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# Scientific and Ethical Approaches for Observational Exposure Studies



SCIENCE

**Office of Research and Development**
National Exposure Research Laboratory

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National Exposure Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

# Notice

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# Abstract

Researchers conduct observational human exposure studies to understand how and the extent to which people come into contact with chemicals and environmental stressors in their everyday lives, through the air they breathe, the food and liquids they consume, and the things they touch. The U.S. Environmental Protection Agency's (EPA's) National Exposure Research Laboratory (NERL) has conducted observational human exposure studies for several decades and uses the information and data from these studies to improve the Agency's understanding of human exposures to chemicals and other stressors and ultimately to support efforts to improve public health. Because these studies involve people as research participants, they are complex and raise numerous scientific and ethical issues that have to be addressed prior to and during their design and implementation. To ensure that EPA's research continues to be based on the most up-to-date science and the highest ethical standards, the Agency has developed this document that contains state-of-the-science approaches for conducting observational human exposure studies. This document is not meant to represent an official Agency "guidance document" but, rather, serves as a resource tool and source of information for NERL and other researchers on which to rely as they develop and conduct observational human exposure studies.

# Foreword

This document is intended as a resource and reference for the U.S. Environmental Protection Agency's (EPA's) National Exposure Research Laboratory (NERL) scientists as they develop and implement observational human exposure studies. The authors recognize that this document also may prove to be useful to others involved in exposure science research, but the document is not meant to represent an official Agency "guidance document" and should not be used for that purpose.

Observational human exposure studies involve the collection of information about individuals and the environment around them. NERL scientists and managers take the protection of human subjects who participate in these studies very seriously. The steps needed to ensure protection of the human subjects are often complex, and the specific actions will vary depending on the objectives of the study and details about the participants.

This document does not provide solutions to all scientific and ethical issues that may arise as such studies are undertaken. That is, it is not possible to identify or address all potential issues in advance or to develop a comprehensive checklist for all such studies. Rather, this document attempts to present and discuss the types of issues that will need to be considered and addressed as NERL researchers plan and implement observational human exposure studies. The researchers will need to work with others—the study team, institutional review board members, EPA's Human Subjects Research Review Official, the participants and their community, and other stakeholders—to identify and address all of the relevant issues for their particular study in order to ensure that the specific elements of the study will respect, safeguard, and protect the human research subjects.

As EPA employees, NERL scientists face both regulatory and moral obligations to ensure the protection of the human subjects participating in observational research. The regulatory requirements are set forth in EPA's human subjects regulations (40 CFR 26). NERL scientists are resolved to meet both the "letter" of the law as set forth in the regulations and also the "spirit" that derives from the most up-to-date thinking and consensus on these sensitive issues. This document provides information on regulatory requirements and the state of the science for a number of issues associated with observational human exposure studies to help NERL scientists meet their goal of conducting these studies based on the most up-to-date and sound science and the highest ethical standards.

To gather information for the scientific and ethical approaches for observational human exposure studies, NERL convened an expert panel workshop on November 28 and 29, 2006, to discuss the state of the science. The 11-member panel discussed their ideas for the content of this document and the state of the science for various elements of observational human exposure studies. The panel agreed that the document planned by EPA should include the following six major topic areas:

(1) identifying elements to be considered in study conceptualization,
(2) ensuring protection of vulnerable groups,
(3) addressing privacy and other concerns related to observational human exposure studies,
(4) creating an appropriate relationship between the participant and investigator,

(5) building and maintaining appropriate community and stakeholder relationships, and
(6) designing and implementing strategies for effective communication.

The structure and content of the current document follow the recommendations of the Expert Panel. These recommendations include pragmatic steps that NERL scientists can undertake during the development and implementation of observational human exposure studies.

# Acknowledgments

This document was developed through the joint efforts of many U.S. Environmental Protection Agency (EPA) staff. Roy Fortmann, Larry Cupitt, Kent W. Thomas, and Peter Egeghy, researchers in the National Exposure Research Laboratory, were primary authors of the document. Linda Sheldon provided input to the development of the document and contributed through discussions with the authors on issues associated with observational human exposure studies. Davyda Hammond assisted in the revision of the external review draft document. Larry Cupitt had primary responsibility for editing the document and coordinating the peer reviews. Internal EPA reviewers included Pamela Williams, Warren Lux, Michael Firestone, Gary Bangs, Julian Preston, Hugh Tilson, Ronald Williams, Cathy Fehrenbacher, and Deirdre Murphy. The EPA Human Studies Review Board, a Federal advisory committee, reviewed the external review draft document and provided advice and recommendations that were addressed in the final revision of the document. John Barton performed the copy edits of the external review and final drafts. Public comments solicited on the external draft were addressed in the final revision of the document.

# Contents

# Executive Summary

Scientists at the U.S. Environmental Protection Agency's (EPA's) National Exposure Research Laboratory (NERL) have conducted observational human exposure studies for several decades to understand how people come into contact with chemicals and other stressors in their everyday lives, through the air they breathe, the food and liquids they consume, and the things they touch. These studies are performed to determine what chemicals people are exposed to, the concentrations of the chemicals, the most important sources contributing to people's exposures, the routes and pathways of exposure, and the factors that have the biggest impact on exposure. The studies help explain when, where, why, how, and how often people are exposed to chemicals and other stressors (e.g., allergens, viruses, mold, radiation, noise) in their everyday environments as they go about their daily activities. Information from these studies helps EPA improve the understanding of people's exposures to chemicals and other stressors and, ultimately, supports EPA's efforts to protect public health.

NERL scientists and managers take the protection of human subjects very seriously. Because observational human exposure studies involve people as research participants, NERL researchers must act to ensure the protection of the human subjects throughout the study. Such studies are often complex, and the specific actions will vary depending on the objectives of the study, the details of the study design and human subjects research protocol, and the details about the participants and the communities in which they live. To ensure that the actions of NERL researchers will properly respect, safeguard, and protect the rights and welfare of the participants in their research, NERL scientists need to be knowledgeable about the scientific and ethical issues that may arise as they plan and conduct their research, and they also need to be diligent in the application of the most up-to-date and sound scientific approaches and of the highest ethical standards to their research.

This document, therefore, was prepared by NERL scientists as a resource and reference for EPA's NERL scientists as they develop and implement observational human exposure studies. The authors recognize that this document also may prove to be useful to others involved in exposure science research, but that this document does not meet the definition of an official Agency "guidance document" (it does not set forth "a policy on a statutory, regulatory or technical issue or an interpretation of a statutory or regulatory issue") and should not be used for that purpose.

As EPA employees, NERL scientists face both *regulatory* and *moral and ethical obligations* to ensure the protection of the human subjects participating in their observational research. The regulatory requirements are set forth in EPA's human subjects regulations (40 CFR 26). The moral obligations derive from the ethical principles of biomedical ethics. NERL scientists and managers are resolved to meet both the "letter" of the law as set forth in the regulations and also the "spirit" that derives from the most up-to-date thinking and consensus on these sensitive issues.

This document provides information on regulatory requirements and ethical issues to consider when performing human subjects research. Knowledge about these requirements and issues will help NERL scientists meet their goal of conducting observational human exposure studies based on the most up-to-date and sound science and the highest ethical scientific standards.

The ethical and moral issues associated with human subjects research has long been the subject of a great deal of thought and discussion, both in the United States and abroad. Issues in biomedical ethics continue to be discussed and debated in today's headlines. Spurred by the atrocities of World War II concentration camps and by the disclosure of unethical treatment of undereducated African-American men and other vulnerable groups by medical staff in the United States, the U.S. and world communities were prompted to establish ethical principles for medical and scientific experiments that involve people as participants. In the United States, the Belmont Report (U.S. DHEW, 1979) is the foundational document in the development of the

ethics of human subjects research. This report lays out the fundamental ethical principles behind research that involves humans as research subjects. These three basic principles, (1) respect for persons, (2) beneficence, and (3) justice, have become the cornerstones for regulations involving human subjects. Ethicists have expanded on those principles since 1979, translating them into ethical requirements that any human subjects research must be both ethically acceptable and scientifically sound.[1] EPA's Science Advisory Board has affirmed, "Bad science is always unethical" (U.S. EPA, 2000).

In an effort to ensure that NERL's observational human exposure studies are founded on the ethical principles of respect for persons, beneficence and nonmaleficence, and justice and adhering to the principle that bad science is always unethical, scientists and managers from NERL have assembled this document as a resource and reference for NERL exposure scientists. These same scientists and managers have sought expert advice, including input from an expert panel workshop; review and comment on the external review draft of the document by the Human Studies Review Board (HSRB), a Federal advisory committee; public comment on the external review draft of the document; and public input about the state of the science for scientific and ethical approaches for design and implementation of observational human exposure studies.

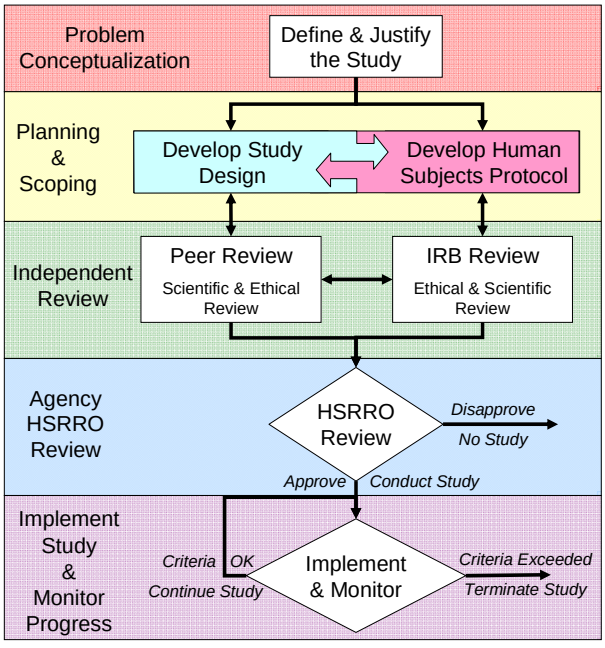
A number of references, both from the bioethics literature and from U.S. regulations, have proven useful to the authors as they have developed this document. Those references are listed in Table 1-4, which is replicated below.

The authors also have relied extensively on the advice of an expert panel that convened in November 2006 to provide advice and guidance about the structure and content of this document. The Expert Panel consisted of 11 nationally recognized authorities from diverse fields — exposure science, environmental health, bioethics, epidemiology, community-based research, law, research in minority communities, public health, toxicology, pediatrics, and children's environmental health.

The Expert Panel Workshop resulted in suggestions for both the structure and the content of this document (ERG, 2007). Following the advice of the Expert Panel, this document is organized in seven sections.

Section 1. Introduction: The background for observational human exposure studies, the scope of this document, and the important scientific and ethical issues that are critical to human subjects and observational research.

Section 2. Elements to be considered in study conceptualization: Incorporating ethical concerns into the scientific effort from the onset and integrating them throughout all phases of study planning and implementation. As shown in the text box below, the planning process involves the initial identification of the research question and justification of the research effort during the problem conceptualization phase. If human subjects research is justified for the study, the scientific and ethical approaches are described in the study design and the human subjects research protocol. The basic elements that should be included in the study design and in the human subjects research protocol are described, and researchers are advised to consider alternative and innovative study designs that maximize the benefits to the study participants and their community. Information is provided on both scientific peer review and ethical review, and the integration of the two. Mandated procedures for review by external peers, by Institutional Review Boards (IRBs), and by the EPA Human Subjects Research Review Official (HSRRO) are detailed.




Stages in the Development of a NERL Observational Human Exposure Study

[1] See, for example, the writings of Beauchamp and Childress in *Principles of Biomedical Ethics* (Beauchamp and Childress, 2001) and the discussion of "What Makes Clinical Research Ethical?" by Emanuel, Wendler, and Grady (Emanuel et al., 2000).

**Table 1-4. Important References in Developing This Document: Some Recent Developments in Defining the Ethics of Conducting Research Involving Human Participants**

| Year | Event/Report | Description |
|---|---|---|
| 1979 | *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (U.S. DHEW, 1979) | The Belmont Report attempts to summarize the basic ethical principles identified by the legislatively created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. The three basic ethical principles are (1) respect for persons, (2) beneficence, and (3) justice. |
| 1991 | The Common Rule 40 CFR 26, Subpart A | The Common Rule is a short name for "The Federal Policy for the Protection of Human Subjects" and was adopted by more than a dozen Federal departments or agencies in 1991. Each agency incorporated the policy into its own Code of Federal Regulations (CFR), with EPA adapting it in Title 40 CFR Part 26, Subpart A. |
| 1993 | *The Institutional Review Board Guidebook* (U.S. HHS, 1993) | The document is intended as a resource and a reference document for IRB members, researchers, and institutional administrators. It is not designed to tell IRBs whether or not specific protocols should be approved; rather, the Guidebook points out issues to which IRBs should pay attention and presents, wherever possible, areas where ethicists have arrived at a consensus on the ethical acceptability of a particular activity or method. |
| 2000 | What Makes Clinical Research Ethical? (Emanuel et al., 2000) | This journal article lays out seven areas of concern that need to be addressed if clinical research is deemed to be ethically acceptable: (1) social or scientific value, (2) scientific validity, (3) fair subject selection, (4) favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for potential and enrolled subjects. |
| 2001 | *Principles of Biomedical Ethics:(Fifth Edition (Beauchamp and Childress, 2001)* | A classic text in biomedical ethics. Core chapters discuss respect for autonomy, nonmaleficence, beneficence, and justice. The chapter on professional-patient relationships discusses issues important to privacy, confidentiality, and protection of subjects. The fifth edition is an update that reflects developments in philosophical analysis, as well as developments in science and medicine. |
| 2002 | *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002) | Developed by the Council for International Organizations of Medical Sciences particularly for use in developing countries, the guidelines relate mainly to ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities, and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health care services. |
| 2003 | *Protecting Participants and Facilitating Social and Behavioral Sciences Research* (NRC, 2003) | This NRC publication targets policymakers, research administrators, research sponsors, IRB members, and investigators. It examines three key ethical issues: (1) obtaining informed, voluntary consent from prospective participants; (2) guaranteeing the confidentiality of information collected from participants, which is a particularly challenging problem in social sciences research; and (3) using appropriate review procedures for minimal-risk research. |
| 2005 | *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children,* (NRC & IOM, 2005) | This National Research Council and Institute of Medicine report reviews the challenges and ethical issues in conducting housing-related health hazards research in the wake of the Maryland Court of Appeals ruling in the case of *Grimes* v. *Kennedy Krieger Institute* that has led to substantial controversy and confusion. The ruling highlighted a range of potential ethical concerns, such as issues involving adequacy of informed consent, parents' perception of risk, duties of researchers to child subjects and their parents, the role of IRBs, and the authority of parents to provide permission for their children to participate in research. This report offers much needed recommendations and practical guidance for the ethical conduct of this type of research. |
| 2006 | EPA adds Additional Human Subjects Protections at 40 CFR 26 | EPA added additional human subjects protections in the Code of Federal Regulations to govern its actions. Subparts B through D apply to research conducted or supported by EPA and are directly applicable to NERL and this document. Subpart B prohibits research involving intentional exposure of children, pregnant women (and their fetuses), or nursing women. Subparts C and D provide additional protections for observational research involving pregnant women and their fetuses (Subpart C) and for children (Subpart D). Subparts K through M and O through Q apply to EPA's use of third-party human research data. |
| 2008 | *International Ethical Guidelines for Epidemiological Studies* (CIOMS, 2008) | This document builds on the CIOMS (2002) document (see above) and extends the discussion to address the special features of epidemiological studies. |

Section 3. Ensuring protection of vulnerable groups: Protections afforded by EPA's human subjects rules and the ethical concerns of involving such groups in observational research. Special requirements for the protection of potentially vulnerable groups, including children, prisoners, pregnant women, handicapped persons, mentally disabled persons, and economically or educationally disadvantaged persons, throughout the planning and implementation process are described.

