal agreement involving EPA support of such studies is awarded or entered into. The order also requires the HSRRO to review all foreign research not subject to the Common Rule prior to

commencement.

Note that the Agency HSRRO approves all EPA research and is an entity distinct from the Director of the HRPO. The HRPO Director helps the PI assemble the needed documents for review by the Agency HSRRO and helps to ensure timely approval and avoid unnecessary delays.

2.6 Health Insurance Portability and Accountability Act (HIPAA-2003)

Effective in April 2003, the HIPAA included both the portability of employees' health insurance as employees change jobs and defined accountability for individuals' protected health information (PHI).

HIPAA recognizes three covered entities, (1) health care providers, (2) health care information clearinghouses, and (3) health care payers, that must have authorization from individual patients or research subjects before individual PHI can be shared or used in research. Because EPA is not a covered entity, it ordinarily does not have to comply with HIPAA. However, if joint human studies are conducted between EPA and a covered entity, HIPAA authorization may be required from each of the study subjects, but many studies qualify for a limited waiver to review PHI. The IRB of record for the study is a good source of information on whether HIPAA regulations for PHI apply.

HIPAA regulations do not apply to studies on existing databases, research in foreign countries, and studies on deceased individuals.

2.7 Scientific and Ethical Approaches for Observational Exposure Studies

In 2008, EPA published the SEAOES document, which provides information and guidance for NERL researchers as they design and implement observational human exposure measurement studies. The document identifies issues that need to be considered in these studies and provides state-of-the-science information on ethical considerations. It includes extensive references to sources of information relevant to ethical considerations in human subjects research studies. The document includes the following sections: (1) Elements to be Considered in Study Conceptualization and Planning; (2) Ensuring Protection of Vulnerable Groups; (3) Privacy, Confidentiality, and Other Concerns Related to Observational Human Exposure Studies; (4) Creating an Appropriate Relationship Between the Participant and Researcher; (5) Building and Maintaining Appropriate Community and Stakeholder Relationships; and (6) Designing and Implementing Strategies for Effective Communication. SEAOES addresses issues related to activities such as selecting and enrolling study participants, informed consent procedures, participant compensation, participant retention, reporting unanticipated observations, the communication of study results, and similar activities. The document adds to existing EPA policies and guidelines. In a single document, it brings together information on approaches and procedures that researchers can use in design and performance of observational studies. NERL researchers are to use the guidance and recommendations provided in SEAOES in the design and implementation of observational studies. The document recommendations also are to be used by second-party researchers funded by NERL.

3.0
TITLE 40 CFR PART 26:

PROTECTION OF HUMAN SUBJECTS OR THE EPA COMMON RULE, INCLUDING SUBPARTS FOR ADDITIONAL PROTECTION OF VULNERABLE POPULATIONS

As described in section 2.4, the EPA Common Rule is codified at subpart A of 40 CFR 26, and this identical regulation is recognized by 14 Federal agencies. As of 2006, EPA has added subparts B, C, and D for the purpose of affording additional protections to special populations. In addition, it added subparts K, L, M, O, P, and Q containing regulations for third-party human research for pesticides and rules for data use, compliance oversight, and other matters. Subparts B, C, and D cover protections for nursing women (B), pregnant women and fetuses (B and C), and children less than 18 years of age (B and D), in research conducted or supported by EPA.

3.1 Subpart B

Subpart B prohibits research conducted or supported by EPA involving intentional exposure of human subjects who are children or pregnant or nursing women. Research involving intentional exposure of a human subject is defined by a "study of a substance in which the exposure to the substance experienced by *a human subject participating in the study would not have occurred but for the human subject's participation in the study."*

This policy does not distinguish between toxic substances and any other types of substances, including therapeutic substances.

If you have questions regarding whether a proposed research project includes intentional exposure research, contact the HRPO or the Agency HSRRO.

3.2 Subpart C

Subpart C provides additional protections for pregnant women and fetuses involved in observational research conducted or supported by EPA. Observational research is defined as *"any human research that does not meet the definition of research involving intentional exposure of a human subject."*

Subpart C also adds the additional protections of subpart B of the DHHS rule (45 CFR 46) but does not include a provision for research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem in pregnant women, fetuses, or neonates (45 CFR 46.207).

3.3 Subpart D

Subpart D provides for additional protections for children involved as subjects in observational research conducted or supported by EPA. The subpart adopts the language of subpart D of DHHS regulations with respect to research not involving greater than minimal risk and research involving greater than minimal risk but preserving the prospect of direct benefit to the individual subject.

EPA did not adopt, hence does not allow for, research involving greater than minimal risk without prospect of direct benefit but likely to yield generalizable knowledge about the subject's condition or research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

3.4 Subparts K, L, M, O, P, and Q

Subparts K, L, M, O, P, and Q (N is reserved) pertain to a variety of issues not typically of concern for EPA researchers. Below is a list of each subpart with a brief description of it.

- **Subpart K:** Basic Ethical Requirements for Third-Party Research for Pesticides Involving Intentional Exposure of Non-pregnant, Non-nursing Adults
- **Subpart L:** Prohibition of Third Party Research for Pesticides Involving Intentional Exposure of Human Subjects Who Are Children or Pregnant or Nursing Women
- **Subpart M:** Requirements for Submission of Information on the Ethical Conduct of Completed Human Research (applies to outside research submitted under the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA] or section 408 of the Food, Drug, and Cosmetic Act)
- **Subpart O:** Administrative Actions for Non-Compliance (with Any Subpart A-L)
- **Subpart P:** EPA Review of Proposed and Completed Research (This subpart establishes the EPA Human Studies Review Board [HSRB], defines its functions, and requires it to review certain submitted non-EPA research.)
- **Subpart Q:** Ethical Standards for Assessing Whether To Rely on the Results of Human Research in EPA actions

3.5 Section 26.101: To What Research Does 40 CFR 26 Apply?

Section 26.101 states that the regulations apply to all research involving human subjects conducted, supported, or otherwise subject to regulation by EPA or other Federal agencies that have adopted the Common Rule.

Section 26.101(b)(1-6) covers exemptions from this policy. Section 26.101(b)(4) is likely to be the exemption most applicable to much of the research at NERL.

Section 26.101(b)(4) states, "Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." However, **only** the Agency HSRRO can make the determination of whether the human subjects research in question is exempt, with or without the support of the IRB of record. The PI and the HRPO Director **cannot** make this determination.

The HRPO can guide the researcher through the language and appropriate documentation to prepare a request for classification as exempt human subjects research.

3.6 Section 26.102: Definitions

Section 26.102 provides a number of important and useful regulatory definitions. The two that are most relevant and impact all NERL research are those of research and human subjects that follow.

- *"Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purpose of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes."*
- *"Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:*
  (1) data through intervention or interaction with the individual, or
  (2) identifiable private information."

Sections 26.101 and 26.102 establish which studies are governed by 40 CFR 26. Currently, most studies involving human data or tissues clearly fall within the definition of human subjects research because the studies meet the definition of research, involve intervention or interaction with a subject, or clearly involve analysis of data with personal identifiers. There are other situations, however, where it is not immediately apparent that a study constitutes human subjects research.

Often, the issue is whether personally identifiable private information is available to the investigator. Clearly, analysis of existing data that is publicly available and cannot under any circumstances be linked to individuals is not human subjects research. However, there are numerous studies involving existing data or tissues that do not contain readily identifiable private information but that can be linked to individual subjects through coded identifiers. These codes could conceivably be used to identify individuals. A determination of whether such studies constitute human subjects research or not often depends on the individual circumstance surrounding access to the data or to keys to any existing codes. The HRPO Director is the individual in ORD who is most fully trained and qualified to make human subjects research/non-human subjects research determination, and research projects that use data from or about humans generally should be referred to the HRPO for such a determination. In difficult or ambiguous cases, the HRPO director may consult with the Agency HSRRO before making a final determination.

3.7 Section 26.103: Assuring Compliance with 40 CFR 26

Section 26.103 requires that any research conducted or supported by a Federal agency or department must be reviewed by an appropriate IRB, and that any organization engaged in such research must have a written assurance in place indicating its compliance with the regulatory requirements of that agency. For most U.S. institutions that engage in human research, including EPA, this written assurance is provided in the form of a Federal Wide Assurance (FWA) issued by DHHS. EPA's FWA number is FWA00012755, and NERL specifically is identified as a component on that assurance. In addition, EPA has a contract with the University of North Carolina (UNC) IRB system to serve as the IRB of record on EPA studies conducted under the Agency's FWA. Investigators who develop research studies within ORD, therefore, usually will use the UNC IRB system as the IRB of record. Use of an alternate IRB can be considered under certain circumstances but requires an IRB Authorization Agreement signed by the Agency HSRRO. The HRPO Director will initiate this action in the occasional cases in which it is required.

EPA-funded research performed by outside researchers without EPA involvement will use the outside researcher's FWA and IRB of record. When EPA investigators collaborate with outside institutions such as the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), or a research university, review by the IRB of each of the engaged institutions is required unless there are signed IRB Authorization Agreements in place allowing one IRB to serve as the IRB of record for more than one of the institutions engaged in the study, thus simplifying the review process by eliminating redundant IRB review. Again, the HRPO Director will initiate an action with the Agency HSRRO when EPA investigators are involved in a study in which this kind of agreement is required.

4.0
DEVELOPMENT, REVIEW, AND APPROVAL OF HUMAN SUBJECTS RESEARCH PROTOCOLS

EPA scientists and their management take the protection of human subjects who participate in their human subjects research studies very seriously and want to ensure that the procedures used in their studies meet the most up-to-date scientific and ethical standards. To address this goal, researchers in NERL have published the SEAOES document, which identifies key scientific and ethical issues in the design and implementation of observational human exposure studies and provides information and resources that will be useful to researchers conducting these studies.

The document was developed with input from a panel of external experts, released for public comment, and reviewed by the Agency's HSRB. The document, available at www.epa.gov/nerl/sots, is to be used by NERL researchers as they develop the technical study design and the human subjects research protocols. Information in the document will be used in preparing the required paperwork, as described below.

The purpose of this chapter is to serve as a "how to" manual for the preparation and review of a human subjects research protocol package. It should be noted that ethical concerns must be incorporated into the scientific effort from the onset of study conceptualization and throughout the study design and implementation. Therefore, the study design and human subjects research protocol should be developed concurrently and fully integrate scientific and ethical concerns. The following discussion outlines the steps, required paperwork, reviews, and necessary EPA management approvals before any human subjects research can begin.

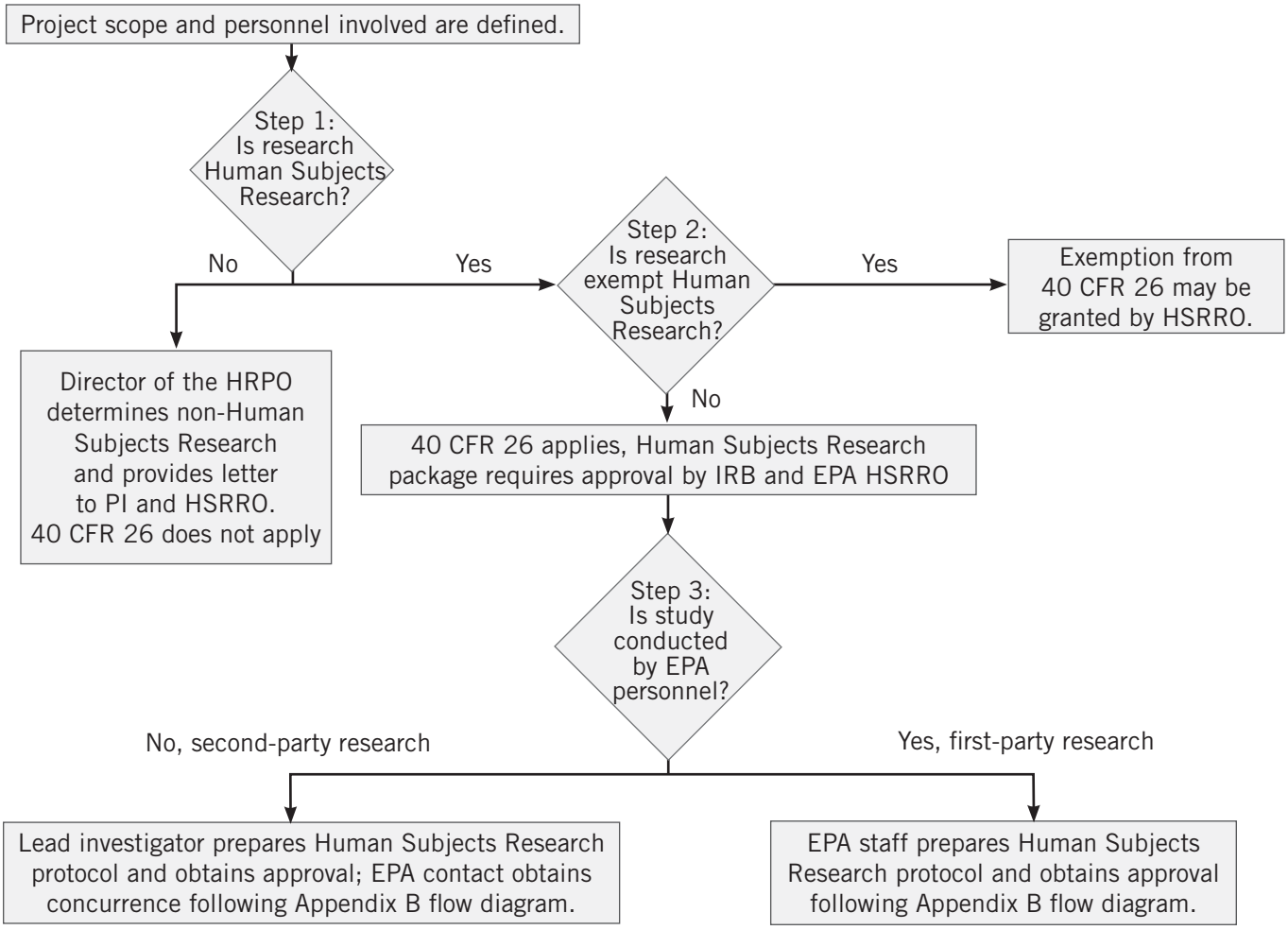


Figure 4-1. Decision process for determining if a study is human subjects research

The PI and his/her management team first must determine whether the proposed research study is human subjects research. This is done during the initial study conceptualization and planning, as described in SEAOES. It involves defining the study objectives, general approach, and involvement of human subjects. Figure 4-1 depicts the decision making process, which is described below.

Step 1: Determine whether the research is human subjects research.

The first decision to be made for getting approval of any research activity is to determine whether the proposed study meets the regulatory definition of human subjects research. The regulatory definition of human subjects research is found in section 26.102 of 40 CFR 26 and in section 3.6 of this document. If a researcher is planning to conduct research that might meet the regulatory definition of research involving human subjects, the HRPO should be contacted for guidance.

If the proposed research does not meet the regulatory definition of human subjects research, the Director of the HRPO is empowered to make an official Agency determination of non-human subjects research for the study and will provide a letter to the PI and to the Agency HSRRO allowing the research to proceed. When research is non-human subjects research, it is not subject to the requirements of 40 CFR 26. See section 4.3.1 "Studies Not Meeting the Definition of Human Subjects Research" for more information.

Appendix A contains a sample memo to request research be declared as non-human subjects research.

If the research is human subjects research, proceed to step 2.

Step 2: Determine whether the research is exempt human subjects research.

If the study is determined to be human subjects research but qualifies as exempt human subjects research under one of the exemption categories of 26.101(b)(1-6) as mentioned in section 3.5, an exemption from the requirements of 40 CFR 26 may be granted by the Agency HSRRO.

The HRPO should be contacted and will assist with this request. See section 4.3.2 "Exempt Human Subject Research" for more information.

Appendix A contains a sample memo to request research be declared as exempt human subjects research.

If the study is nonexempt human subjects research, 40 CFR 26 applies, and a human subjects research protocol package will need to be created and approved by an IRB and the Agency HSRRO. The process for receiving approval will vary depending on whether the research is first- or second-party research. NERL is not involved in third-party research.

Proceed to step 3.

Step 3: Determine the role of EPA personnel in the proposed study.

The final decision to be made is whether the proposed research will involve EPA personnel, such as investigators, project officers (POs), collaborators, or Co-Is, with another entity outside of EPA.