Section 4. Addressing privacy and other concerns related to observational human exposure studies: Ethical issues and regulatory requirements concerning privacy, including third-party involvement and observations of nonstudy hazards. Unlike clinical research that is conducted in an institutional setting, observational human exposure studies take place in the participants' "personal" environments as they go about their everyday lives, presenting an even greater challenge in meeting the ethical obligation to respect the privacy of the participants.

Section 5. Creating an appropriate relationship between participant and investigator: Issues surrounding recruitment, informed consent, payment, and the researcher's need to support the welfare of the participants. An appropriate relationship built on openness and trust requires strong and effective bidirectional communication. Informed consent ensures that the participant understands the range of risks associated with participation and the voluntary nature of participation, and provides essential protections to the participant. Recent observations by various national and international review committees on the appropriate level of payment to research participants are presented. This is a complex ethical issue, balancing the issue of fairness against the possibility of undue influence and the loss of free consent. Other topics include participant recruitment, retention strategies, research rights, and grievance procedures.

Section 6. Building and maintaining appropriate community and stakeholder relationships: Involving the community in the research effort to improve the research both scientifically and ethically. Various approaches are discussed related to issues such as defining the community, identifying who represents the community, recognizing and addressing cultural differences, and the importance of language, power relationships, and partnerships.

Section 7. Designing and implementing strategies for effective communication: Ongoing, interactive dialogue among researchers, participants, the community, stakeholders, and the public to establish effective communications and to foster a relationship of trust. To facilitate information dissemination to participants, communities, and stakeholders, this section of the document describes communication strategies, implementation plans, communication groups, timetables, communication materials, and other tools available to researchers.

This document does not and, indeed, could not provide solutions to all scientific and ethical issues that may arise as observational human exposure studies are undertaken. No document could identify and address all potential issues in advance, nor is it possible to develop a comprehensive checklist for all such studies. Rather, this document attempts to present and discuss the types of ethical and scientific issues that will need to be considered and addressed as NERL researchers plan and implement observational human exposure studies. The researchers will need to work with others — the study team, IRB members, EPA's HSRRO, the participants and their community, and other stakeholders — to identify and address all of the relevant issues for any particular study. The authors are confident that this document will be helpful to NERL scientists in their endeavors to assure that all of NERL's observational human exposure studies will respect, safeguard, and protect the participants in that research.

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## SECTION 1

# Introduction, Purpose, and Scope

Observational human exposure studies are an important research tool for understanding people's contact with pollutants and other stressors in the environment, that is, their exposure.[2] Such studies allow researchers to collect information about people's exposures to chemicals and other stressors under real-world conditions during their normal day-to-day activities. Exposures occur through the air we breathe, the food we eat, the water and beverages we drink, and the surfaces that we touch as we go about our daily routines. To understand and characterize people's exposures to chemicals, two things have to be known: (1) the concentrations of the chemicals in the environment that people inhale, ingest, or touch; and (2) the human activities that bring people into contact with the media containing the chemicals.[3] This document addresses issues associated with observational human exposure studies that are conducted by the National Exposure Research Laboratory (NERL) of the U.S. Environmental Protection Agency (EPA) in an effort to understand and characterize the exposures that people encounter as they go about their daily lives.

Because observational human exposure studies involve human participants, they are complex in their design and implementation. As in all research involving human participants, observational human exposure studies carry both regulatory obligations for the protection of human subjects (40 CFR 26) and ethical obligations to the study participants: namely, to respect their autonomy, to not inflict harm (nonmaleficence), to avoid harm and to maximize their benefits (beneficence), and to treat all participants fairly (justice) (See, for example, *Principles of Biomedical Ethics*, Beauchamp and Childress, 2001). Ethical obligations have to be carefully considered as they relate to the scientific elements of these studies. Therefore, it is important that researchers recognize and understand these obligations and use the most up-to-date scientific and ethical approaches in the design and implementation of observational human exposure studies.

## 1.1 Observational Human Exposure Studies

As we are using the term in this document, "observational human exposure studies" are studies that involve the collection of environmental samples, data, and information from study participants in their everyday environments as they go about their normal activities. These are studies where the NERL researchers do not intentionally try to control the study variables or outcomes, but instead merely observe both the variables and the outcomes. They involve neither the deliberate exposure of participants nor the control of environmental conditions in a way that impacts the participants' naturally occurring exposures. This scientifically based definition needs to be distinguished at the outset from the broader regulatory term "observational" so that the scope and limits of this document are clear. EPA Regulation 40 CFR 26 (Protection of Human Subjects) at Subpart B, first, defines research involving *intentional exposure* of a human subject as "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" [40 CFR 26.202(a)]. It then goes on at Subpart C to define *observational* research as "any human research that does not meet the definition of *research involving intentional exposure of a human subject*" (40 CFR

[2] *Exposure*, as it is used throughout this document, is a technical term that is defined as the "contact of a chemical, physical, or biological agent with the outer boundary of an organism [e.g., a person]. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact." (The definition is taken from *Guidelines for Exposure Assessment* [EPA/600/Z-92/001, May 1992]). See the Glossary for more information and the definition of additional terms.

[3] The term "chemical" is used in this document as a surrogate term for all stressors, including chemical, physical, or biological agents.

26.302). By defining "observational" so broadly, a regulatory category is created that encompasses a range of study types whose only common feature is that they do not entail "intentional exposure" as defined in the regulations. Moreover, some of these "observational" study types do not involve the study of exposures at all but rather "observe" other sorts of phenomena. The observational human exposure studies with which we are concerned here, on the other hand, are exposure studies, but they represent a narrower group of studies as defined *scientifically* at the beginning of this paragraph. Although they would generally be expected to fall within the regulatory category of "observational research", they are not synonymous with it. (For a more thorough discussion of the scientific and regulatory meanings of *observational* and *exposure*, with examples, please see Appendix A.)

Observational human exposure studies are performed for many different purposes. They have been used extensively in the fields of social behavioral, economic, biological, medical, epidemiological, and exposure research to collect information that relates one or more variables (e.g., exposure to a chemical) to its result (e.g., the concentration of an exposure biomarker in blood). There are many examples of observational human exposure studies that have been conducted over the past decade, and the reader is referred to the *Journal of Exposure Science and Environmental Epidemiology* and to *Environmental Health Perspectives* for examples of the objectives, designs, and results of these studies.

NERL researchers have conducted and relied on observational human exposure studies for more than three decades. Examples of studies conducted or funded by NERL are listed in Appendix A, Table A-1. Common goals in those studies included those that follow.

- Identify which chemicals or other stressors that people are exposed to during their normal activities in the environments that they occupy.
- Measure the concentrations of the chemicals to which people are exposed.
- Identify the most important routes and pathways of exposure.
- Identify the factors that impact people's exposures (i.e., determine the when, why, how, and how much that people are exposed to chemicals in the environment).

These studies involve many different types of data collection efforts and typically include observations, measurements, and information on the following items.

- Chemical concentrations in environmental media (air, water, soil, floor dust, and dust on surfaces)
- Chemical concentrations in the diet (food and beverages).
- Biomonitoring (measurements of biomarkers of exposure in urine, blood, and saliva)
- Time, location, and activity information
- Information on personal activities, product use, diet, occupation, and other factors that may impact exposure
- Information on the characteristics of the environments that study participants occupy (homes, schools, offices, public access buildings, etc.)

The information obtained in observational human exposure studies is used to better understand people's contact with chemicals in the environment and to improve exposure assessments and risk assessments. This information is also essential for developing risk mitigation strategies and for developing educational materials and programs for reducing exposures and risks to chemicals or other stressors in the environment (see Table 1-1).

## 1.2 Ethical Issues in Observational Human Exposure Studies

By definition, observational human exposure studies involve human subjects. Whenever their research involves human subjects, EPA researchers are required to ensure the protection of the study participants by complying with the Agency's human subjects rules as set forth in 40 CFR 26.

The Common Rule (Subpart A of the rules) represents basic regulatory actions (common to more than a dozen Federal departments or agencies) that are intended to ensure the protection of all human subjects. The central requirements of the Common Rule are twofold:

(1) that people who participate as subjects in covered research are selected equitably and give their fully informed, fully voluntary written consent; and

(2) that proposed research be reviewed by an independent oversight group referred to as an institutional review board (IRB) and approved only if risks to subjects have been minimized, and risks are reasonable in relation to anticipated benefits, if any, to the subjects and to the importance of the knowledge that may realistically be expected to result.

| Table 1-1. Examples of the Impact of Observational Human Exposure Studies on Pollution Levels and Regulatory Actions | | |
|---|---|---|
| **Pollutant** | **Observational Study Result** | **Impact/Action/Result** |
| Particulate Matter (PM) | Observational panel studies demonstrated the appropriateness of ambient measurement of fine particles as a surrogate for a population's longitudinal exposure to fine PM. | Resolved questions in NAS review of PM science and provided a "generally consistent finding that ambient particle concentrations are a key determinant of the longitudinal variation in personal exposure." (NRC, 2004). These results have been instrumental in support of the National Ambient Air Quality Standard for PM (U.S. EPA, 1999). |
| Volatile Organic Compounds (VOCs) | EPA's Total Exposure Assessment Methodology (TEAM) studies found levels of about a dozen common organic pollutants to be 2- to 5-times higher inside homes than outside. Use of products containing organic chemicals may result in very high and persistent pollutant levels. | EPA, States, and the Consumer Product Safety Commission worked together to influence manufacturers to voluntarily reduce emissions of toxic chemicals from consumer products, building materials, and furnishings, and to develop mitigation strategies and educational materials to teach people how to reduce their contact with chemicals indoors. As a result, contact with toxic chemicals indoors has been reduced (see www.cpsc.gov/CPSCPUB/PUBS/450.html). |
| Formaldehyde | Studies found elevated formaldehyde levels indoors and helped identify indoor sources. | EPA worked with HUD, CPSC, and other agencies to limit formaldehyde in building or consumer products and to educate the public on how to reduce exposures (see www.epa.gov/iaq/formalde.html). |

EPA has adopted additional protections for children and pregnant or nursing mothers in Subparts B through D. These sections apply to all research either conducted or funded by EPA and are, therefore, directly applicable to NERL's observational human exposure studies.[4] Subpart B prohibits EPA from conducting or supporting research that involves intentional exposure of "a pregnant woman (and, thereby, her fetus), a nursing woman, or a child." NERL researchers conducting (or funding) observational human exposure studies must comply with all of these regulatory requirements, including seeking review and approval by an IRB and by the Agency's Human Subjects Research Review Official (HSRRO) before beginning any human subjects research. EPA's human subjects rules also define a variety of fundamental terms—from "human subject" to "research" to "intentional exposure" to "observational research." Understanding these regulatory definitions is vital for NERL researchers to comply with the regulatory requirements.[5]

To more effectively ensure the protection of human subjects, NERL scientists and managers need to understand the ethical principles and issues that prompted the development of the regulatory requirements in the first place and to be knowledgeable about the most recent thinking and guidance on protection of human subjects.

The Belmont Report (U.S. DHEW, 1979) is a foundational document in the development of the ethics of human subjects research in the United States. Because of the adverse publicity and political embarrassment arising from the unethical treatment of African-American men in the Tuskegee Syphilis Study, Congress passed the National Research Act of 1974, which called on the Department of Health, Education, and Welfare (DHEW) to codify its rules on human subjects research and established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission was charged with identifying the basic ethical principles that should underlie human subjects research. The commission published the Belmont Report in 1979. This report established three basic principles: (1) respect for persons; (2) beneficence; and (3) justice, which have become the cornerstones for regulations involving human subjects (see Table 1-2).

In 1981, the Department of Health and Human Services (HHS) issued regulations based on the Belmont Report. Ten years later, the core HHS regulations (Subpart A) were adopted by almost all of the Federal departments and agencies that conducted or sponsored human subjects research as the "Common Rule."

Since 1991, ethical thought and regulatory processes for the protection of human subjects have continued to evolve and grow. For example, many ethicists expand the elements contained in the principle of beneficence from the Belmont Report into two principles: (1) beneficence, meaning to prevent or remove harm and

[4] Subparts K, L, M, O, P, and Q of 40 CFR 26 set basic ethical requirements that have to be met if human subjects data from a person or group external to EPA and not funded by EPA (a third party) are to be used by EPA in specified rulemaking actions. These subparts do not apply to NERL researchers and will not be discussed further in this document.

[5] The Glossary (Appendix F) lists definitions for a number of important terms; definitions that come from the regulatory language are identified with their specific CFR citation.

to maximize the possible benefits; and (2) nonmaleficence, meaning not to inflict harm (Beauchamp and Childress, 2001).