EPA personnel may be involved as investigators in first-party research (conducted in-house by EPA staff) or as Co-Is in second-party research (e.g., in contracts or cooperative agreements with entities outside of EPA). First-party research is designed and led by EPA staff as the PI(s). First-party research in NERL requires approval by an IRB listed on EPA's FWA. Except in unusual circumstances, this will be the UNC IRB, and the protocol package will be created using the UNC IRB forms. Following approval by the UNC IRB, the protocol package will be submitted to the HRPO, who will submit it to the Agency HSRRO for review and approval. The first-party human subjects research review procedure is detailed in section 4.2 "Process for Review and Approval of a Typical NERL Study Design and Human Subjects Research Protocol Package" and is summarized in Appendix B.

Second-party research is designed and led by an entity outside of the Agency, such as a contractor or cooperative agreement partner. Regardless of whether EPA is involved as a Co-I, the second party will be responsible for preparation of the research protocol and obtaining approval from the contractor's IRB. The second party should use forms required by their organization's IRB, which likely will be consistent with the UNC IRB forms, but not the same. If EPA personnel will also be engaged in the research, the HRPO should be consulted about whether to seek an IRB Authorization Agreement with the awardee institution or whether the research also will have to be reviewed by the UNC IRB. If the UNC IRB will be reviewing the research in addition to the second-party-institution's IRB, the EPA contact (PO, Work Assignment Contracting Office Representative, or PI) will prepare a protocol package to be submitted to the UNC IRB, using the UNC forms and the protocol package approved by the second-party-institution's IRB. The EPA investigator will submit the approved protocol package to the EPA HRPO, who will submit it to the Agency HSRRO for review and approval. See section 4.4, "Collaboration and Consultation on Research Primarily Conducted Outside NERL," for further information. If there are questions at any point in the process, contact the EPA HRPO for assistance. A PO, collaborator, or one unsure of the classification of one's role should contact the Agency HRPO.

It is likely that research by second parties will continue in NERL, thus requiring a meshing of second-party IRB human subjects research requirements with those of NERL. The PI, Branch Chief and Division Director are responsible for ensuring that IRB protocols developed by second parties for NERL meet all EPA requirements.

In addition, remember that all human subjects research studies supported by EPA must either be approved or be determined to be exempt research by the EPA HSRRO before any contract, grant, cooperative agreement, CRADA, interagency agreement, or any formal agreement can be completed. Please

contact the Agency HRPO or HSRRO for assistance with approval of any of the above agreements, contracts, or grants.

Requests for applications and requests for proposals do not need HSRRO approval until after the contract is awarded, but approval is needed prior to the awarding of a contract and, again, prior to the beginning of the research.

4.1 Elements of the Human Subjects Research Protocol Package

The final human subjects research protocol package submitted to the Agency HSRRO will include the following items.

- NERL study design, including a section on "Considerations for Protection of Human Subjects in the Study"
- Consent forms approved and stamped by the IRB
- Questionnaires and advertising approved and stamped by the IRB
- Ethics training reports required by the IRB
- RB-approved research protocol
- IRB-approval letter(s)
- Copies of extramural scientific reviews and responses
- NERL fact sheet
- NERL sign-off sheet with signatures
- Cover memo from the PI to the HRPO requesting review of the protocol

The following subsections describe the individual elements of the protocol package. Section 4.2 subsequently describes the process for preparing, reviewing, and approving the package.

4.1.1 NERL Study Design

The foundational document for a human subjects research study is the NERL study design. The study design document should contain sufficient detail to enable independent review and assessment of the scientific soundness of the study and the approaches that will be followed to ensure that the study meets the highest scientific and ethical standards. Elements recommended for inclusion in the study design of an observational exposure study are presented in section 2 of the NERL SEAOES document, available at www.epa.gov/nerl/sots).

The following elements may be included in a study design.

- Introduction and background, including the purpose and scope of the study
- The desired outputs and outcomes of the study, including the objectives and the hypotheses to be tested
- A brief description or overview of the study
- The technical approach and conceptual model that accounts for
  - sources of the chemicals being studied;
  - potential routes and pathways of exposure;
  - factors that may impact exposure and other relevant stressors;
  - selection and characteristics of the study participants,eligibility criteria, recruitment, retention, and payment approaches;
  - justification for sample size, the methodology for selecting participants, and the sampling methods;
  - characteristics of the community in which the study will be performed;
  - environmental conditions, factors, or end points to be measured, including sampling and analysis approaches and methods (with description of expected performance);
  - survey design and questionnaires and other survey instruments, as applicable (with description of prior use and validation in similar studies);
  - pilot studies that may be undertaken;
  - quality assurance (QA) project plan and quality control;
  - time frame for the study;
  - exposure scenarios to be considered;
  - burden of the study on the participants;
  - resources available; and
  - feasibility.
- Discussion of alternative study designs and approaches considered and reasons for rejecting other approaches and selecting the one proposed
- An analysis plan that considers
  - information and data needs, including data storage, security, access, and release;
  - nature of the measurement data (e.g., variability, QA);
  - how the collected data will be used, and how the proposed analyses will address objectives of the study; and
  - hypotheses to be tested and statistical power and sample size required to test the hypotheses.
- Resources required or available
- Project organization and management, including team members and their roles and responsibilities
- Communications plan
- Schedule

Investigators should follow the recommendations presented in SEAOES during study design and preparation of the design document. The format and content of the study design document will be prescribed by the policies of the PI's division. The document will contain a section or appendix titled "Considerations for Protection of Human Subjects in the Study." This section or appendix will address the recommendations of SEAOES with respect to scientific and ethical considerations in the design and implementation of studies involving human subjects and provide documentation that the elements of SEAOES have been addressed. For example, this section will include the justification for the study, justification for including human subjects, the basis

for participant payment plans, approach for community involvement, plans for technician training on collateral hazards, etc. The format for this section or appendix and elements to be addressed in this section or appendix of the study design document are summarized in Appendix C of this document.

4.1.2 Consent Form/Informed Consent Process

As described in the SEAOES document, informed consent is a process, not a form. Information must be presented to enable potential subjects to decide voluntarily whether to participate as research subjects. Informed consent is the fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used to obtain informed consent should be designed to educate the potential research subjects using language they understand. Informed consent language and documentation, especially the explanations of the study purpose, duration, experimental procedures, alternatives, risks, and benefits, must be written in "lay language." Current recommendations suggest that informed consent language be understood by individuals with an 8th- to 10th-grade reading level, although researchers should be aware that many individuals read below this level.

The process of obtaining informed consent, the required elements of a consent form, and the documentation of informed consent must be consistent with 40 CFR 26 sections 116 and 117. In most cases, the IRB of record will provide a template or suggestions for a consent form consistent with the Common Rule. The UNC IRB has a variety of sample consent forms at http://ohre.unc.edu/forms.php. Additional information about the informed consent process is included in SEAOES at www.epa.gov/nerl/sots.

More detailed information and guidance can be found at the website of the DHHS Office for Human Research Protection at www.hhs.gov/ohrp/policy/index.html#informed. In addition to the requirements of the IRB of record, the EPA has requirements and language to be included in the informed consent document.

In the consent form, under the section regarding, "What will happen if you are injured by this research?" insert the following language.

> All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. The US EPA has not set aside funds to pay you for any such illness or injuries, or for medical care related to such injuries or illness. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a *research related injury or illness occurs, you should contact the Director of the EPA HRPO at 919.966.6217*.

For first-party research approved by the UNC IRB, under the section, "What if you have questions about your rights as a research participant?" the last sentence must be amended as follows.

> *All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919.966.3113 or by email to IRB_subjects@unc.edu. and/or the Director of the EPA HRPO at 919.966.6217.*

4.1.3 Surveys and Questionnaires

The Paperwork Reduction Act of 1995 (44 U.S.C. 3501) requires that agencies receive Office of Management and Budget (OMB) clearance before requesting most types of information from the public ("information collections"), including surveys and questionnaires, from more than nine study participants. EPA maintains an Information Collection Request (ICR) Center within the Office of Environmental Information to assist EPA employees in preparing an ICR. More information about the process and necessary documentation can be found at http://intranet.epa.gov/icrintra/. Experience with the system suggests the process takes between 6 to 9 months for OMB clearance.

> The Paperwork Reduction Act defines a collection of information as follows.
>
> *"Collection of information means, except as provided in Sec. **1320.4**, the obtaining, causing to be obtained, soliciting, or requiring the disclosure to an agency, third parties or the public of information by or for an agency by means of identical questions posed to, or identical reporting, recordkeeping, or disclosure requirements imposed on, **ten or more persons**, whether such collection of information is mandatory, voluntary, or required to obtain or retain a benefit."*

Note that for it to be necessary for an OMB review, the survey or questionnaire needs to include more than 9 individuals in a 12-mo period. Most studies will reach this threshold. However, some small-scale pilot studies or research on collection and validation of methodologies may not require more than nine individuals.

The Paperwork Reduction Act does allow for exceptions. These exceptions can be found at 5 CFR 1320.3(h).

Two exceptions that apply to some research within ORD are shown below.

> (1) CFR 1320.3(h)(5): *Facts or opinions obtained initially or in follow-on requests, from individuals*

(including individuals in control groups) under treatment or clinical examination in connection with research on or prophylaxis to prevent a clinical disorder, direct treatment of that disorder, or the interpretation of biological analyses of body fluids, tissues, or other specimens, or the identification or classification of such specimens.

(2) CFR 1320.3(h)(7): *Examinations designed to test the aptitude, abilities, or knowledge of the persons tested and the collection of information for identification or classification in connection with such examinations.*

For further guidance on the need for information collection clearance for EPA research, contact the Director of the HRPO or the EPA ICR Center (http://www.epa.gov/icr).

4.1.4 Advertising, Brochures, and Other Required Items

Complex research studies often require a wide range of additional items that must be reviewed and approved by the IRB and EPA. Some common examples include recruitment brochures, advertising (both print and online), clinic recruitment letters, and surveys. Include all IRB approved additional documents in the protocol package.

4.1.5 Ethics Training Requirements

All EPA investigators conducting human subjects research must have formal human research ethics training. UNC-Chapel Hill has joined the Collaborative IRB Training Initiative (CITI), and this is now the default for satisfying basic educational requirements. CITI is a Web-based program on issues relating to human subjects research. The CITI Web site is maintained by the University of Miami, with content developed by a national consortium. More than 400 institutions are using CITI for their mandatory training, with more than 140,000 individual registrants.

CITI contains modules on topics including ethical principles, IRB regulations, informed consent, and vulnerable populations. Each module has a short quiz at the end to assess understanding. The modules have been grouped for (1) Biomedical Research, (2) Social and Behavioral Research, and (3) Research Involving Data and Specimens Only. Users select the grouping that best reflects their area of research, and the other modules are available options. For more detailed information and links to the CITI Web site, please visit www.ohre.unc.edu/educ.php.

All personnel involved with a human research project submitted for UNC IRB review must have completed the CITI Basic Course.

EPA and contractor personnel should choose UNC as their institution when registering for the training. The EPA HRPO and the CITI Web site can offer additional guidance or help with CITI training issues.

Annual Continuing Education. Following completion of the basic education requirement, all personnel who remain engaged in human subjects research are required to complete continuing education on an annual basis, with the schedule determined by the date on which basic training was completed. New IRB approvals will not be granted, and active protocols may be suspended if the continuing education requirement has not been completed on time. The annual continuing education requirement may be satisfied by one of the following methods, each requiring approximately 1 h to complete.

- Completion of the online CITI Refresher Course modules. As with the CITI Basic Course, refresher modules are grouped by categories of research activity.
- Attendance at one lecture or seminar with a primary focus on human research issues. The Agency HSRRO and the HRPO offer courses periodically that will satisfy this requirement.

4.1.6 IRB Research Protocol

The research protocol is prepared according to the instructions of the IRB that will review the protocol. For most first-party research and for some second-party research in which EPA is involved as a Co-I, this will be the UNC IRB. Instructions and IRB application forms can be found at www.ohre.unc.edu/index.php.

All individuals listed on the protocol application must meet the training requirements specified by either the UNC IRB or the IRB responsible for the protocol review.

Organization affiliation should be listed for all investigators and study staff. Questions regarding completion of the IRB application should be directed to the IRB or the Agency HRPO.

For second-party research led by an entity outside the Agency, the organization's IRB will specify the instructions and application forms.

4.1.7 IRB Approval Letters

The final package submitted to the HRPO for review and approval by the Agency HSRRO will include all IRB approval letters.

4.1.8 External Scientific Reviews (Peer Review)

Prior to submission of a research protocol for IRB review, the PI is responsible for obtaining external scientific peer review of the study design document. The primary objective of the external peer review is evaluation of the following topics:

- scientific merit,
- justification for conducting research involving human subjects, and
- concerns regarding issues of the ethical and safe treatment of study subjects.

All human subjects research in NERL will require an external

peer review regardless of the scope of the study or number of human subjects involved. The PI's division will establish the policy for extramural peer review requirements in the division (e.g., number of reviews, format of the review, etc). The plan for the extramural peer review will be developed by the PI and approved by the Branch Chief and Division Director.

External reviews must be formal, written comments by experts in the field. The PI should provide a written response to each comment in the review, indicating whether the changes suggested by the reviewer have been made, and, if not, why not. Under certain circumstances, reviews conducted by or required by outside collaborators, funding agencies, or regulatory bodies, such as the Food and Drug Administration (FDA) and NIH may serve this purpose if they address the required elements of the review. As described below, the response to the comments will be reviewed by the Branch Chief and the Division Director during the NERL final review of the research protocol.

The extramural review comments and written responses to comments will be included in the final research protocol package to be submitted to the Agency HSRRO for review and approval.

4.1.9 Fact Sheet

A fact sheet provides a brief summary of any high-visibility project or activity to the EPA Assistant Administrator for ORD and, if warranted, to the Administrator. All NERL projects involving human subjects research will require a fact sheet.

Fact sheets, although for internal EPA use, are written in a nontechnical, jargon-free style because information from the fact sheets also may be used by the EPA Office of Public Affairs and by Regional and Program Offices to disseminate information about the research project to interested parties, including the general public.

Fact sheets are required at the beginning of a research project and may be required at other stages of the project. The Branch Chief, Division Director, and the NERL Communications Office should be consulted regarding these requirements. The fact sheet should be no more than two pages in length, written in the format specified by the NERL Communications Office, and include the information listed below. The draft fact sheet will be written following the guidance provided by the NERL Communications Office. It will be approved by the Branch Chief and Division Director prior to being included in the package. The HRPO maintains complete files of fact sheets for reference and review. In parallel, the draft fact sheet will be submitted to the NERL Communications Office, which will send a final copy of it to ORD Senior management and will maintain a file that includes the fact sheet.

The fact sheet must include the following five categories of information.

(1) Impact Statement: Explain why this research is important to the Agency, emphasizing the benefits to be gained.

(2) Background: Explain why this research is being conducted.

(3) Study Description: Provide a brief, nontechnical description.

(4) Timeline: Include projected starting and closing dates and the current status of IRB and EPA review.

(5) Contact: Provide name, NERL division, e-mail address, and telephone number of the contact person.

4.1.10 NERL Sign-Off Sheet

The required sign-off sheet can be found in Appendix D. The names of all reviewers should be typed or printed and approving officials should sign the sheet.

4.1.11 Cover Memorandum

The PI should prepare a memorandum to the EPA HRPO requesting review of the protocol by the HSRRO. The request should be routed through the PI's Branch Chief and Division Director. It should briefly describe the study and the role of NERL in the study and should list the complete contents of the accompanying protocol package.

4.2 Process for Review and Approval of a Typical NERL Study Design and Human Subjects Research Protocol Package

For studies in NERL involving human subjects, an integrated approach will be followed for preparation of the study design and human subjects research protocol package, as described in the SEAOES document. Section 4.1.1 "NERL Study Design" and section 2 of SEAOES describe "Elements To Be Considered in Study Conceptualization and Planning" and provide the recommended approach for developing the study documents and for independent scientific and ethical review. The document stresses that the consideration of scientific and ethical issues be addressed concurrently. The entire package of documentation for a human subjects research study in NERL is prepared and reviewed in stages by the NERL division, the IRB, and EPA. All required reviews and responses are obtained in writing, and approvals are recorded on the NERL sign-off sheet or other supporting documentation. Appendix B contains a flow diagram of the process.

- **Step 1: Study Design and Human Subjects Research Protocol Preparation**
  To facilitate scientific and ethical review, the PI and research team members should develop a comprehensive and detailed study design that describes the technical approach for the study. Elements that may be included in the study design document are described in section 4.1.1 "NERL Study Design" and section 2 of SEAOES. Concurrently, and following the instructions of the IRB of record, the PI and Co-Is will prepare drafts of the human subjects research protocol and the informed consent form. The PI and research team will develop the proposed study design and address ethical considerations

in collaboration with other technical staff, stakeholders, community representatives (as appropriate), statisticians, the branch and division QA staff, and the branch and division management. As part of the study design document, the PI and research team will include a section or appendix on "Considerations for Protection of Human Subjects in the Study" that includes elements described in SEAOES and summarized in Appendix C of this guidance document.