**Table 1-2. *The Belmont Report*— Principles and Recommendations**

| Ethical Principle | Regulatory Manifestation |
|---|---|
| **Respect for Persons**<br>• Individuals should be treated as autonomous agents.<br>• Persons with diminished autonomy are entitled to protection. | **Informed Consent**<br>• Subjects must be given the opportunity to choose what will or will not happen to them<br>• The consent process must include (1) information, (2) comprehension, and (3) voluntariness |
| **Beneficence**<br>• Human subjects should not be harmed.<br>• Research should maximize possible benefits and minimize possible harms. | **Assessment of Risks and Benefits**<br>• The nature and scope of risks and benefits must be assessed in a systematic manner. |
| **Justice**<br>• The benefits and risks of research must be distributed fairly. | **Selection of Subjects**<br>• There must be fair procedures and outcomes in the selection of research subjects. |

In 2000, Emanuel, Wendler, and Grady considered the ethical principles involved in clinical research and proposed seven ethical requirements to be addressed in research with humans (Emanuel et al., 2000). Their published article specifically addressed clinical research, but the issues are similar for observational human exposure studies. Their ethical requirements are summarized and briefly explained in Table 1-3. The requirements are a logical extension of the ethical principles enunciated in the Belmont Report and manifest themselves in additional requirements for social or scientific value; for processes to ensure the scientific integrity of the research; and for independent review of the design, the subject population, and the risk-benefit ratio. The principle of respect for subjects also includes additional emphasis on the welfare of the subjects.

More recently, there has been increased scrutiny and discussions of the ethics of research involving human participants,[6] and a number of respected institutions have addressed many important scientific and ethical issues on this topic, including the National Research Council (NRC) in its report, *Protecting Participants and Facilitating Social and Behavioral Sciences Research* (NRC, 2003), a joint NRC and Institute of Medicine (NRC & IOM, 2005) committee in the report on *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children*; the Council for International Organizations of Medical Sciences (CIOMS) under the World Health Organization in its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002) and in the *International Ethical Guidelines for Epidemiological Studies* (CIOMS, 2008); and the National Ethics Advisory Committee of New Zealand in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities* (NEAC, 2006).

**Table 1-3. Seven Ethical Requirements for Clinical Research**
From Emanuel, Wendler, and Grady (2000)

| Requirement | Explanation |
|---|---|
| Social or scientific value | Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge |
| Scientific validity | Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data |
| Fair subject selection | Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research, and the rich and socially powerful are not favored for potentially beneficial research |
| Favorable risk-benefit ratio | Minimization of risks; enhancement of potential benefits and risks to the subject are proportionate to the benefits to the subject and to society |
| Independent review | Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research |
| Informed consent | Provision of information to subjects about the purpose of the research and its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate |
| Respect for potential and enrolled subjects | Respect for subjects by<br>• permitting withdrawal from the research,<br>• protecting privacy through confidentiality,<br>• informing subjects of newly discovered risks or benefits,<br>• informing subjects of results of the research, and<br>• maintaining welfare of subjects. |

[6] The term "human participants" often is used in this document. It denotes the importance of the study participant being actively engaged in a partnership with the researchers to address the objectives and goals of the study. The term should be considered to be synonymous with the term "human subject" as used in the Common Rule and in documents used to describe regulatory requirements for studies involving human subjects.

Collectively, these documents have reaffirmed the basic ethical principles asserted in the Belmont Report and have attempted, in some cases, to expand scientific and ethical reasoning and understanding to define approaches for dealing with additional elements of human subjects research. These additional elements, which often have been identified because of specific incidents or case studies, include issues such as those described below.

- Payment to participants—How much is adequate and fair, without being an undue inducement?
- Non-study hazards—What is the researcher's responsibility to identify hazards in the home that are not part of the study?
- Third-party issues—Are there people other than the participant who may be impacted during the study and by the study results? If so, what needs to be done to protect their interests and to respect them as persons?
- Community involvement—How should the community be involved in the design and implementation of studies?

These documents, together with EPA's regulatory requirements for the protection of human subjects, serve as important references for the subsequent sections of this document (see Table 1-4).

## 1.3 Purpose of This Document

This document is meant to serve as a resource of current scientific and ethical information for NERL researchers as they develop and conduct observational human exposure studies. The increased scrutiny of research studies involving human participants makes it imperative that researchers ensure that their research protocols for protection of human subjects in observational human exposure studies incorporate the most up-to-date ethical approaches. Protocols for protecting study participants in research studies have been developed by experts in both academia and various Federal agencies and adopted by the research community because they ensure that observational research meets the highest ethical and scientific standards. However, because ethical and scientific approaches for human subjects research continue to be refined and evolve over time, there is a continuing need to evaluate the latest approaches and ensure that researchers are using state-of-the-science approaches in their design and implementation of such studies.

The purpose of this document is to provide information that researchers in EPA's Office of Research and Development's NERL can use in the design and implementation of observational human exposure studies to ensure the protection of the human study participants. It is intended to be a resource tool for NERL's exposure science researchers, but it is not intended to serve as a "guidelines" document or a "how-to" checklist. This document does not meet the Office of Management and Budget (OMB) definition for an official Agency "guidance document" ("Guidance document - an agency statement of general applicability and future effect, other than a regulatory action … that sets forth a policy on a statutory, regulatory or technical issue or an interpretation of a statutory or regulatory issue" [U.S. OMB, 2007]). The authors, as researchers, perceived the need to provide this document for themselves, their co-workers, and their collaborators, but do not presume to speak for the whole of the Agency. The authors have tried to (1) identify major areas and elements of observational human exposure studies for which ethical issues need to be considered, (2) provide information on the state of the science for selected approaches for applying ethical principles to the conduct of these studies, and (3) provide sources of information that researchers can use in the design and implementation of these studies.

The emphasis of this document is to identify and discuss ethical issues and approaches in observational human exposure studies. As the document title implies and as discussed in Section 2, scientific and ethical issues are intrinsically bound together in research involving human subjects. Therefore, it is essential that scientific and ethical issues be considered together, not separately. In this document, scientific issues and approaches are discussed as they relate to and impact ethical issues. However, it is beyond the scope of this document to present a comprehensive discussion of the scientific approaches for observational human exposure studies. To include a comprehensive discussion of scientific approaches in this document would reduce the utility of the document by increasing the complexity of the presentation and the length of the document.

This document does not provide solutions to all scientific and ethical issues that may arise as such studies are undertaken. That is, it is not possible to identify or address all potential issues in advance or develop a comprehensive checklist for all such studies. Rather, this document attempts to present and discuss the types of issues that will need to be considered and addressed as NERL researchers plan and implement observational human exposure studies. The researchers will need to work with others—the study team, IRB members, EPA HSRRO, the participants and their community, and other stakeholders—to identify and

**Table 1-4. Important References in Developing This Document: Some Recent Developments in Defining the Ethics of Conducting Research Involving Human Participants**

| Year | Event/Report | Description |
|---|---|---|
| 1979 | *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (U.S. DHEW, 1979) | The Belmont Report attempts to summarize the basic ethical principles identified by the legislatively created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. The three basic ethical principles are (1) respect for persons, (2) beneficence, and (3) justice. |
| 1991 | The Common Rule 40 CFR 26, Subpart A | The Common Rule is a short name for "The Federal Policy for the Protection of Human Subjects" and was adopted by more than a dozen Federal departments or agencies in 1991. Each agency incorporated the policy into its own Code of Federal Regulations (CFR), with EPA adapting it in Title 40 CFR Part 26, Subpart A. |
| 1993 | *The Institutional Review Board Guidebook* (U.S. HHS, 1993) | The document is intended as a resource and a reference document for IRB members, researchers, and institutional administrators. It is not designed to tell IRBs whether or not specific protocols should be approved; rather, the Guidebook points out issues to which IRBs should pay attention and presents, wherever possible, areas where ethicists have arrived at a consensus on the ethical acceptability of a particular activity or method. |
| 2000 | What Makes Clinical Research Ethical? (Emanuel et al., 2000) | This journal article lays out seven areas of concern that need to be addressed if clinical research is deemed to be ethically acceptable: (1) social or scientific value, (2) scientific validity, (3) fair subject selection, (4) favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for potential and enrolled subjects. |
| 2001 | *Principles of Biomedical Ethics:(Fifth Edition (Beauchamp and Childress, 2001)* | A classic text in biomedical ethics. Core chapters discuss respect for autonomy, nonmaleficence, beneficence, and justice. The chapter on professional-patient relationships discusses issues important to privacy, confidentiality, and protection of subjects. The fifth edition is an update that reflects developments in philosophical analysis, as well as developments in science and medicine. |
| 2002 | *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002) | Developed by the Council for International Organizations of Medical Sciences particularly for use in developing countries, the guidelines relate mainly to ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities, and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health care services. |
| 2003 | *Protecting Participants and Facilitating Social and Behavioral Sciences Research* (NRC, 2003) | This NRC publication targets policymakers, research administrators, research sponsors, IRB members, and investigators. It examines three key ethical issues: (1) obtaining informed, voluntary consent from prospective participants; (2) guaranteeing the confidentiality of information collected from participants, which is a particularly challenging problem in social sciences research; and (3) using appropriate review procedures for minimal-risk research. |
| 2005 | *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children,* (NRC & IOM, 2005) | This National Research Council and Institute of Medicine report reviews the challenges and ethical issues in conducting housing-related health hazards research in the wake of the Maryland Court of Appeals ruling in the case of *Grimes* v. *Kennedy Krieger Institute* that has led to substantial controversy and confusion. The ruling highlighted a range of potential ethical concerns, such as issues involving adequacy of informed consent, parents' perception of risk, duties of researchers to child subjects and their parents, the role of IRBs, and the authority of parents to provide permission for their children to participate in research. This report offers much needed recommendations and practical guidance for the ethical conduct of this type of research. |
| 2006 | EPA adds Additional Human Subjects Protections at 40 CFR 26 | EPA added additional human subjects protections in the Code of Federal Regulations to govern its actions. Subparts B through D apply to research conducted or supported by EPA and are directly applicable to NERL and this document. Subpart B prohibits research involving intentional exposure of children, pregnant women (and their fetuses), or nursing women. Subparts C and D provide additional protections for observational research involving pregnant women and their fetuses (Subpart C) and for children (Subpart D). Subparts K through M and O through Q apply to EPA's use of third-party human research data. |
| 2008 | *International Ethical Guidelines for Epidemiological Studies* (CIOMS, 2008) | This document builds on the CIOMS (2002) document (see above) and extends the discussion to address the special features of epidemiological studies. |

address all of the relevant issues for their particular study to ensure that the specific elements of the study will safeguard and protect the human research subjects.

In addition to being an information resource for NERL researchers, this document provides useful information for contractors and grantees funded by NERL to consider during the design and implementation of their exposure science research. Although not its intended audience, this document also may prove to be useful to other researchers, within and outside of EPA, who are involved in observational human exposure studies.

## 1.4 Process for Developing the Document

This document was written by exposure science researchers in EPA's NERL, with substantial input from experts within and outside of the Agency. Information relevant to the process and the document has been routinely posted on the EPA Web site at http://www.epa.gov/nerl/sots.

NERL staff began this work by hosting a series of stakeholder meetings in the summer of 2006 to seek input on the content and format of the document. In November 2006, NERL convened an expert panel to provide its advice and guidance about the scope and content of this document. The Expert Panel consisted of 11 nationally recognized authorities in diverse fields: exposure science, environmental health, bioethics, epidemiology law, community-based research, research in minority communities, public health, toxicology, pediatrics, children's environmental health, etc. Details about the Expert Panel and the workshop can be found in Appendix B. The summary report from the Expert Panel may be accessed online at http://www.epa.gov/nerl/sots/workshop-report.pdf.

The structure and content of the current report follow the recommendations of the Expert Panel. Specifically, the Expert Panel recommended that this document should include the following six major topic areas:

(1) elements to be considered in study conceptualization,
(2) ensuring protection of vulnerable groups,
(3) addressing privacy and other concerns related to observational human exposure studies,
(4) creating an appropriate relationship between the participant and investigator,
(5) building and maintaining appropriate community and stakeholder relationships, and
(6) designing and implementing strategies for effective communication.

These recommendations include pragmatic steps that NERL scientists can undertake during the development and implementation of observational human exposure studies. Note that each step may require consideration and application of multiple ethical and scientific principles, and the same ethical principle may be fundamental to several of the topic areas. As a result, the same ethical principle may be discussed in several sections throughout this document.

Using the advice of the Expert Panel, an internal review draft of the document was written. Based on the comments from internal EPA reviewers, the internal review draft was revised, and an external review draft was prepared. The external review draft was submitted for peer review by EPA's Human Subjects Review Board (HSRB), a Federal advisory committee consisting of a panel of experts chartered to review and advise the Agency on the scientific and ethical underpinnings of human subjects research efforts. The external review draft also was announced in the *Federal Register* and made available for public review and comment. The document subsequently was revised in response to comments from the HSRB and from the public in preparation for publication and release as an EPA report. EPA's response to comments was posted to the draft report's docket (EPA-HQ-ORD-2007-0972) at www.regulations.gov.

## 1.5 Organization of the Document

The document is organized along the lines that the Expert Panel recommended. It has seven sections, an introduction followed by a section addressing each of the major topic areas. The content of each section also is based on recommendations from the Expert Panel Workshop. Because the authors concluded that the discussion for each topic area needed to be complete in and of itself (i.e., capable of standing independently without having to reference other sections), there may be some issues or topics that are discussed in several sections. Appendixes include additional descriptions of NERL observational human exposure studies, details about the process for developing this document, a list of acronyms and abbreviations, a glossary, and other supplemental information. The main body of the document includes the following sections.

- Introduction, Purpose, and Scope (Section 1) lays out the background for observational human exposure studies, the scope of the document, and some of the important scientific and ethical issues that are critical to human subjects and observational research.

- Study Conceptualization and Planning (Section 2) establishes that ethical concerns are to be incorporated in the scientific effort from the very beginning and includes ethical issues such as justifying the study because of its social and scientific merit and ensuring scientific validity and independent review.
- Protection of Vulnerable Groups (Section 3) discusses some of the special protections afforded to vulnerable groups by EPA's human subjects rules and the ethical issues of involving such groups in observational research.
- Ensuring Privacy and Confidentiality (Section 4) lays out the ethical issues and the regulatory requirements, including observations of nonstudy hazards and the recently discussed issues of third-party involvement or concerns.
- The Relationship Between the Participant and the Researcher (Section 5) builds on the ethical principles of respect for persons and beneficence to discuss the issues around recruitment, informed consent, payment, and the researcher's need to support the welfare of the participants.
- Community and Stakeholder Relationships (Section 6) begins with the principles of fairness, justice, and equity and of respect for persons to develop approaches to demonstrate respect for culture and to empower the participants' community to endure, including the need to build trust in the community and with stakeholders through open and honest communications and legitimate power sharing.
- Strategies for Effective Communication (Section 7) builds on the presumption of an ongoing, interactive dialogue and exchange of ideas between researchers and the participants, community, and stakeholders and focuses on steps that the researcher needs to take for effective communications. The section discusses communication strategies, implementation plans, communication tools, reporting of results, and approaches for effective communications, two-way communications between the researchers, participants, community, and other stakeholders.

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## SECTION 2

# Elements to Be Considered in Study Conceptualization and Planning

Consideration of the scientific and ethical approaches for observational human exposure studies begins at the very beginning of the study and continues throughout it. Because such studies involve human participants, researchers will have to consider the ethical issues associated with the regulatory requirements for human subjects review and approval. Beyond that, however, ethical principles and issues should be an integral part of all elements of the study and should be included as soon as a study is proposed.

In laying out seven requirements for determining whether a research trial is ethical, Emanuel, Wendler, and Grady (Emanuel et al., 2000) listed the requirements in rough chronological order, from conception of the research to formulation of the plan and protocol to implementation of the research study. This section follows their outline as this document highlights areas that NERL exposure science researchers should consider as they develop plans for an observational human exposure study. Table 2-1 shows the ethical requirements and the topics in this section relevant to each requirement.

The first stage in the research process is to understand the state of exposure science and EPA's programmatic needs for exposure data. NERL scientists and managers must decide whether an observational human exposure study is necessary and justified to meet the Agency's need. If so, then NERL staff will begin to plan for a study. A variety of important issues will need to be considered (identifying and enlisting stakeholders and community representatives, forming a research team, maximizing benefits for participants, precluding conflicts of interest, etc.).

The planning phase will culminate in the development of a science-based study design in an ethically sound human subjects research protocol. Adhering to the principal that "Bad science is always unethical" (U.S. EPA, 2000), the research must first be judged to be scientifically sound to meet ethical standards. Peer review by independent and knowledgeable experts will be used by NERL to assess the scientific validity of its proposed research. But passing scientific peer review is just the first hurdle: sound science is not necessarily ethical. NERL's observational human exposure studies also must meet both the ethical requirements set forth in human subjects regulations and the ethical standards demanded of responsible researchers by their peers and society. Peer review will focus on the study design and the science but also necessarily will incorporate relevant ethical considerations. IRB review will focus on ethics and the protection of the human research participants but also necessarily will incorporate evaluation of the adequacy of the study design and other relevant aspects of the science. The principle that unsound science is unethical science demands that exposure of human subjects to any research risk whatsoever, even minimal risk, cannot be justified if the research will not answer the scientific questions that motivated the research in the first place.

After independent reviews evaluate both the scientific and ethical aspects of the proposed research, EPA policy requires that the proposed study undergo internal EPA review, and that the human subjects research protocol undergo evaluation by the Agency's Human Subjects Research Review Official (HSRRO). The HSRRO, located in the EPA Office of the Science Advisor, ensures that Agency studies comply with the Common Rule and all directives of 40 CFR 26 providing guidance and principles to govern Federal agency sponsored human subject research.. Only after HSRRO approval can any research actually begin. As the NERL study is implemented, project data and concerns of the participants will be monitored on a continuing basis and compared with previously established standards and

**Table 2.1. Seven Requirements for Determining Whether a Research Trial is Ethical**
From Emanuel, Wendler, and Grady (2000)

| Requirement | Explanation | Topics in this Section |
|---|---|---|
| Social or scientific value | Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge | Defining the study problem<br>Justifying the study<br>Identifying a research team |
| Scientific validity | Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data | Study design<br>Feasibility<br>Sample size determination<br>Representativeness of the sample<br>Information collection rule<br>Quality assurance<br>Study design document |
| Fair subject selection | Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research, and the rich and socially powerful are not favored for potentially beneficial research | Ethical issues in fair subject selection |
| Favorable risk-benefit ratio | Minimization of risks; enhancement of potential benefits and risks to the subject are proportionate to the benefits to the subject and to society | Designing in benefits for participants<br>Assessing benefits and risks of study participation |
| Independent review | Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research | Scientific peer review<br>Conflicts of interest<br>Developing the protocol for ethical review<br>Ethical review<br>EPA review of scientific and ethical issues |
| Informed consent | Provision of information to subjects about the purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate | Informed consent<br>Ensuring that participant behaviors are not adversely changed |
| Respect for potential and enrolled subjects | Respect for subjects by<br>• permitting withdrawal from the research,<br>• protecting privacy through confidentiality,<br>• informing subjects of newly discovered risks or benefits,<br>• informing subjects of results of the research, and<br>• maintaining welfare of subjects | Establishing criteria and standards for monitoring scientific and ethical issues during a study |

criteria to evaluate whether the study is on target for meeting its objectives, or if some unforeseen circumstances indicate that the study should be stopped immediately on either scientific or ethical grounds.

## 2.1 Scientific Value of a Proposed Observational Human Exposure Study

NERL's planning for an observational human exposure study begins with an assessment of the state of exposure science and of EPA's programmatic needs for exposure data. NERL scientists and managers must decide whether an observational human exposure study is necessary scientifically and whether it is justified to meet the Agency's need.

### *2.1.1 Defining the Study Problem*

Observational studies historically have been performed for many different purposes and in many different fields of research—social behavioral, economic, biological, medical, epidemiological, and exposure science. NERL has used observational human exposure studies to understand how people come into contact with pollutants in their everyday lives, with the ultimate goal of protecting public health. NERL's exposure research program addresses critical science needs directly related to Agency goals for protection of human health. The research program is driven by key exposure science questions that may be generated from a number of different sources, including legislative mandates (e.g., the Food Quality Protection Act, the

Clean Air Act, the Safe Drinking Water Act), program offices or research planning groups in the Agency, scientific peers and researchers, or collaborators. Communities also may identify concerns about exposures in their locales. NERL's observational human exposure studies collect data to improve exposure and risk assessments, to develop risk management strategies, and to substantiate informational and educational materials for use by EPA program offices (e.g., Office of Pollution Prevention and Toxic Substances, Office of Air and Radiation, Office of Children's Health Protection).

Emanuel et al. (2000) contend that an ethical research study must provide a worthwhile social or scientific value. Ideally, observational human exposure studies can provide both a scientific value *and* a social value to the participants and their community when feasible. Whenever possible, researchers should work with communities to develop studies that can help address community problems and maximize the benefit to the participants and the community, both of which also assume a burden for participation in a research study.

The study problems addressed in past observational human exposure studies conducted or supported by NERL have varied substantially, as described in Appendix A of this document. As shown in Table A-1, NERL's studies have addressed exposures to particulate matter (PM), air toxics, persistent organic chemicals, and nonpersistent chemicals including pesticides. The studies have examined single routes of exposure (air) and multimedia exposures, including dietary exposure. The studies range from small-scale pilot studies to large probability-based samples. They have included cross-sectional, longitudinal, and convenience samples. Table A-1 demonstrates that many of the studies are small in scale and were intended to test a methodology to see if it may prove useful for a subsequent large-scale probabilistic human exposure research effort. Both small-scale and large-scale human exposure studies do involve human subjects. This means that the studies must meet *both* ethical standards *and* regulatory requirements. Regardless of the study's scale, the scientific study design must be technically sound and appropriate to meet the objectives of the study. But the nature and objectives of the scientific inquiry will be different when the study is designed to test a methodology versus when the study is intended to measure a representative distribution of people's exposures. Defining the study problem is a critical and fundamental first step in the scientific process, because it will establish the objectives that the research will be designed to achieve and the uses to which the research data will be put. The details of the scientific design of the study will naturally be strongly influenced by the objectives that the research is intended to meet.

### *2.1.2 Justifying the Study*

Justification of any human study includes both a scientific and an ethical justification. In the list of seven ethical requirements that must be met for human subjects research to be considered ethically acceptable, four of those requirements, (1) respect for subjects, (2) informed consent, (3) favorable risk-benefit ratio, and (4) fair subject selection, are founded on the traditional ethical principles enunciated in the Belmont Report and codified in the Common Rule (Emanuel et al., 2000). But three requirements, (1) social or scientific value, (2) scientific validity, and (3) independent review, apply directly to the scientific aspects of the study. Similarly, Guideline 1 from the CIOMS (2002) document reiterates the foundational principle that "scientifically invalid research is unethical." Beyond the traditional ethical expectations of respect for, protection of, and fairness to the research subjects, CIOMS requires investigators and sponsors to ensure that the research be "scientifically sound," that it "conform to generally accepted, scientific principles," and that all researchers be "qualified" and "competent."[7] Text Box 2-1 identifies a number of elements that should be considered in justifying an observational human exposure study. As discussed below, a critical element to support justification of both the scientific and ethical elements of a study is the use of independent scientific and ethical peer review.

[7] Guideline 1 states "research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature." The commentary on the guideline goes on to say, "Among the essential features of ethically justified research involving human subjects**,** including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research protocol submitted for review and clearance to scientific and ethical review committees."

**Text Box 2-1. Elements to be Considered in Justifying a Study**

- The research problem and questions to be addressed in the study
- The objectives of the study or the hypotheses to be tested
- A discussion of why human participants are required for the study, including a discussion of alternative designs that were considered
- Available information on the need for the study (i.e., it is not redundant and the research question has not been already answered)
- Available information from the scientific literature demonstrating the relevance of the proposed study
- A discussion of the general technical approach and scientific soundness of the approach
- An assessment of the needed competencies and qualifications of all personnel involved in conducting the research
- The likelihood of success in meeting the study goals and objectives (including an evaluation of the accuracy, precision, and quality assurance of the data needed to attain the study goals and objectives)
- Justification for the investment of time and money

### *2.1.3 Identifying a Research Team To Plan and Implement the Study*

Once the study problem has been defined and justified, the next step in developing the research study is to form the research team. The team should be diverse, including the technical experts (e.g., exposure researchers, statisticians, chemists), stakeholders, and representatives and members of the community in which the study likely will be performed. Information on identifying potential conflicts of interest among researchers early in the planning stage is discussed in Section 2.5.2. For scientific, ethical, and practical reasons, the community should be appropriately involved throughout the study, including throughout the planning phase. Information on identifying and engaging community members in the process is described in Section 6 of this document. The joint NRC-IOM committee reviewing ethical issues for research conducted in the homes and communities of the participants (like much of NERL's human exposure research) concluded that "When researchers discuss a planned study with community representatives, understand their concerns and needs, and respond to them, protocols can be strengthened both scientifically and ethically" (p. xii, NRC & IOM, 2005).

## 2.2 Ensuring Scientific Validity of the Research Study

To facilitate scientific and ethical review, the research team members should develop a comprehensive and detailed study design that describes the technical approach for the observational study. Although the format and scope may vary depending on the specific study, there are a number of basic elements generally included in the study design.

Translating the information developed in defining the problem and justifying the study into a real, workable, feasible study design and human subjects protocol is an iterative process involving input from all of the members of the research team. Scientific and technical expertise is required to assure the scientific integrity of the research, including developing the conceptual model[8] for the effort and devising a reliable sampling and analysis plan. Stakeholder input is critical to assuring that the generalizable research information from the study actually will be applicable for addressing the study problem. Community input is particularly important during the planning stage because the community representatives can provide valuable information about the community members (the future study cohort), the cultures of the community, community values, community concerns, feasibility of working in the community, information needed to develop the technical approach, and information on important factors like pollutant sources and other stressors in the community. (Additional considerations for communicating and working with both the participants and the community in which they live are the topics of Sections 5 through 7 of this document.)

In developing the study design and the human subjects protocol, the research team often will have to deal with a variety of complex issues, including how to maximize benefits for participants, the community, and the stakeholders, and how to ensure the integrity, generalizability, and representativeness of the study.

### *2.2.1 Study Design*

In epidemiology, the concept of study design has been structured to include (1) experimental studies, like drug trials, where the variables are isolated and controlled (See discussion on experimental studies in Appendix A.) and (2) observational studies where the variables are not controlled intentionally, but are simply

[8] A conceptual framework or model is often an effective approach to describe the relationship between the predicted exposures of the population and the population stressors, laying out the predicted pathways and routes of exposure (e.g., see Cohen Hubal et al., 2000). A conceptual model often is illustrated by a block diagram that represents the major scientific processes and interactions. The model is often very useful in developing an analysis plan that describes the hypotheses or objectives of the study, identifies the data needed to address the objectives, and specifies the analyses that will be done to test the hypotheses or address the objectives.

observed along with the outcome or response measures. Clearly, the NERL human exposure observational studies (see Table A-1) fall into the latter category. Such studies may be cross-sectional studies (where a subset of the population is observed at the same time); cohort studies (which measure the same variables and response measures in a group of people repeatedly over time); case control studies (where the observed population is separated into two groups based on the outcome or response measure [the case group and the control group], and exposure variables between the two groups are analyzed for differences); or studies that combine approaches. The research may collect data from the participants once (e.g., in a large-scale, randomized design to collect a representative sample of the population, like many of the National Human Exposure Assessment Survey [NHEXAS] studies); over a few days (e.g., NERL's Particulate Matter [PM] panel studies); from a cohort in different seasons or years (e.g., NERL's Detroit Exposure Aerosol Research Study [DEARS]; the NHEXAS study in Maryland); or a series of cross-sectional studies repeated one after another with a different group of participants each time. (This latter case often is necessitated to minimize time and expenses associated with being in the field and because of limitations of sampling equipment or field technicians to assist in the collection of the data.)

Although much of the literature on study design involves experimental studies (like drug trials), there is much that can be learned about the design of observational studies in epidemiology, including understanding their strengths and weaknesses. Web sites, like "Epidemiology for the Uninitiated" (Coggin et al., 1997, available at www.bmj.com/epidem/epid.html), provide useful basic information on important topics for observational studies and their design.

The specific details of the study design and the sampling approach to be used will depend very much on the objectives to be achieved in the study. Based on the objectives, a good study design must first clearly state the research question (or hypothesis to be tested) and must also define in advance what outcome or response measure will be used to test the question or hypothesis. Study designs that are vague or which propose to test some outcome measures against a variety of potential factors do not represent sound science. Statistically, a correlation is likely to be found between an outcome and some factor if enough factors are tested—whether there is an actual biological or physical relationship or not. This highlights the importance of statistics as an integral part of the study design process. Including individuals with appropriate statistical knowledge and experience on the research team from its very beginning is critical to a scientifically sound study design. (See, for example, Dallal, 2001, "Some Aspects of Study Design" in *The Little Handbook of Statistical Practice* at www.StatisticalPractice.com, and at www.tufts.edu/~gdallal/LHSP.HTM).