- **Step 2: Initial Reviews**
  After completion of the draft study design, the PI must obtain at least two internal technical reviews prior to submission of the study design document to the Branch Chief. The PI must then provide written responses to the reviewers' comments and revise the study design, if necessary. The Branch Chief will review the study design and determine if it is acceptable for external peer review.
- **Step 3: External Peer Reviews**
  For all NERL human subjects research, an external peer review of the study design must be completed. The PI's division will establish the policies and procedures for conducting the external peer review. The PI, in consultation with the Branch Chief, will prepare a plan for external peer review. The plan will be submitted to the Division Director for approval. Following approval, the PI will proceed with the external peer review. As described above, external reviews must be formal, written comments by experts in the field. The PI should provide a written response to each comment in the review, indicating whether the changes suggested by the reviewer have been made and, if not, why not. Following the external peer review, the PI will revise the study design as required and prepare the human subjects research protocol that will be submitted to the IRB. The entire package, to include the study design, human studies research protocol, informed consent form, brochures, advertising, and other materials to be used in the study will be assembled into the research protocol package.
- **Step 4: NERL Human Subjects Advisory Panel Review**
  The complete study design and human subjects research protocol package will be reviewed by a NERL Human Subjects Advisory Panel prior to submitting the package to the IRB. The panel will consist of the NERL Associate Director for Health, the PI's Division Director, the PI's Branch Chief, and at least one additional NERL staff member designated by the NERL Associate Director for Health. The panel will serve primarily in an advisory role, reviewing the research protocol, meeting with the PI to discuss the study, and providing verbal and written comments to the PI. Recommendations from this panel should be considered by the PI, and changes made to the research protocol package, as appropriate, prior to submitting the package to the IRB. The PI also should obtain concurrence from the Branch Chief and Division Director prior to submitting the package to the IRB.
- **Step 5: IRB Approval**
  Following concurrence by the Branch Chief and Division Director, the package will be submitted to the IRB for review.
- **Step 6: Branch Chief and Division Review**
  Following receipt of IRB approval, the PI should submit the complete protocol package, including all components described above at the beginning of this section, to the Branch Chief for approval. The Branch Chief will transmit the package with approval to the Division Director for final NERL approval. The PI then will incorporate any necessary changes into the protocol prior to resubmission of the package to the IRB (if required) and to the HRPO for consideration.
- **Step 7: Administrative Approval**
  The package next will be reviewed and approved by the Director of the HRPO. If any changes in the protocol or consent form are required during this portion of the EPA review process, the amended protocol must be resubmitted to the UNC IRB or to the IRB of record for the study for approval. After final HRPO review, the completed package is to be copied to the PI and Division Director. The Director of the HRPO then will forward the complete protocol package to the EPA HSRRO for final Agency review and approval.
  The HRPO **requires** one copy of the complete protocol and completed sign-off sheet for record keeping and tracking.
- **Step 8: Study Commencement**
  Recruitment of human subjects can begin only after the Agency HSRRO sends a memorandum of approval to the HRPO Director and the PI. Copies of this memorandum must be distributed to the Branch Chief, Division Director, and the Associate Director for Health.
- **Step 9: Record Management**
  The HRPO maintains the official file for approvals and ethics oversight of all human subjects research projects
  Following initial approval, the PI must ensure that the HRPO is provided copies of all documents needed to maintain a complete and current file, including but not limited to copies of all protocol amendments and renewals, current stamped consent forms, questionnaires, advertising materials, IRB approval letters, and reports of adverse events.
  In short, **If sent to the IRB, send a complete copy to the HRPO. If sent by the IRB, send a complete copy to the HRPO.**

4.3 Protocol Review Procedures for Special Cases

The procedure for preparation, review, and approval of human subjects research may differ from that specified above in the following special cases.

4.3.1 Studies Not Meeting the Definition of Human Subjects Research

Before beginning an investigation using either data or tissue involving human subjects, the investigator should consult the HRPO Director to determine whether the proposed research is subject to EPA Regulation 40 CFR 26. The rules governing that decision are complex. Some studies will be considered human subjects research and, therefore, are subject to 40 CFR 26 and require a complete protocol package. Other similar studies may not be human subjects research, are not subject to 40 CFR 26, and do not require a typical protocol package.

No protocol package is required for human research activities that do not meet the regulatory definition of human subjects research. Instead, the PI must write a memo, routed through the PI's Branch Chief and Division Director, to the HRPO Director describing the study and the reasons why the proposed research is not human subjects research (see Appendix A). The HRPO must concur in writing before such research can proceed. In the event of uncertainty as to whether a study is human subjects research, further consultation with the IRB of record and/or the Agency HSRRO will be conducted by the Director of the HRPO.

4.3.2 Exempt Human Subject Research

Some protocols may be determined to be human subjects research but are still exempt from 40 CFR 26. 40 CFR 26, section 26.101, lists the exemption categories and the criteria that apply to them, for example:

> 40 CFR 26.101(b)(4): *Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.*

PIs should consult their Branch Chief first for guidance regarding classification of human subjects research as exempt. Exempt human subjects research will not require IRB review or assembly of a protocol package but still will require a formal exemption determination by the Agency HSRRO before the study can proceed. The Director of the HRPO will help facilitate review by the Agency HSRRO. The PI must write a memo, routed through the PI's Branch Chief, Division Director, and HRPO Director, to the EPA HSRRO describing the study and requesting approval as exempt human subjects research (see Appendix A).

4.3.3 Waiver of Informed Consent

Occasionally, human subjects research may qualify for a waiver of informed consent. This is granted by the IRB. For NERL research protocols, this is usually because the study presents no more than minimal risk to the study subjects and also meets the other criteria for waiver found at 40 CFR 26.116(c) or (d). In these cases, the PI should request a waiver of informed consent from the IRB during the initial application process. If the IRB grants the request, the PI, in the cover memorandum to the Director of the HRPO, routed through the Division Director, should include the reason for requesting the waiver from the IRB.

As with all human subjects research studies, final approval by the Agency HSRRO is still required before the study can proceed.

4.4 Collaboration and Consultation on Research Primarily Conducted Outside NERL

NERL investigators frequently collaborate or consult on studies primarily conducted at other institutions, such as other EPA laboratories, extramural contractors, co-operators, government agencies, and universities. Note that *collaboration*, as defined below, implies that EPA is *engaged* in the research under the regulations, whereas *consultation* does not.

Collaboration means involvement as a Co-PI or Co-I, the possession of or access to identifiable private information, or interaction or intervention with subjects. Collaboration by a NERL investigator means that EPA is *engaged* in the human subjects research under the regulations and requires NERL approval. Decisions of whether an individual is a consultant or collaborator will be made by the HRPO Director in consultation with the PI, Branch Chief, and Division Director. The HRPO director may consult the Agency HSRRO for guidance in complex situations.

Consultation, on the other hand, implies less direct involvement with a study, no interaction or intervention with subjects, and no possession of identifiable private information. Consultants may, on occasion, be co-authors on publications, but their involvement is typically not at the same level as that of collaborators. Consultation by a NERL investigator does not mean that EPA is *engaged* in research under the regulations and, thus, does not cause the same regulatory requirements to kick in.

Further guidance on engagement can be found at the DHHS Office of Human Research Protections Web site, http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm.

5.0
OBSERVATIONAL HUMAN EXPOSURE STUDIES

Observational human exposure studies are conducted by researchers in NERL to improve our understanding of when, why, and how people come into contact with chemicals and other stressors in their everyday environments. These studies typically involve measurements of chemicals in the food people eat, the water they drink, the air they breathe, and dust on the surfaces they touch. In addition, information about the study participants and their homes, work environments, and activities are collected, as well as biomonitoring samples. Results of these studies are used by the Agency to develop exposure and risk assessments and, as necessary, risk mitigation strategies. Although observational studies do not involve intentional exposures, there are many scientific and ethical issues that need to be considered in designing and conducting these complex studies. Because they involve both adults and children who volunteer to participate in the studies, protections must be appropriate for both types of participants.

NERL has prepared the SEAOES document as a resource of information for researchers planning and implementing observational exposure studies. Researchers planning observational exposure studies are to use the recommendations in SEAOES as they develop their study design and human subjects research protocol. These same recommendations also are to be used by second-party researchers funded by NERL.

6.0
INTENTIONAL EXPOSURE STUDIES

40 CFR 26, Subpart B defines *research involving intentional exposure of a human subject as the "study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study"*. One consequence of this definition is that "scripted" studies generally will fall within the category of *research involving the intentional exposure of human subjects*. Scripted studies are those studies during which measurements are performed while a participant is asked to perform specified activities. An example would be a study in which participants consume a diet containing food items that are determined and specified by the research because they may, or may not, contain chemicals of interest to the researchers. Another example would be a script for daily activities, including cooking, cleaning, and other routine activities, during which measurements of pollutants are made. Although these may be routine activities that would probably be performed by a study participant anyway, the scripting of such activities, instead of allowing them to occur naturally, causes the research to fall within the category of "intentional exposure," as defined in 40 CFR 26. Many "intervention" studies also will meet the regulatory definition of "intentional exposure."

Researchers considering studies involving intentional exposure of human subjects should consult with the HRPO to discuss the potential study and study design prior to developing the study design. The HRPO, in consultation with the EPA HSRRO, will make a determination as to whether a proposed study is an intentional exposure study. If the study is determined to be an intentional exposure study, the HRPO will advise the PI of special requirements for the human subjects research protocol.

7.0
STUDY OF HUMAN DATA, HUMAN TISSUES, AND ENVIRONMENTAL SAMPLES COLLECTED IN HUMAN SUBJECTS RESEARCH

7.1 Purpose

Before beginning an investigation using human data, human tissues or samples, or environmental samples from another study involving human subjects, the researcher must consult the HRPO Director to determine whether the proposed research is human subjects research, non-human subjects research, or exempt human subjects research. The rules governing the decision are complex. Some studies will be considered human subjects research and, therefore, are subject to 40 CFR 26 and require a complete NERL protocol package. Other studies may be similar, except for a slight nuance, and considered non-human subjects research or exempt human subjects research and, therefore, not subject to 40 CFR 26 and not requiring a standard NERL protocol package.

Even if an IRB has decided that a particular study is exempt from further review, only the Agency HSRRO has final authority over whether or not a study is exempt and whether or not it will be subject to 40 CFR 26.

7.2 Definitions

Human tissue is defined as any cells, cell lines, fluids, or other biological tissues originally collected from a living person.

Environmental samples may include samples such as indoor or outdoor soil, water, dust, surface wipe samples, diet samples (solid food and/or beverages), and air monitoring samples.

7.3 Genetic Studies

As with many types of biological research, the possibility of identifying individuals with disease susceptibility may occur, especially in studies that correlate genetic changes or biomarkers with susceptibility to specific disease states. Such studies must have stringent safeguards for subject privacy and confidentiality. Most IRBs have specific requirements for the use of human material in genetic studies, especially with respect to informed consent.

7.4 Stored Specimens

There are several categories of stored specimens collected in human subjects research, including specimens to be stored for previously stipulated tests; for as-yet-undesignated tests, but excluding genetic studies; for as-yet-undesignated tests that may include genetic studies, with personal identifiers accompanying the specimen; and for as-yet-undesignated tests that may include genetic studies, but with no associated personal identifiers. Each category has specific requirements for protection of the research subject.

7.5 Specimens Obtained from Other Researchers or Commercial Tissue Banks

Many opportunities exist for researchers to obtain specimens of human origin from other colleagues or from commercial tissue banks. A guiding principle is that the PI should only use specimens that were obtained in an ethical manner.

In some circumstances, the HRPO Director may require proof of IRB approval of the protocol being used to procure, store, and distribute the specimens or contracts/bills of sale for the specimens. The PI must notify the HRPO Director before any research is initiated involving any human specimens.

8.0
ADVERSE EVENTS AND UNEXPECTED EVENTS

Even the most careful researcher using a well-thought-out protocol may have a research subject who has an adverse or unexpected event during participation in a research study. Below is the text from the UNC IRB Standard Operating Procedures Manual on the definitions and reporting requirements associated with an adverse or unexpected event.

8.1 Definitions

"Adverse event" or "adverse experience" is an undesirable and unintended, though not necessarily unanticipated, injury or physical or emotional consequence to a human subject.

"Serious Adverse Events" (SAEs) are those that are fatal or life threatening; result in significant or persistent disability; require or prolong hospitalization; result in a congenital anomaly/birth defect; or, in the opinion of the investigators, represent other significant hazards or potentially serious harm to research subjects or others.

"Unexpected" or "unanticipated" refers to adverse events or other problems in the research where the nature and/or severity are not consistent with the information already provided to the IRB, including the investigator's brochure, research protocol, or consent form.

"Unanticipated Problems" (UPs) may or may not include specific events experienced by individual subjects, but are developments within the research activity that suggest a potential for increased risks to subjects or others.

8.2 Serious Adverse Events and Unanticipated Problems Occurring at Sites for Which a UNC-Chapel Hill IRB Has Direct Oversight Responsibility

In case of an SAE or an UP, the PI is required to submit a written report to the IRB, with the time frame for the report depending on the type of event being reported. The PI's report should contain enough information for the IRB to judge whether or not the event raises new questions about risks to participants or the research design. This report is reviewed by one or more experienced IRB members (typically including the chair), and a decision is made as to whether or not the report should be presented and discussed at a convened meeting.

In case of an adverse event that is both serious and unanticipated that occurs at a site for which a UNC IRB has direct oversight responsibility, the PI must notify the IRB within 24 h (or by the next working day).

In case of an adverse event that is serious but not unanticipated, the PI must notify the IRB within 5 working days.

In case of an adverse event that is not serious, but is unanticipated, the PI must notify the IRB within 10 working days.

In case of an UP involving risks to subjects or others but not meeting the definition of an adverse event, the PI must notify the IRB within 10 working days.

In multicenter studies, at sites outside the jurisdiction of the UNC IRB, investigators are required to report adverse experiences that occur in subjects enrolled elsewhere (i.e., by non-University investigators) only when the adverse event is **both** serious **and** unexpected. However, sponsors often require that adverse events that do not meet these criteria be reported to the IRB, and the investigator should do so. Documentation of such reports will be filed in the IRB file after review by a chair or a designated individual. The chair, at his/her discretion, may add review of these reports as an agenda item at a convened meeting. For multisite studies in which a Data and Safety Monitoring Board (DSMB) is performing aggregate analysis of adverse events, the IRB should receive a copy of the DSMB report. The following table summarizes IRB reporting timelines for SAEs and UPs.

8.3 Adverse Event Written Report

The adverse event written report submitted to the IRB must contain the following information.

- IRB study number
- Title of protocol
- Name of PI and relevant department, division or center
- Subject identifier (study number/reference of subject)
- Date and site of event
- Description of event (nature of injury or other adverse occurrence, assessment of severity, and assessment of relationship to study)
- Handling/response to the event

Event type	Serious	Unanticipated	Report within
Adverse	•	•	24 hrs or next working day
Adverse	•		5 working days
Adverse		•	10 working days
Non adverse		•	10 working days

- Any proposed changes in protocol or consent form due to event
- To whom else the event has been reported
- Signature of PI

8.4 IRB Responsibilities Following Receipt of Serious Adverse Event/Unanticipated Problem Report

The chair or a designated subcommittee of the IRB will review the SAE/UP and will decide whether the report should be presented and discussed at a convened meeting. If an adverse event occurring at the University is related to the study intervention and is both serious and unanticipated, the IRB will notify the Institutional Official and the event will be reviewed by the IRB at a convened meeting.

If an SAE or UP poses serious risk to subject safety, the chair or designated subcommittee may immediately suspend the study before presenting the report to the convened meeting. If the IRB suspends or terminates a study due to an SAE or UP, it must notify the Institutional Official, who, in turn, is responsible for making any required reports to the appropriate Federal regulatory agencies.

If this unanticipated SAE is a death or serious injury, the IRB must notify the University's General Counsel immediately after it receives notification.

It is the investigator's responsibility to make all required reports of adverse events to the FDA and/or sponsor. Investigators may have additional reporting responsibilities outlined in individual contracts that are not covered by this procedure.