The study design must carefully consider each item of data or information that is to be collected during the study and how the data will be used in the analysis. All of the data needed to complete the analysis and test the hypothesis must be collected, otherwise the research objectives cannot be met, and the study should not go forward. Alternatively, data that are unrelated to the study analysis should not be collected. Collection of such data imposes a burden on both the participants and research staff with no known potential for benefit. Collecting, validating, and archiving such data wastes time and money and inappropriately burdens the participants. If there is no solid analysis plan for a particular data item, such data should not be collected. If the researchers actually believe that some factor may represent a potentially overlooked variable, then they should collect the information to test that hypothesis correctly. But, just collecting the data "while we can," with no plan for how to analyze and use the data, wastes resources, imposes unnecessary burden, and often proves tempting as a statistical correlation hunt. Finally, the study design must be described in sufficient detail to be properly evaluated. Preparation of the study design document is described in a later section, but the overriding goal is to provide enough information to allow proper review of the science behind the study design by the research team, the scientific peer community, and the IRB panel members.

### *2.2.2 Feasibility*

The authors consider the evaluation of the feasibility of accomplishing the study to be one of the most critical components of the development of the study design. Evaluating the feasibility of the research project involves considering not only whether there are sufficient resources to accomplish the study, but whether or not the study is feasible from a scientific and ethical perspective. If the research team concludes that the study is not feasible, there will be no further effort to develop the study. There may be practical limitations that preclude conduct of the study as initially conceived. Because "scientifically invalid research is unethical" (Guideline 1, CIOMS, 2002), it is essential that scientific and ethical considerations be considered together. Text

Box 2-2 includes some examples of the types of questions that may be asked when evaluating the feasibility of a study.

**Text Box 2-2. Is the Study Feasible?**

- What are the sample size requirements? Can enough participants be enrolled into the study from the proposed community, considering the eligibility criteria and anticipated response rate? What is the predicted retention rate if this is a repeated measurements study? Is that acceptable?
- Is the research question well defined, and can we measure the variables and the outcome metrics?
- Are the measurement methods specific and accurate enough to accomplish the research?
- Does the analysis plan provide results to test the research questions and to meet the study objectives?
- Will the community be receptive to this study?
- Are there cultural mores, societal values, or other factors associated with the community that would make it difficult to conduct the study in the community? Is the study morally acceptable to the community?
- Is there a community structure that will allow the research team to engage the community in the study?
- What is the burden on the community?
- What is the burden on the participants? Is it acceptable?
- What is the risk-benefit balance? Is it acceptable, considering the burden on the participants?
- Are there sufficient resources available to conduct a study of this size?
- Are resources available for community outreach and sustained interactions with the community? Are resources available to support community members involved in the study?

### *2.2.3 Sample Size Determination*

One critical issue in assuring that an observational human exposure study is scientifically valid (and, thereby, not invalid and unethical) is the issue of sample size. EPA's Science Advisory Board has stated, "Bad science is always unethical; research protocols that are fundamentally flawed, such as those with sample sizes inadequate to support reasonable inferences about the matter in question, are unjustifiable" (p. 2, U.S. EPA, 2000).

A study has to have an adequate size to meet the study objectives. If the sample size is too small, the results may not be statistically significant, and the results may not be either valid or generalizable. Such a result would be a waste of resources or cause undue burden on study participants without generating the intended generalizable knowledge that will benefit society. On the other hand, if the study sample size is larger than necessary to meet a study objective, this also may result in a waste of resources or the imposition of needless burden on participants.

Sample size determination is an important step in planning a study, but it can be a difficult task (Lenth, 2001). Sample size determination also may be confounded by other issues that will reduce the number of measurements that may be used in the analysis. For example, participants in a longitudinal study may "drop out" over time (some may move, others may tire of participation, etc.), so that the number of participants at the end of the study will be less than the number that started the study. The study design must account for the attrition of participants over time and plan ahead to recruit enough participants to ensure that a statistically useful number of participants complete the study. Often NERL scientists have used historical retention rates to estimate the sample size needed for a study. (See discussion of retention rates in NHEXAS publications.)

In addition, some participants or their environments may not have concentrations above the detection limit. Depending on the nature of the research question, data below the analytical detection limit may, or may not, be useful in addressing the research question: sample size may need to be increased to account for missing values and values below detection. Pilot studies and environmental studies (with no participants as human subjects) may prove useful in understanding the range of concentrations to be expected and may provide insight into how to adjust the sample size appropriately. In surveys, like NERL's National Human Activity Pattern Survey (NHAPS) for example, some randomly selected participants simply may refuse to participate, decreasing the number of samples and perhaps biasing the data.

It is critical that sample size be determined at the time of study conceptualization and planning and not after the study already has been conducted. Researchers must include experts with the appropriate statistical expertise on the research team at its very inception. For additional information and insight, readers should refer to biostatistics books, Web sites, and other references (Lenth, 2001; Castelloe, 2000; Kraemer and Thiemann, 1987; Van Belle and Fisher, 2004; Wackerly et al., 2001; Dallal, 2001) about this very important topic.

### *2.2.4 Representativeness of the Sample*

In addition to concerns about the sample size being sufficient to provide statistically significant results, researchers also must be concerned about the individuals who participate in a study and of what group or population they may be representative. Research, as defined in the Common Rule, is "a systematic investigation … designed to develop or contribute to generalizable knowledge." How "generalizable" the

results of an observational study may be depends on the representativeness of the sample (the participants). A review of former NERL studies (Table A-1) shows a wide variety of approaches to selecting the participants, both probability sampling and nonprobability sampling. Some of the studies have involved randomized sampling (e.g., NHAPS, NHEXAS), selecting a cohort of interest and then using a randomized sample (e.g., Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants [CTEPP], DEARS) or a convenience sample (e.g., some panel studies), purposeful selection (judgment sampling) by the research team (for methods testing studies), recruiting the whole population in a locale or of a particular cohort (e.g., as proposed for the National Children's Study [NCS]), or simply a convenience sample (in small pilot studies).

The approach used to select the participants has depended on the objectives of the study. Research to understand and describe the distribution of exposures in the general population (like NHEXAS) or of the population or cohort in a particular state or region (like CTEPP or Agricultural Health Study [AHS]), has required a large number of randomly-selected participants. Randomized selection is recognized as a valid statistical method to get a sample that is representative of the larger population from which the participants were selected. Pilot studies performed to evaluate a method or to estimate the likely range of exposure concentrations often have employed either purposeful sampling, where the researchers use information on the relevant characteristics of the population to select those participants who will exhibit a wide range of activity levels or potential exposure concentrations, or convenience sampling, where the researchers select the most accessible members of a population

NERL's observational human exposure studies also have routinely collected information about the participants' activities by using questionnaires and surveys. Survey design is both a science and an art because the design of surveys is based on statistics and science, but designing a good and effective questionnaire is often an art that requires understanding the individuals being surveyed. Text Box 2-3 identifies some of the areas of art involved in designing an effective questionnaire.

Understanding the process for selecting participants and the statistical-scientific requirements of questionnaire design are both components of survey sampling and design. A variety of references can provide the researcher with information about the issues in survey sampling and design. (See http://home.ubalt.edu/ntsbarsh/Business-stat/stat-data/Surveys.htm and www.statpac.com/surveys/, for example.) But the research team must include or have access to the appropriate survey statistics expertise as it plans the research study.

**Text Box 2-3. Questionnaire Considerations**

- Questions should be simple and in a language the individual can understand.
- Questions should be unambiguous.
- Questions should be relevant to the study.
- Questions should not be too personal.
- The questionnaire should be as short as possible.
- The questions should not be leading (e.g., internally suggestive of the answer).
- Questions should follow a logical order.

### *2.2.5 Information Collection Rule*

As Federal employees, NERL researchers also must be aware of Information Collection Rule requirements. The Paperwork Reduction Act stipulates that every Federal agency must obtain approval from OMB before collecting the same or similar information from 10 or more members of the public. An Information Collection Request (ICR) is required if the same or similar information is being collected from 10 or more non-Federal respondents within a 12-month period, even if the information collection is voluntary. Generally, any survey, questionnaire, monitoring, reporting, or recordkeeping requirement imposed on non-Federal respondents by EPA will require an ICR. Information collections associated with all cooperative agreements funded by the EPA require an ICR. When an ICR is required, it must be approved by OMB before the collection begins, regardless of whether the collection of information is mandatory, voluntary, or required to receive a benefit. The principal investigator must prepare an ICR and submit it to the appropriate Office of Environmental Information Desk Officer.

An ICR

- describes the information to be collected,
- provides justification for why the information is needed, and
- estimates the time and cost for the public to answer the request.

Information about ICRs and their requirements is available to NERL and other EPA staff members at http://intranet.epa.gov/icrintra/index.html.

### *2.2.6 Quality Assurance Project Plan*

Data of unknown or uncertain quality can undermine the scientific integrity of a study and render an otherwise sound study invalid. NERL scientists must be diligent in the implementation of the procedures and processes specified in a well-developed quality assurance project plan (QAPP). A discussion of quality assurance programs and QAPPs is outside of the scope of this document. There are many good references on the topic, including the EPA Web site, www.epa.gov/quality/.

### *2.2.7 The Study Design Document*

The study design document should contain sufficient detail to allow 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. The research team can meet regularly to specifically evaluate the plan. It should be noted that a study design is not the same as an implementation plan. The latter includes an even greater level of detail describing how the study will be performed and includes protocols and operating procedures. Text Box 2-4 lists a number of elements that may be appropriate to include in a study design.

**Text Box 2-4. Elements That 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; and 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 project plan and quality control;
  - timeframe 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, quality assurance);
  - 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 roles and responsibilities
- Schedule

## 2.3 Ethical Issues in Ensuring Fair Subject Selection

One of the ethical principles of human subjects research is that selection of participants should be fair. In Section 2.2.4, the discussion centers on understanding what population or cohort the participants in a research study represents, and how such a selection may be influenced by the research questions and study objectives. That consideration actually represents the first component of ensuring that subject selection is fair. That is, the scientific goals of the study should be the primary basis for determining what groups or individuals should be recruited and enrolled in a study. Participants should not be recruited either because of privilege or because of vulnerability or their inability to look out for their own interests properly. Similarly, groups or individuals should not be excluded peremptorily without consideration of the risks and benefits to them as individuals. Section 3 of this document discusses protection of vulnerable groups and concludes that NERL researchers should include vulnerable groups in observational human exposure studies only if their participation is critical to the success and applicability of the research. Even then, EPA and NERL researchers will have to meet stringent standards for protecting the rights and safety of the vulnerable participants. "The essence of fairness in human subjects research is that scientific goals, considered in dynamic interaction with the potential for and distribution of risks and benefits, should guide the selection of subjects." (Emmanuel et al, 2000). On the other hand, as discussed in Section 3, many study problems specifically address exposures of vulnerable groups to chemicals and other stressors. Researchers should not avoid research studies that will,

of necessity, include vulnerable groups to address the study hypotheses or objectives simply to avoid the more stringent requirements for working with these groups.

## 2.4 Ensuring a Favorable Risk-Benefit Ratio

### *2.4.1 Designing in Benefits for the Participants*

Study designs vary depending on the objectives of the study, existing knowledge on the research question, and the hazard being studied (NRC & IOM, 2005). Recent ethical discussions about study designs in human subjects research (cf., Recommendation 7.1, p. 143, NRC & IOM [2005] and Emanuel et al. [2000]) support the development of innovative study designs to maximize the benefit[9] to the study participants, as well as to the community and the greater society beyond. Observational human exposure studies generally collect data that contribute to generalizable knowledge that will benefit the community and society as a whole, but they often do not provide obvious direct benefit to study participants. Therefore, it is important to include elements in the study design that can offer benefits to the participants wherever possible. This is not always straightforward, but one way that participants, as well as communities, can benefit from these studies is by incorporating strong educational components into the conduct of the research. For example, brochures, videos, and other materials that educate study participants on safety around the home or on how to reduce their exposure to chemicals can be distributed during the study. EPA's program offices, including the Office of Children's Health Protection, the Office of Pollution Prevention and Toxics, the Office of Pesticide Programs, the Office of Drinking Water, and others have Web sites with substantial amounts of informational and educational materials available that could be distributed to study participants. Other organizations, such as the American Lung Association, the American Cancer Society, the American Academy of Pediatrics (AAP), and various environmental groups, have materials of which study participants may not be aware that could be used as educational materials when relevant.

In addition, approaches that provide direct benefits to study participants will need to be tailored to the particular study population and community. Feedback from potential participants in focus groups and input from community representatives may be useful in identifying these approaches.

### *2.4.2 Assessing Benefits and Risks of Study Participation*

For all research involving human participants, the Common Rule requires researchers to ensure that potential risks "are reasonable in relation to the anticipated benefits," and that risks are minimized (40 CFR 26.111). It is most useful if the assessment of benefits and risks is begun early in the scoping and planning phase of a study.

Unlike some biomedical research that involves the study of interventions or procedures that hold out the prospect of direct diagnostic, therapeutic, or preventative benefit for the study participants, observational human exposure studies often do not have a similar prospect of direct benefit to the participant. Therefore, the risk-benefit balance is based on the balance between the risks to the participants and the expected benefits to society (generalizable knowledge). The risks to participants must be reasonable [40 CFR 26.111(a)(2)] in relation to the importance of the knowledge gained. This assessment of the risk-benefit balance, therefore, needs to be performed in the initial planning of the study to be included in the justification for the study (Section 2.2).

If there is no prospect of direct participant benefit, and the study participants are children, moreover, EPA is permitted to conduct or support *only* those observational human exposure studies that meet *both* the regulatory definition of "observational" *and* the regulatory definition of "minimal risk." The latter is defined in the Common Rule at 40 CFR 26.102(i) and reiterated in Subpart D of the EPA Rule at 40 CFR 26.402(g): "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." In applying this definition, EPA adheres to the consensus standard that the reference population for this definition is normal children living in safe, healthy environments. In its discussion of the perception of risks and benefits, the NRC & IOM (2005) report on housing health hazards in children notes that the children participating in these studies may be at risk for physical harms or adverse health outcomes because they live in housing (or otherwise occupy environments) with health hazards. However, such risks are not *introduced* by the research but, rather, would be present whether or not the children were involved in a research study. As a consequence, the study still would meet the regulatory criteria for minimal risk as long as the research *itself* introduced no risks over and above those minimal risks

[9] Payment to participants is never considered a benefit of a study.

experienced by normal children living in safe healthy environments.