References:

45 CFR 46.103(b)(5)(i)

45 CFR 46.111(a)(6)

45 CFR 46.113

21 CFR 56.108(b)(1)

21 CFR 312.32

21 CFR 312.64 (b)

21 CFR 314.80

21 CFR 812.150 (a)(1)

9.0
NERL EMPLOYEES AS RESEARCH SUBJECTS

Because the protection of human research subjects is a high priority throughout EPA, protections extend to NERL employees who choose to experiment on themselves, participate in NERL human studies, or request co-workers to take part in these studies.

9.1 Purpose

This chapter describes additional requirements governing the participation of EPA employees as subjects in human research activities.

9.2 Requirements for Participation of an EPA Employee as a Research Subject

For any research activity meeting the definition of human subjects research in 40 CFR 26 or EPA Order 1000.17A, Change A1, EPA employees participating as subjects are subject to the following additional guidelines and requirements.

- Employees are very strongly discouraged from conducting research on themselves. Alternatives to using employees include identifying subjects through an approved recruitment mechanism or procuring anonymous specimens from internal or external specimen banks. The HRPO can assist investigators in identifying resources for suitable subjects or specimens.
- There cannot be direct or indirect coercion of employees to participate as research subjects in NERL investigations. Supervisors cannot ask employees they supervise to participate as subjects in EPA research studies.
- No employee may participate as a subject in human subjects research that circumvents oversight by an IRB or by Agency review and approval procedures.
- All employees must go through the same screening process required for nonemployee subjects, including identical inclusion and exclusion criteria for participation and signing informed consent.
- The study protocol must contain a statement of the expected number and duration of time periods that the employee will be expected to spend in the study. A copy of this statement must be provided to the employee. The consent form must appropriately cover additional liability issues, if any, that are generated by employee participation either on his/her own time or on government time.
- An employee who feels that his or her rights have been breached or to whom an injury has occurred should contact the HRPO Director, and/or the Chairman of the IRB at the telephone numbers listed in the consent form.

9.3 EPA Employees in Non-Human Subjects Research Activities

Some activities involving human subjects are not human subjects research because they do not meet the definition of research. Such studies are not subject to 40 CFR 26 and do not require approval by the Agency HSRRO. The decision as to whether a human research activity meets the definition of human subjects research is made by the HRPO Director, with input, if necessary, from the appropriate IRB or the Agency HSRRO.

For some procedures that involve very low risk of personal injury and low risk of ethical mistreatment, an EPA PI may be granted permission to participate as a subject or to include other EPA employees as subjects. To obtain this permission, the PI must write a memorandum describing the non-human subjects research activity, including risks, and the reasons the activity does not meet the definition of human subjects research. The memorandum must be sent through the Branch Chief to the HRPO Director and must be approved by both before the study can begin.

The following collections and procedures may fall into this category.

- Human exposure air monitoring samples and data from active or passive monitors
- Indoor or outdoor air monitoring data or samples from active or passive monitors
- Indoor or outdoor soil, water, dust, or other environmental media samples
- Breast milk samples
- Breath collection
- Buccal specimens
- Dermal wipes
- Fecal specimens
- Hair specimens
- Nail specimens
- Nasal lavage
- Spontaneously generated sputum
- Saliva collection
- Urine specimens
- Routine pulmonary function (spirometry and body plethysmography)
- Blood pressure
- Pulse oximetry
- Heart rate variability

The Director of the HRPO may make additions or deletions as needed.

Note that several common types of samples, including venous blood samples, are not included. Venipuncture is more invasive and can have more significant consequences than the other listed procedures. Semen samples are not included because of issues concerning privacy and embarrassment surrounding the collection process. Neither genetic analyses nor other analyses that may yield sensitive or potentially unfavorable information may be performed on any samples collected under this category unless the samples are pooled or are otherwise completely anonymous, with no means of determining the identity of the donors.

9.4 Survey Questionnaires

For questionnaire completion by employees to be allowed without OMB review, the following conditions must be met.

- When employees are administered questionnaires to evaluate questions and/or the time needed for completion, individual answers to questions cannot be entered and stored in a database. Only evaluative information, such as suggested changes in wording, format, or time to completion can be collected.
- Answers to individual questions from employee questionnaires may be entered and stored in a database if, and only if, the questionnaires are completely anonymous, and the identity of the employees cannot be determined by other means.

LIST OF ACRONYMS AND ABBREVIATIONS

BC	Branch Chief
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
Co-I	Co-investigator
CRADA	Cooperative Research and Development Agreement
DD	Division Director
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FWA	Federal Wide Assurance
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protocol Office
HSRB	Human Studies Review Board
HSRRO	Human Subjects Research Review Official
ICR	Information Collection Request
IRB	Institutional Review Board
NERL	National Exposure Research Laboratory
NIH	National Institutes of Health
OMB	Office of Management and Budget
ORD	Office of Research and Development
PHI	Private health information
PI	Principal investigator
PO	Project Officer
QA	Quality assurance
SAE	Serious adverse event
SEAOES	*Scientific and Ethical Approaches for Observational Exposure Studies*
UNC	University of North Carolina
UP	Unanticipated problem

APPENDIX A
TEMPLATES FOR MEMORANDUMS FOR HUMAN SUBJECTS RESEARCH REQUESTS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

Date:

Subject: Request for Study Approval as Non-Human Subjects Research

From:

Through:To: XXXXXXXXXXXXXXXXXXXXX
Director, Human Research Protocol Office

CC:

This section should contain the following information.

- Description of the study—Two to three paragraphs describing the reason for the study and a description of the methods and samples required for the study. List who is involved in the research, what roles they will fulfill in the study, and what access to samples or data they will require.
- What identifiers will be collected with the data (or provided with the samples if purchased from a commercial vendor or from another outside source), and what identifiers the research team will have access to.
  - Does the contract or bill of sale from the samples include language that specifically states that no personal identifying data will ever be shared with users of the samples?
  - Will the samples be provided with a code? Often this code can be traced back to the sample donors, so researchers obtaining these samples must de-link the provided code with the samples by randomizing the samples to make them anonymous.
- A request that the research be classified as non-human subjects research.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM
Date:

Subject: Request for Study Approval as Exempt Human Subjects Research

From:

Through:

Through: XXXXXXXXXXXXXXXXXXXXX
Director, Human Research Protocol Office

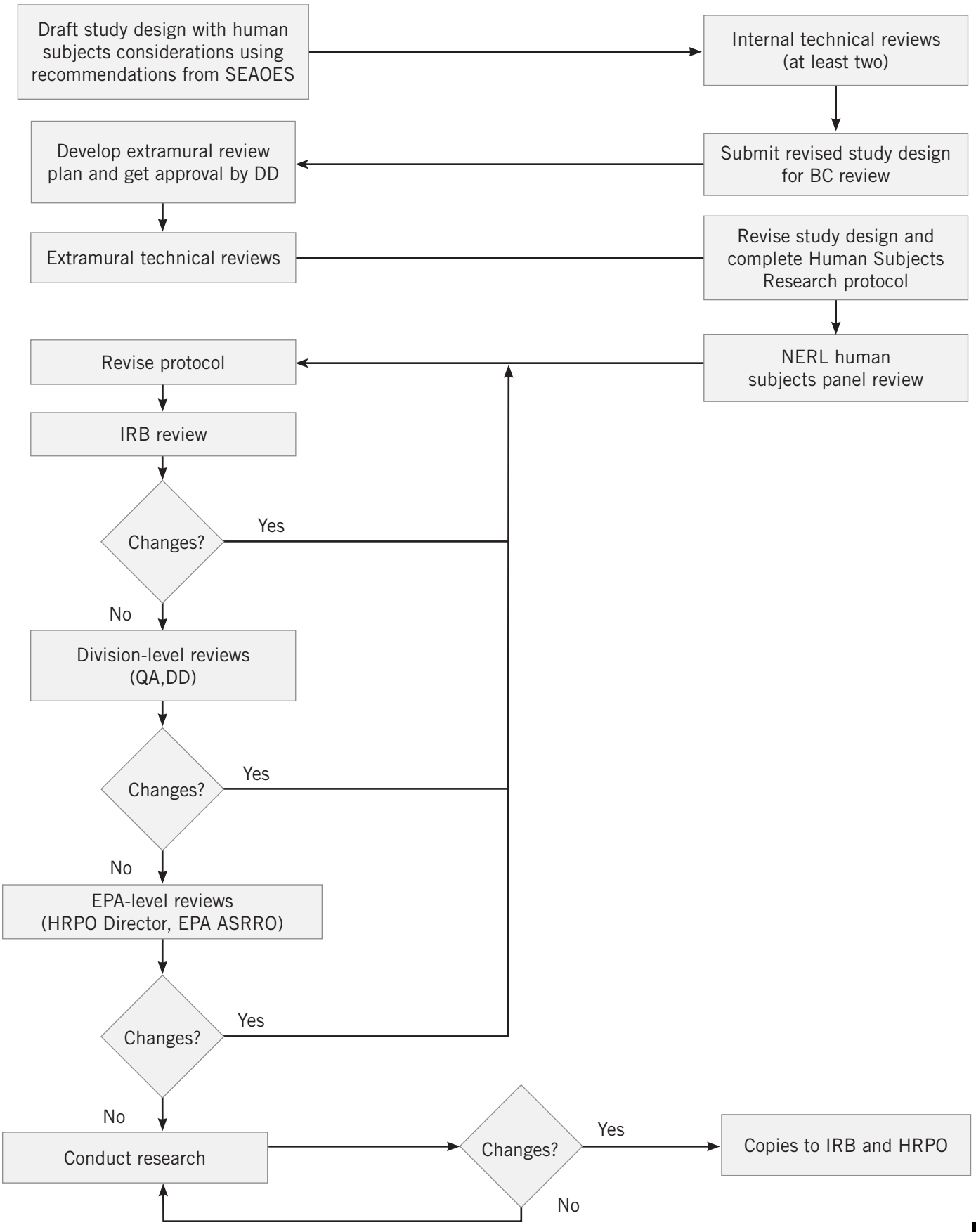
To: XXXXXXXXXXXXX
EPA Human Subjects Research Review Official