However, the existence of greater than minimal background risks that are not introduced by the research, nonetheless, raises additional ethical considerations. The joint NRC & IOM Committee on Research on Housing-Related Health Hazards Involving Children discussed the ethical arguments that arise when scientists conduct research that observes children in poor-quality housing. They point out that a researcher's first duty of beneficence under the Common Rule requires that the risks of the research actions be proportionate to ["reasonable in relation to"; 40 CFR 26.111(a)(2)] the benefits of the research, and that the risks be minimized. They acknowledge, however, that some have argued that the "best interests of the child" also obligates researchers to "rescue" children from harm and to provide better living conditions. They conclude that, properly applied, the ethical principle of beneficence does indeed direct researchers who observe serious harms to child subjects to take steps to try to prevent the harms. However, they also argue that the researcher's duty does not extend to "personally and directly prevent harm by removing the child from the harmful environment" (p. 60, NRC & IOM, 2005). They conclude instead that "it is unrealistic and unfair to hold individual research investigators responsible for ameliorating the social circumstances that they study" and that "a nuanced balancing of the benefits and risks of research" is an ethically sound approach that is firmly established in Federal regulations (p. 60, NRC & IOM, 2005). Balancing the ethical obligation to mitigate risks or harms observed during research with the reasonable limits on an investigator's moral responsibility for the social circumstances surrounding the research will be the subject of later sections of this document, particularly Section 4.3.1.

Assessing the risks and benefits of the research study can be very difficult for the researchers, especially because the researchers and the community or participants may perceive the risks and benefits quite differently. (See the discussion in NRC & IOM [2005], for example.) To understand the community's perspective better, the researcher may find it helpful to discuss the assessment of risks and benefits with members of the research team, community representatives, and relevant stakeholders. The research team should consider the use of a community advisory board (CAB) to provide input to the assessment of the risks and benefits of the study. The group could include individuals who are representative of the population to be studied, community representatives, exposure scientists, and bioethicists. The group should include experts familiar with the human subjects research regulations, preferably including someone who has served on IRBs. Obtaining input from the group can be accomplished by submitting the study concept and general study design to the group for review and feedback, even before a full study design has been developed. (See the discussions of CABs in Sections 5 and 6.) Ultimately, it will be the review by the members of the IRB that will determine whether the balance is appropriate and justifiable.

## 2.5 Independent Scientific and Ethical Review

Because issues of science and ethics are intrinsically bound together in human subjects research (Emanuel et al., 2000; CIOMS, 2002), it is important that scientific and ethical reviews be considered together, not separately. Scientific reviews are performed to ensure the scientific soundness of the study, whereas ethical reviews are performed to ensure proper action and the protection of the human subjects in a research study. A study that is not scientifically sound could expose study participants to unnecessary risk or inconvenience and burden, with no additional societal benefits (i.e., no increase in generalizable knowledge). EPA's Science Advisory Board has stated that "bad science is always unethical" (U.S. EPA, 2000), and CIOMS declares that "scientifically invalid research is unethical" (CIOMS, 2002).[10] It is clear, therefore, that the ethical review has to consider the scientific aspects of the study also.

There may be multiple levels of review during development of the study design and human subjects research protocol for an observational human exposure study. The research team is responsible for the design of the study and for ensuring that adequate peer review is

[10] CIOMS (2002) Guideline 2 asserts "Ethical review committees—All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study." The CIOMS document continues, "According to the Declaration of Helsinki (Paragraph 11), medical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where indicated, animal experimentation. Scientific review must consider, *inter alia*, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary."

performed to evaluate both the scientific and ethical approaches for the study. Following completion of a draft study design, researchers should engage a diverse group of experts to review the study design and human subjects aspects. The scope of the study should dictate the level of the review (i.e., internal or external independent peer review). A small pilot study to evaluate measurement methods or to collect screening level data in preparation for a large study may not require as extensive review as a larger study.

When the scientific soundness of the study has been evaluated and found to be feasible, and the final study design is completed, the human subjects research protocol should be developed and submitted to the IRB for review and approval. For studies conducted or supported by EPA, additional review and certification of the human subjects research protocol is required by EPA Order 1000.17 A1. (available online at www.epa.gov/oamrtpnc/forms/1000_17a.pdf). Review and approval of the protocol and associated documents must be obtained from EPA's HSRRO, located in the EPA Office of the Science Advisor, before any work begins. Any changes made to the protocol after IRB approval must be submitted to and approved by the IRB.

### *2.5.1 Scientific Peer Review*

For all studies, regardless of the scope, the research team should solicit review and comment on the scientific approach by experts external to the research team. A peer review panel consisting of individuals who were not involved in the design of the study can be formed to review the scientific soundness of the study. It is important for the panel to consist of individuals with experience and background appropriate to the study and to include members with knowledge of the ethical principles for protection of human subjects in these types of studies. The panel also would benefit from including someone with sufficient background and expertise in statistics to evaluate whether the study design, sample size, and proposed data analyses are appropriate and adequate to address the study objectives or test the hypotheses. For small studies, the peer review panel may consist of individuals within the organization conducting the study if they have not been involved in developing the study design. For larger and complex studies, it is recommended that an external peer review panel be convened to review both the scientific and ethical soundness of the study design.

For research conducted or sponsored by NERL, human subjects research efforts will undergo both a scientific review and an ethical review. The director of the division conducting or funding the observational research is the manager with the primary responsibility for ensuring that the scientific and the ethical reviews are conducted, and that the review comments are properly addressed. The study design will be reviewed for scientific quality by independent and knowledgeable reviewers. Depending on the scope of the study, the appropriate NERL associate director or the NERL laboratory director will make the final determination about (1) the process for selecting scientific peer reviewers (including the range of disciplines to be included), (2) the nature and scope of the review process (e.g., charge to the reviewers and scope of the review; letter reviews, convening a peer panel, or both; the size and nature of the panel review; etc.), and (3) the adequacy of the responses to the scientific review.

### *2.5.2 Conflicts of Interest*

It is recommended that potential conflicts of interest among researchers or study participants be identified at all stages of study planning and implementation, but particularly early in the study during the planning stage. There can be many sources of potential conflicts of interest, including sources of project funding, pressures to publish, consulting arrangements of the investigators, employment of investigators' family members with affected parties, participation in affected advocacy groups, collaborations or relationships with experts on the IRB or other independent review committees, institutional conflicts for any contractors who may be involved, or a wide range of other situations.

Any situations that constitute actual conflicts of interest and all potential or apparent conflicts of interest must be reported to the IRB for their review and resolution. The CIOMS (2002) guidelines for research protocols involving human subjects specify that all sponsors of the research be identified, and that the protocol include actions to disclose and address potential conflicts of interest. Concerns about conflicts of interest also need to be identified and discussed with the researchers, community, and other stakeholders to make a determination of the existence of conflicts, and how they should be avoided or handled.

Even if actual conflicts of interest do not exist, researchers should recognize that there can be perceived conflicts of interest that can be just as damaging as real conflicts of interest. Perceptions by participants, community members and representatives, stakeholder groups, and the public may be substantially different from the reality of the situation. This is especially likely to occur when external sources, such as industry, are

involved in funding research. Even though researchers may develop agreements with funding organizations that ensure researcher autonomy, a perception may exist that the funding organization will bias the study (Resnik and Wing, 2007). Concerns about perceived conflicts of interest should be discussed with the IRB and other relevant review committees, in addition to the researchers, the community, and other stakeholders. The IRB must be made aware of any circumstances that may give rise to actual conflicts of interest or to the appearance or perception of a conflict of interest. The IRB's recommendations about how to resolve any such conflicts must be strictly adhered to by NERL researchers.

### *2.5.3 Develop the Human Subjects Protocol for IRB Review*

IRBs may have specific format requirements for their human subject research protocols. Traditionally, the human subjects research protocols for research conducted or funded by NERL have included descriptions of the project, including title and description of the research; the duration of the project; the type of data to be collected; the objectives of the study; the number of samples; a description of the participants and participant recruitment procedures; the informed consent procedures and forms; estimates of participant risk and burden, an assessment of benefits and the risk-benefit ratio; and actions to protect the participants. CIOMS has developed a comprehensive list of items that they recommend for inclusion in a human subjects research protocol (Appendix 1, CIOMS, 2002). Many of the items that they identify are also useful for observational human exposure studies. (The CIOMS items can be found in Appendix C of this document.) The authors recommend that anyone developing a human subjects protocol for observational human exposure studies review and utilize the CIOMS list of topics, as appropriate. Text Box 2-5 identifies a number of topics that should be considered in development of the human subjects research protocol.

In addition, the authors' experience leads them to suggest that three additional topics beyond those from the CIOMS (2002) document also may need to be considered in a human subjects protocol: (1) approaches to minimize changes in participant behavior because of participation in the study (see Section 2.3.4); (2) approaches to minimize therapeutic misconception (see Section 5.4.1); and (3) actions to involve the community in a community-based participatory research

**Text Box 2-5. Potential Topics in a Human Subjects Research Protocol**

1. Title
2. Summary in lay language
3. Justification for the study
4. Ethical issues and proposed resolution
5. Summary of previous research
6. Affirmation of Belmont Principles and 40 CFR 26 compliance
7. Previous history or use of the protocol
8. Information on the location and demographics of research
9. Information on funding organization, researcher partners, and collaborators
10. Names, qualifications, and experience of investigators
11. Objectives, hypotheses, assumptions, and variables
12. Study design
13. Sample size and power and statistical analysis plan
14. Criteria and justification for subject selection
15. Justification for use of vulnerable groups, if any
16. Process of recruitment
17. Actions to involve the community in a community-based participatory research program
18. Description and explanation of any and all interventions
19. Measurements or data to be collected
20. Any clinical or other tests
21. Rules or criteria for removing subjects or terminating the study
22. Adverse events and unanticipated problems—reporting and responses
23. Potential benefits to subjects or others
24. Expected benefits of the research to the population
25. Informed consent process and responsibilities
26. Protections for the consent/assent of vulnerable participants
27. Efforts to minimize "therapeutic misconception"
28. Approaches to minimize changes in participant behavior
29. Payments
30. Plans for informing subjects about items that could affect subjects' willingness to continue in the study
31. Plans to inform subjects about the results of the study
32. Privacy and confidentiality
33. Security of personal information and when, how, and by whom private information can be revealed
34. All foreseen uses of personal data or biological materials
35. Procedures for data and safety monitoring and oversight of the study and the criteria for identifying, reporting, and responding to adverse events, including ethical breaches, environmental measures in excess of reporting standards, and collateral observations, and criteria for prematurely terminating the study if necessary
36. A list of the references cited in the protocol
37. The source and amount of funding
38. Protocols for dealing with financial or other conflicts of interest
39. Schedule
40. Arrangements with sponsors regarding publication rights and procedures
41. Reasons for not publishing the study findings
42. Procedures for preventing falsification of data

(CBPR) effort, as appropriate (see Section 6, especially Section 6.10).

### 2.5.4 Ethical Review

In the United States, ethical reviews of studies involving human subjects are performed by IRBs. The Common Rule specifies requirements (40 CFR 26.107 – 115) for IRB membership, IRB functions and operations, IRB review of research, and other details related to IRB review and approval of research. Emanuel states that "the independent ethical review of [human subjects research] should involve individuals with training in science, statistics, ethics, and law, as well as reflective citizens who understand social values, priorities, and the vulnerability and concerns of potential subjects" (Emanuel et al., 2000). It is beyond the scope of this document to include detailed discussions on IRB membership, operations, processes, etc. The reader is referred to the Common Rule, as well as a number of other available references (e.g., OHRP, 2007; CFR, 2006; U.S. HHS, 1993; NRC, 2003).

It is essential that research with human subjects be carried out or strictly supervised by suitably trained, qualified, and experienced investigators. For all research subject to the Common Rule, these qualified researchers are expected to prepare a human subjects research protocol (as in Section 2.5) and to submit the protocol to be ethically and scientifically appraised by one or more suitably constituted IRBs, independent of the investigators.

There are a number of other issues associated with IRBs that may impact researchers conducting observational human exposure studies. As an example, there has been concern about the transparency of IRBs. Questions have been raised about what information the IRB should make available to the public regarding membership on the IRB for review of individual projects, the discussions held with the researchers, the IRB's concerns about the research protocol, the researchers' response, etc. Should this information be documented in files that the researchers can make available to the participants, community, stakeholders, and the public? At the present time, there is no clear approach as to how to address these issues. Because these issues are associated with the IRB, not the researcher, it is outside the scope of this document to recommend approaches for IRBs to address these concerns. IRB processes and procedures will continue to evolve as recommended by various committees and workgroups (e.g., as reported in NRC & IOM, 2005; NRC, 2003; U.S. HHS, 1993).

All human subjects research conducted or sponsored by NERL is subject to both the 40 CFR 26 requirements and procedures set forth in EPA Order 1000.17 Change A1 (www.epa.gov/oamrtpnc/forms/1000_17a.pdf). The EPA order establishes as policy that all research will comply with the Common Rule and with the order. All human research studies must be reviewed and approved by the EPA HSRRO before the work can begin.

In NERL, the director of the division conducting or funding the research is the manager with the primary responsibility for developing the human subjects research protocol and for having that protocol reviewed by an independent IRB acceptable to the EPA HSRRO. The protocol also will be reviewed by the NERL HSRRO and by the appropriate NERL associate director before it is submitted to the IRB. Under 40 CFR 26.109, the IRB can demand changes to the research protocol and is the final authority for approving or disapproving the research activity.

### 2.5.5 Internal EPA Review of Scientific and Ethical Issues

After IRB approval is obtained, the division director will be the primary manager responsible for preparing a request for review and approval or exemption of the human subjects research by the EPA HSRRO. The division director will ensure that the request is consistent with EPA Order 1000.17 A1 and all other policies or procedures that the EPA HSRRO may have established. The EPA HSRRO shall be the final authority for approving or disapproving the research effort. The EPA HSRRO may request additional reviews or establish additional policies and procedures for seeking review and approval. No human subjects research will begin—not even recruiting of potential participants—until the EPA HSRRO has approved or exempted the research.

## 2.6 Informed Consent

Informed consent is discussed extensively in Section 5 of this document. The major focus is that informed consent is a process, not a form, that "should be an on-going, interactive dialogue between research staff and research participants involving the disclosure and exchange of relevant information, discussion of that information, and assessment of the individual's understanding of the discussion" (Recommendation 4.1, IOM, 2002). These comments emphasize how important true two-way communication is to comprehension, the second pillar in the informed consent process. Informed consent is built on three "pillars:" (1) information; (2)

comprehension; and (3) voluntary participation, or "voluntariness" (U.S. DHEW, 1979). Informed consent requires "provision of information to subjects about the purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate" (Emanuel et al., 2000).

## 2.7 Ensuring That Participant Behaviors Are Not Changed Adversely Because of Being in the Study

The goal of observational human exposure studies is to collect information on people's exposures to chemicals in their real-world environment *as they carry on their normal daily activities*. Researchers who conduct these studies, however, recognize that participation in a study may affect behavior. This cannot always be avoided, as simply agreeing to participate in a study may impact the participant's activities and schedules. For example, this occurs when technicians visit homes to collect samples or when participants are asked to collect samples (e.g., food, urine), or to complete surveys, activity logs, or questionnaires. These types of changes in behavior may or may not affect the outcome of the study.

Some changes in behavior can affect the study outcome. The Hawthorne Effect is a well-recognized phenomenon. It is an effect on an outcome variable caused by the fact that the participants of the study know they are participating in the study. The Hawthorne Effect originally referred to the increase in worker productivity observed when a worker is singled out and made to feel important; the increased productivity was not related to the environmental factors that were being studied. The effect was described based on a series of industrial productivity studies from 1927 to 1932. Similarly, some changes in participant behaviors may change the observations, measurements, and conclusions from observational human exposure studies. For example, participants may do more cleaning in their home because they do not want the researchers to think they are poor housekeepers; this could affect the measurement of environmental concentrations in the home. In a study of chemicals from consumer products, participants may think that because the researchers are studying the products, the products must be harmful. Therefore, study participants may elect not to use the products during the study in the same manner as they would normally. Alternatively, prospective participants may choose to use more of the household product to qualify for the study. As a result, the participant's exposure to the chemicals could be either more or less than "normal."

Any change in a participant's behavior that is related to the research question being addressed in the study may impact the study results. Researchers should try to anticipate how a study may impact participant behaviors and ensure that the study design and implementation protocols do not cause changes in behavior that may cause harm to a participant during a study. A number of study elements with the potential to influence participants' behavior are listed in Text Box 2-6.

**Text Box 2-6. Study Elements That Could Affect People's Behavior**

- Eligibility criteria
- Recruiting approach and materials
- Enrollment approach
- Payments
- Retention strategy
- Types of measurements made and data collected
- Protocols for data collection
- Protocols for visits to homes
- Interactions with participants
- Communications

It is very difficult to predict in advance how these elements may be interpreted and acted on by the participants. Researchers may learn from the experiences of others, including the "lessons learned" from experts and their publications. They may wish to engage the community representatives (see Section 6) in a thorough discussion of the issue. Community-based focus groups or pilot studies also may demonstrate how the various elements of the study may have an unintended impact. Additionally, researchers can be very careful in the informed consent process (see Section 5.1), to ensure that participants not only know, but that they understand the facts of the study (Gilbert, 2006), and that they comprehend that the goal is to observe and measure the participant's exposures during their normal, everyday activities.

## 2.8 Criteria and Standards for Monitoring Scientific and Ethical Issues

Ethical requirements do not end when the participants sign the consent form and agree to participate. Indeed, as was stated above, informed consent is a process, not a form, and the process is an on-going dialogue between participants and researchers that continues throughout the study and beyond. In discussing respect for both potential and enrolled

subjects, Emmanuel et al. (2000) identify five actions that demonstrate respect for subjects, including

(1) permitting withdrawal from the research,
(2) protecting privacy through confidentiality,
(3) informing subjects of newly discovered risks or benefits,
(4) informing subjects of results of other relevant research, and
(5) maintaining welfare of subjects.

The authors conclude that these requirements can be met by diligent exercise of data and safety monitoring and oversight of the research effort. (Data and safety monitoring and oversight also are discussed throughout Section 4, but especially in Section 4.5 entitled "Data and Safety Monitoring and Oversight" and in Section 7.8, "Reporting Unanticipated Results and Observations." The reader also is referred to those sections.)

Creation of data and safety monitoring and oversight organization and procedures, combined with careful consideration of actions to ensure the ethical protection of participants, is perhaps the most important aspect of planning and implementing an observational human subjects study. The monitoring must include both the technical aspects of the study—like planning for actions if unsafe environmental conditions are observed—and also the ethical aspects of the study, such as those items listed above. The team of people involved in data and safety monitoring and oversight have to establish and implement mechanisms to get feedback on a continuing basis from the participants, in addition to monitoring and reviewing the scientific data.

CIOMS recommends that all human subjects research protocols contain "A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary" (Appendix A, CIOMS, 2002). To be consistent with this recommendation, the research team will need to develop and implement an approach for monitoring the scientific and ethical issues during the study, so that changes can be made to the study, or the study can be stopped if necessary. Criteria and standards need to be established against which study activities and results can be evaluated, and these criteria and standards need to be incorporated into the study design, the human subjects research protocol, and the QAPP.

In developing an approach to monitor scientific and ethical issues during the study, the research team may choose to

- identify the individual, team, advisory committee, or data safety monitoring board (DSMB) responsible for monitoring the progress and results of the study;
- develop roles and responsibilities;
- develop a schedule and timeline for the activities to be conducted;
- develop goals for interim data analysis and prepare an analysis plan;
- identify what data will be analyzed, how it will be processed and validated, and who will perform the analyses;
- develop a plan for reporting interim results to the research team;
- develop standards for reporting scientific and ethical issues to the research team; or
- develop criteria for evaluating scientific and ethical issues that arise during the study.

In a well-designed observational study for which the research team has adequately prepared, it is unlikely that there will be scientific issues requiring that the study be stopped. Nonetheless, it is important for criteria to be established for when the study needs to be changed or terminated. An example might be the participant retention rate. In a study with repeated measurements, a certain sample size is required to obtain statistically significant results. If the retention rate is poor, and too many participants drop out of the study, it may not be possible to meet the study objectives, and early termination of the study may be warranted (see Text Box 2-7 for issues that warrant early termination). However, it is anticipated that the study design would include contingency planning (for example, related to replacement).

Developing criteria for study elements that may have associated ethical concerns as a study progresses will no doubt be more difficult than reviewing the measurement data. Nonetheless, assuring the ethical safety of the participants is critically important. There are no standard formulas for dealing with ethical concerns. For example, if the privacy of a number of study participants is compromised by a technician conducting the measurements in their homes, what criteria should be used to evaluate the severity of the issues? How many landlord-participant problems are too many before the study needs to be changed to exclude participants who rent their dwellings? Despite the challenges, the team of people involved in the data and safety monitoring and oversight effort should work diligently, with input from the community, to establish open and continuing channels of communication with participants, the community, and stakeholders – with the goal of ensuring that their involvement in the research effort is, and

remains to be, based on the three pillars of informed consent: (1) that the parties are fully informed of all of the relevant and useful information, (2) that the information is understood by the parties, and (3) that all parties continue to participate voluntarily. With diligent effort to continue an open dialogue with the involved parties – combined with thoughtful review and oversight of the technical study results and procedures – the monitoring and oversight team can ensure that participants are free to withdraw from the research at any time; are fully informed about the technical study results; understand any new information about relevant risks and benefits; and that the privacy and confidentiality of the subjects is properly protected. Through these efforts, the monitoring and oversight team will ensure that the welfare of the research subjects remains a focus of the study effort.

**Text Box 2-7. Examples of Issues That May Cause a Study To Be Stopped Early**

- Participant recruiting and enrollment—low response rates, disproportionate enrollment of select groups, problems associated with advertising, inadequate selection criteria
- Informed consent—difficulties with the process and materials, poor comprehension
- Participation—poor response to questionnaires, poor compliance with researcher requests in data collection activities
- Burden—higher than predicted
- Changes in participant behaviors—potential changes because of participation in the study
- Grievances—participant issues
- Retention—high dropout rates
- Community issues—poor interactions, lack of support
- Third-party issues—problems with landlords, spouses, or others
- Collateral observations—identification of nonstudy hazards, difficulty reporting
- Unanticipated results—high contaminant concentrations measured, unexpected results
- New data indicating that participation in the study (or observations measured in the study) represent a risk to participants or others

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## SECTION 3

# Ensuring Protection of Vulnerable Groups

Concern for the protection of vulnerable groups is fundamental to modern ethical thought and guidelines. The Belmont Report was "meant to provide broad principles that could be used to generate specific rules and regulations in response to [U.S.] research scandals such as Tuskegee and Willowbrook.[11] It focuses on informed consent, favorable risk-benefit ratio, and *the need to ensure that vulnerable populations are not targeted for risky research*" [emphasis added] (Emanuel et al., 2000).

The Common Rule requires IRBs to assure that "additional safeguards have been included in the study to protect the rights and welfare of these [vulnerable] subjects" [at 40 CFR 26.111(b) in CFR, 2006a]. If an observational human exposure study includes vulnerable research participants, it is essential that the investigators be cognizant of the special issues and requirements of research involving vulnerable populations. Researchers have to justify the involvement of vulnerable populations in the research study and include the appropriate safeguards for protection of their safety and welfare. The Common Rule protections are discussed further in the IRB guidebook (U.S. HHS, 1993). EPA regulations include not only the general protections for vulnerable populations found in the Common Rule (Subpart A) but also define additional protections for children and for pregnant or nursing women (and their fetus or nursing child) in Subparts B, C, and D (CFR, 2006a).

The section begins by identifying or defining vulnerable groups and then discusses ethical issues that may be important in conducting observational human exposure studies involving those groups, especially children and pregnant women. The discussions about the ethical issues are based largely on EPA's human subjects regulations and on the recommendations from the Council for International Organizations of Medical Sciences document, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002).

## 3.1 Identification of Vulnerable Groups

In the United States, human subjects regulations (45 CFR 46 and 40 CFR 26) do not formally define vulnerable populations. Instead, the Common Rule gives examples of potentially vulnerable groups (see Text Box 3-1). In addition, HHS extends added human subjects protections to pregnant women, human fetuses, neonates, prisoners, and children as vulnerable groups (45 CFR 46, Subparts B, C, and D, see CFR, 2006b). Analogous but somewhat more stringent protections for children, pregnant or nursing women, and fetuses are specified in Subparts B, C, and D of the EPA Rule (40 CFR 26). The regulations do not preclude other groups from being considered vulnerable, however, and the National Institutes of Health (NIH), in its Human Participant Protections Education for Research Teams online tutorial (NIH, 2002), lists students or employees and terminally ill or comatose patients as potentially vulnerable groups.

CIOMS defines vulnerable persons as those who are relatively (or absolutely) incapable of protecting their own interests. Vulnerability here refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Vulnerable persons may have insufficient power, intelligence, resources, strength, or needed attributes to protect their

[11] For more information about these and other research scandals, see *Ethical and Policy Issues in Research Involving Human Participants, Vol. I*, Report and Recommendations of the National Bioethics Advisory Commission, Bethesda, MD, August, 2001. See p. 153 for information about the Willowbrook State School experiments. The report is available at www.bioethics.gov/reports/past_commissions/nbac_human_part.pdf (Accessed September 3, 2007).

own interests (CIOMS, 2002) (see Text Box 3-2). Because of their incapacity to protect their own interests, ethically perceptive researchers will plan and implement special provisions for the protection of the rights and welfare of the vulnerable persons.

**Text Box 3-1. Potentially Vulnerable Groups Identified in U.S. Regulations**

| | |
|---|---|
| Common Rule: Examples of vulnerable groups (40 CFR 26) | • Children<br>• Pregnant women (and their fetuses)<br>• Nursing women (and their neonates)<br>• Prisoners<br>• Handicapped persons<br>• Mentally disabled persons<br>• Economically disadvantaged persons<br>• Educationally disadvantaged persons |
| EPA extends stringent protections to these groups (40 CFR 26) | • Children<br>• Pregnant women (and their fetuses)<br>• Nursing women (and their neonates |
| HHS extends additional protections to these groups (45 CFR 46) | • Children<br>• Pregnant women and fetuses<br>• Nursing women and neonates<br>• Prisoners |
| Additional vulnerable groups in NIH training materials | • The terminally ill<br>• Students and employees<br>• Comatose patients |

Although Federal regulations define vulnerability in terms of the person's ability to protect their own interests or particular sensitivity to risks because of physical condition, the lay public may perceive a broader definition of vulnerability as it relates to education, economics, social status, and other factors. As shown in Text Boxes 3-1 and 3-2 and described above, the concept of vulnerability is broader than that presented in the Common Rule. It is not adequate to simply check the list in Text Box 3-1 to identify if a potentially vulnerable group is included in an observational study. The researchers should assess the potential vulnerability of a study population within the study by evaluating the characteristics (e.g., socioeconomic status) of the study population within the context of the study by considering the various design elements of the study, as discussed in Section 2.