CC:

This section should contain the following information.

- Description of the study—Two to three paragraphs describing the reason for the study and a description of the methods and samples required for the study. List who is involved in the research, what roles they will fulfill in the study, and what access to samples or data they will require.
- What identifiers will be collected with the data (or provided with the samples if purchased from a commercial vendor or from another outside source), and what identifiers the research team will have access to.
- Under what section of 26.101 (b) the exemption will be classified?
- A request that the research be classified as exempt human subjects research.

APPENDIX B
FLOW DIAGRAM FOR THE NERL REVIEW PROCESS



APPENDIX C
GUIDANCE FOR PREPARATION OF THE SECTION OR APPENDIX ON "CONSIDERATIONS FOR PROTECTION OF HUMAN SUBJECTS IN THE STUDY"

To facilitate the NERL internal scientific and ethical review of a study design for an observational exposure study, the study design document must include a section or appendix entitled "Considerations for Protection of Human Subjects in the Study." The section should discuss the approaches that the researchers intend to follow to address potential ethical issues in the design and implementation of the study. This section or appendix may reference specific sections of the study design document or briefly describe how the researchers have addressed the scientific and ethical issues identified in the SEAOES document. If an element identified in SEAOES is not relevant to the study being proposed, the researchers should describe why the element does not need to be addressed. The recommended outline for this section or appendix of the study design is presented below with reference to the relevant sections of the document.

Study Element	**SEAOES Section**
1.0 Elements To Be Considered in Study Conceptualization and Planning	2
1.1 Justification for the Proposed Study—Define the study problem, science questions to be addressed, study objectives, and/or hypotheses to be tested. Describe the scientific justification for the study, including relevance, need for the data, etc.	2.1
1.2 Justification for Including Human Subjects in the Research	2.1.2
1.3 Ensuring Scientific Validity of the Research Study—Include a brief overview of the study design and detailed discussions of the approaches for determining feasibility, sample size, and representativeness of the sample.	2.2
1.4 Ethical Issues in Ensuring Fair Subject Selection	2.3
1.5 Ensuring a Favorable Risk-Benefit Ratio—Discuss benefits and risks to participants and approach for maximizing benefits to the participants.	2.4
1.6 Scientific and Ethical Reviews—Discuss plan for internal and external reviews.	2.5
1.7 Conflicts of Interest	2.5.2
1.8 Considerations for Ensuring That Participant Behaviors Are Not Changed Adversely Because of Being in the Study	2.7
1.9 Proposed Approaches for Monitoring Scientific and Ethical Issues During the Study	2.8
2.0 Ensuring Protection of Vulnerable Groups	3
2.1 Identification of Vulnerable Groups in the Study	3.1
2.2 Justification for Involving Vulnerable Persons in the Study	3.2
2.3 Consideration of Special Requirements for Vulnerable Groups (Children, Women, Other)	3.4-3.6

Study Element	SEAOES Section
3.0 Privacy, Confidentiality, and Other Concerns Related to Observational Human Exposure Studies	4
3.1 Privacy Issues	4.1
3.2 Confidentiality of Information and Participation	4.2
3.3 Non-Study Hazards with Mandated Reporting Requirements—Describe plans for identifying, addressing, and reporting (including hazard communication and staff training).	4.3
3.4 Other Non-Study Hazards—Describe plans for identifying, addressing, and reporting.	4.3
3.5 Third Party Issues—Describe plans for identifying third parties and issues, addressing issues, and reporting/communications.	4.4
3.6 Plans for Data and Safety Monitoring and Oversight (See also section 1.9 above)	4.5
4.0 Creating an Appropriate Relationship Between the Participant and Researcher	5
4.1 Informed Consent Process—Describe approaches for information, comprehension, and voluntary participation.	5.1
4.2 Payments to Research Participants—Describe type, amount, justification, basis for payment type and amounts, and comparison to similar studies; describe how payments will not serve as inducements or change behavior in the study; describe special considerations for studies with children and other vulnerable groups.	5.2
4.3 Research Rights and Grievance Procedures	5.3
4.4 Recruitment Strategies—Ethical Considerations	5.5 and 5.7
4.5 Retention Strategies—Ethical Considerations	5.6 and 5.7
5.0 Building and Maintaining Appropriate Community and Stakeholder Relationships	6
5.1 Proposed Approach(es) to Community Involvement	6.1
5.2 Issues in Community Involvement—Describe considerations and issues as identified in SEAOES.	6.2
5.3 Other Stakeholders—Describe approach for identifying, interacting with, and communicating with stakeholders other than the community.	6.4
6.0 Designing and Implementing Strategies for Effective Communication	7
6.1 Communication Strategy and Implementation Plan—Describe the general approach and communication strategy, individuals and groups involved, and timeline for completing the communication plan.	7.1-7.5
6.2 Communications with Study Participants—Describe approaches and plans for communications and reporting during all phases of the study.	7.6
6.3 Communications with the Community—Describe approaches and plans for communications and reporting during all phases of the study.	7.6
6.4 Communications with Other Stakeholders, the Public, and the Media—Describe approaches and plans for communications and reporting during all phases of the study.	7.6-7.10
6.5 Reporting Unanticipated Results or Observations—Describe special considerations and the approach for determining “reporting levels.”	7.8

APPENDIX D
NERL HUMAN RESEARCH SIGN-OFF SHEET

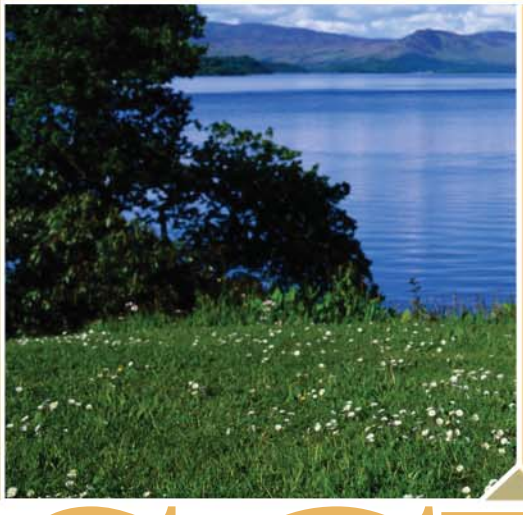
PI (Name/Division): _____

PROTOCOL TITLE: _____

NAME OF APPROVING IRB: _____

IRB-ASSIGNED PROTOCOL NUMBER: _____

REVIEWS *(Attach to EPA Protocol Package)*		
Reviewer	Signature	Date
Peer Reviewer 1 (printed or typed)		
Peer Reviewer 1 (printed or typed)		
Other		
APPROVALS		
Official	Signature	Date
NERL Advisory Panel (AD for Health)		
IRB	(Attach signed approval letter)	
Branch Chief		
Division Quality Assurance Officer		
Division Director		
HRPO Director	(Indicated by approval letter)	
Agency Human Subjects Research Review Official	(Indicated by approval letter)	
		Revised June 2009



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United States
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