**Text Box 3-2. Potentially Vulnerable Groups Identified in International Guidance**

(Council for International Organizations of Medical Sciences, 2002)

- Junior or subordinate members of a hierarchical group; examples include employees, students, members of the armed forces, police, and others who work for, or closely with researchers; they may have expectations of preferential treatment if they agree to participate or fear of disapproval or retaliation if they refuse to participate in a study.
- Elderly persons, who may acquire attributes that define them as vulnerable with advancing age.
- Residents of nursing homes.
- People receiving welfare benefits or social assistance.
- People with low or no incomes (poor and unemployed).
- Homeless persons.
- Nomads.
- Refugees or displaced persons.
- Some ethnic and racial minority groups.
- People with incurable diseases (in clinical studies).
- The politically powerless.
- Members of communities unfamiliar with modern medical concepts (applies to clinical studies)

## 3.2 Justification for Involving Vulnerable Persons in Observational Research

The Common Rule requires IRBs to ensure that the selection of subjects is equitable [40 CFR 26.111(a)(3)] and instructs the IRB to consider the "purposes of the research and the setting in which the research will be conducted." CIOMS goes further and recommends that "Special justification is required for inviting vulnerable individuals to serve as research subjects" (CIOMS, 2002).[12]

[12] In the commentary on Guideline 13 in CIOMS (2002), the committee states that the central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of the burdens and benefits of research participation. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in the CIOMS document (Guidelines 14 and 15) and include children, and persons who, because of mental or behavioral disorders, are incapable of giving informed consent. Ethical justification of their involvement usually requires that

- the research could not be carried out equally well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention, or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class—either the actual subjects or other similarly situated members of the vulnerable class;
- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive, or therapeutic products that will become available as a consequence of the research;
- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated

CIOMS recommendations, although written to address biomedical research, also generally are applicable to observational human exposure studies. The authors of this document consider the CIOMS requirement that the research could not be carried out equally well with less vulnerable subjects to be particularly important. EPA and NERL researchers should include vulnerable groups in observational human exposure studies only if their participation is critical to the success and applicability of the research. Even then, EPA and NERL researchers will have to meet stringent standards for protecting the rights and safety of the vulnerable participants. For example, EPA regulations governing observational research with *children* are even more stringent than the CIOMS guideline. If such research does not hold out the prospect of direct benefit to the child, *no increase whatsoever over minimal risk is permitted*.

However, many observational human exposure studies are developed specifically to study the exposures of selected vulnerable groups to chemicals and other environmental stressors in everyday environments. So, researchers should be prepared to address the issues associated with vulnerable groups in observational research. Furthermore, as discussed in Section 3.4, there has been increased concern in recent years that exclusion of vulnerable groups from research studies is not ethical. Failure to conduct research with vulnerable groups may deprive them of the benefits of research. NIH, for example, has a policy (NIH, 1998) with a goal of increasing participation of children in research.

## 3.3 Minimal Risk and Vulnerable Groups

EPA has codified protections for children, pregnant or nursing women, and fetuses in Subparts B, C, and D of the EPA human subjects rule (40 CFR 26). Subpart B strictly prohibits research involving intentional exposure of children or pregnant or nursing women (and, therefore, exposure of her fetus).

EPA's regulations do allow for observational research involving fetuses and pregnant women (40 CFR 26 Subpart C) or children (40 CFR 26 Subpart D) but with additional protections in place and with strict limitations on research that presents more than minimal risk (CFR, 2006a).[13] When considering vulnerable groups, *The Institutional Review Board Guidebook* (U.S. HHS, 1993) states that "IRBs should therefore determine whether the proposed subject population would be more sensitive or vulnerable to the risks posed by the research as a result of their general condition or disabilities. If so, the procedures would constitute more than minimal risk for those subjects."

When conducting observational human exposure studies, it is recommended that researchers consult these regulations and guidebooks. NERL researchers also will need to ensure that all of the requirements in Subparts B, C, and D of the EPA Human Subjects Rule are met.

## 3.4 Research Involving Children

Children long have been recognized as a vulnerable group in research studies. EPA and HHS both extend special protections to children (CFR, 2006a,b). There are many books, reports, and research manuscripts that specifically address issues associated with research involving children (e.g., NRC & IOM, 2005; IOM, 2004; Kodish, 2005; NRC, 2003; AAP, 2003).

CIOMS has drafted guidelines for including children in biomedical research (Guideline 14, CIOMS, 2002). The guidelines require an investigator to provide the assurances shown in Text Box 3-3 before undertaking research involving children.

**Text Box 3-3. Assurances Required by CIOMS Before Research Involving Children May Begin**

- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and
- a child's refusal to participate or continue in the research will be respected.

The participation of children in some observational human exposure studies is critical to characterizing children's exposures to chemicals in the environment. It is well recognized that children are not "little adults," and that their exposures to chemicals differ (and, in

with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and,

- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

[13] *Minimal risk* is defined at 40 CFR 26.102(i) and again at 40 CFR 26.402(g). It "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

some cases, are higher) from those of adults. Children are behaviorally and physiologically different from adults. Their interaction with their environment, through activities such as playing on floors, mouthing of hands and objects, and handling of food, may increase contact with contaminated surfaces. Children have proportionately higher breathing rates, relative surface area, and food intake requirements that also may increase exposure. Differences in absorption, metabolism, storage, and excretion may result in higher biologically effective doses to target tissues. Immature organ systems may be more susceptible to toxicological challenges. Windows of vulnerability, when specific toxicants may permanently alter the function of an organ system, are thought to exist at various stages of development. Because the factors influencing children's exposures to chemicals are not characterized well (Cohen Hubal et al., 2000), it is sometimes important that observational human exposure studies involve children.

Because children are so vulnerable, there long has been concern about including them in research studies, and biomedical research often excluded children. However, in recent years, there has been concern that excluding children from research is not ethical. NIH's *Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects* (NIH, 1998) has a goal of increasing participation of children in research. The policy of NIH is that children must be included in all human subjects research conducted or supported by NIH, unless there are scientific and ethical reasons not to include them. Proposals or applications to NIH for research have to present an acceptable justification if children will be excluded from a research study. Of course, as discussed above, if the research topic is irrelevant to children, the CIOMS guidelines would recommend that they be excluded from the research.

Observational human exposure studies conducted by NERL are not expected to involve greater than minimal risk. It will be the responsibility of the NERL researchers to present adequate information for the IRB to demonstrate that the research does not involve greater than minimal risk. Researchers designing observational research studies should carefully evaluate the risks and benefits specific to their study and the participants involved. In developing the study design and human subjects protocols, researchers need to ensure that the protocols ensure the protection of the rights and welfare of the participant children, and that risks and harm are minimized. The perception of risks and benefits, both by the individual and by the family or community, may influence the risk-benefit determination. It may prove useful for the research team to consult with other experienced researchers who have conducted similar studies and with members of the IRB to ensure that the information included in the human subjects research protocol is adequate for the IRB's review.

It is recommended that researchers consider all of the potential issues associated with involvement of children in their studies in developing the study design and research protocols, including the role of the family. EPA's human subjects rule for observational research not involving greater than minimal risk to children (40 CFR 26.404) (i.e., the kinds of observational human exposure studies that NERL exposure research is likely to entail) focuses on obtaining assent of the children and permission of their parents or guardians. But the role of the family goes far beyond their involvement in the informed consent process. In observational human exposure studies, even when children are the participants, the parents or guardian play a key role in the collection of data and information during the study. For studies with very young children, family members supply all of the information relevant to the child. NERL researchers need to ensure that both the child and the parents or guardians and other caregivers are informed fully and are willing participants. Without their willing participation, the research cannot be successful.

## 3.5 Women as Research Subjects

Women are routinely included as research participants in observational human exposure studies. However, pregnant women and their fetuses are vulnerable groups and require special protections. EPA's human subjects rule prohibits intentional dosing studies and provides additional controls for observational research (40 CFR 26, Subparts B and C).

CIOMS (2002) includes two guidelines for biomedical research involving women as research subjects. The first of these, number 16, states that women should not be excluded from biomedical research because of the potential for becoming pregnant during a study. The document continues, "A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the benefits of new knowledge derived from the trials." The second relevant CIOMS guideline, number 17, asserts that, if involved in a research study, pregnant women should be fully informed, and included only if the

research benefits pregnant women and is thoroughly supported by reliable evidence in animal studies.

Although the CIOMS guideline specifically addresses biomedical research, the ethical concepts behind the guidelines generally may be applicable to observational human exposure studies. EPA's human subjects rule is completely consistent with the HHS rule in adding additional protections for pregnant women and fetuses involved in observational research (40 CFR 26.304 and 45 CFR 46.204). These additional protections (specified in 45 CFR 46.204 subparagraphs *a* through *j*) reflect the CIOMS recommendations by requiring: availability of data from previously conducted studies to assess the risk to pregnant women and fetuses; scientific necessity for inclusion of pregnant women and fetuses (i.e., providing benefit to the woman or fetus, or producing important, but otherwise unobtainable, biomedical knowledge); that risk is reduced to the least possible level for achieving the objectives of the research; and other protections.

## 3.6 Other Potentially Vulnerable Groups

HHS specifies additional protections for prisoners as a potentially vulnerable group in Subpart C of 45 CFR 26. Additional requirements for other vulnerable groups in research studies are not specifically defined in either EPA's or HHS' human subjects rules. Nonetheless, other groups (as discussed in Section 3.1) may be considered to be vulnerable and, as such, may warrant additional consideration and protection as required in the Common Rule. For these other potentially vulnerable groups, such as employees, students, handicapped persons, mentally disabled persons, and economically or educationally disadvantaged persons, nursing home residents or otherwise incapacitated elderly, etc., the Common Rule requires researchers and IRBs to fully evaluate the protocols to ensure that the safety and welfare of the groups will be protected. As discussed in Section 3.1, It also should be noted that, although Federal regulations define vulnerability in terms of the ability to protect one's own interests, the lay public may perceive a broader definition of vulnerability as it relates to education, economics, social status, and other factors. The researcher should evaluate vulnerability in this broader context to ensure that adequate safeguards are included for potentially vulnerable populations that do not meet the definition of the Federal regulations.

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## SECTION 4

# Privacy, Confidentiality, and Other Concerns Related to Observational Human Exposure Studies

Observational human exposure studies are designed to describe people's contact with pollutants as they go about their everyday lives. Of necessity then, these studies take place in the locations that participants often consider to be personal and private. Clinical research studies generally are conducted in a research facility, a clinic, a hospital, or some other institutional or medical setting. Survey research may be conducted by mail, over the phone, or in another "neutral" setting. But, observational human exposure studies are conducted in the participants' "personal" environment—their home, daycare center, school, vehicle, workplace, or other environments that people occupy during their routine daily activities. This difference in the research setting means that researchers involved in observational human exposure studies have an even greater challenge in meeting the ethical obligation to respect the privacy of the participants.

When exposure science researchers like those at NERL enter a home to carry out their studies, the "expectations and constraints may be strikingly different than when research is carried out in a medical setting" (p. 64, NRC & IOM, 2005). The legal precept of freedom from unreasonable search and seizure and the historic and deeply rooted principle that "a man's home is his castle" contribute to a belief in the "sanctity of the home" (see the discussion on pp. 62-66, NRC & IOM, 2005).

The joint NRC and IOM report *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children* discusses the ethical issues associated with entering a participant's home to conduct research and explores the researchers' responsibilities that derive from conducting research in people's homes (NRC & IOM, 2005). These housing-related discussions are particularly relevant to observational human exposure studies, which often include environmental and biological measurements in people's homes or personal locations. Many of the topics identified in that report are discussed in this section (Text Box 4-1).

**Text Box 4-1. Topics in Section 4**



## 4.1 Privacy Issues

Privacy refers to an expectation that a person is free from intrusion into personal matters and is free from the presence or view of others. The *Institutional Review Board Guidebook* defines privacy as "control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others" (U.S. HHS, 1993). Beauchamp and Childress find that the right to privacy is based on the principle of respect for autonomy. "We often respect persons by respecting their autonomous wishes not to be observed, touched, or intruded upon…. A loss of privacy occurs if others use any of several forms of access, including intervening in zones of secrecy, anonymity, seclusion, or solitude" (pp. 295-296, Beauchamp and Childress, 2001).

Although research participants may agree to allow researchers to enter their home or other zone of personal space to conduct their research measurements, they have not abrogated their right to privacy. "When individuals voluntarily grant others some form of access to themselves, their act is an *exercise* of the right to privacy, not a *waiver* of that right" (p. 297, Beauchamp and Childress, 2001). Researchers should remember that they are guests in the homes for a specific purpose. "When people visit a home, there are social expectations about what is acceptable behavior. People who are invited into a home are expected to be sensitive to and respectful of the host's customs and values" (p. 65, NRC & IOM, 2005).

By their very nature, observational human exposure studies encroach on the privacy of a research participant. Entry in a participant's home (or other personal zones) does represent a loss of privacy, but researchers should be careful to ensure that their presence does not become a violation of the individual's right to privacy. The relationship between the researcher and the participant may be complicated, and there may be conflicts between the researcher's role and their ethical obligations (NRC & IOM, 2005). In entering a participant's personal space, it may be difficult, or impossible, to avoid making observations unrelated to the research question, thereby further intruding on the participant's personal privacy. Indeed, there may be ethical and legal obligations for the researchers to respond to those observations. Beauchamp and Childress suggest that "policies carefully specify the conditions of access that will and will not count as a loss of privacy or a violation of the right to privacy. The policy should accurately define the zones that are considered private and not to be invaded, and should also identify interests that legitimately may be balanced against privacy interests" (Beauchamp and Childress, 2001).

Observational human exposure studies also may infringe on the privacy of other individuals, for example, other members of the participant's family or household. Researchers should strive to minimize the intrusion and loss of privacy and to show respect for the privacy of study participants and third parties at all times (see Text Box 4-2 for a list of relevant privacy issues). It is incumbent on the researcher to recognize privacy issues in the design and implementation of the research study. The NRC & IOM report suggests that researchers anticipate the ethical issues that arise from conducting research in a person's home, and that they take steps to correct them (1) by thinking through the issues as part of the study design; (2) by discussing the issues during the informed consent process; and (3) by ensuring that the frontline staff that enter a participant's home "understand their role as members of the research team, how that role differs from the role of neighbor or friend, and how they should respond when they make observations that are not part of the protocol" (p. 66, NRC & IOM, 2005).

**Text Box 4-2. Privacy Issues**

- Researchers should develop an anticipatory plan for how to deal with privacy issues during the study. The plan should include a list of potential observations that could be of concern and a plan for how they will be handled.
- The plan needs to address both the legal and ethical obligations of the researcher in response to situations where privacy is compromised.
- Privacy issues will vary depending on the culture of the population being studied. What one individual or group may find as an invasion of privacy, another group may not have a concern about.
- Privacy issues involve individual participants and may extend to third parties, including the community.
- Researchers may find a meeting with community representatives to learn about the community residents and potential privacy issues to be helpful. Community representatives can help the researcher identify potential privacy issues and offer advice on how to address them.
- Researchers may wish to respect the privacy of occupants sharing the study participant's household or other study locations by providing advance notification of study visits and by giving them the opportunity not to be present during those visits.
- Field staff should be trained on how to minimize breaches of privacy and how to handle privacy issues.
- The informed consent process and form should address how the researcher will handle privacy issues such as collateral observations of household hazards

## 4.2 Confidentiality

Confidentiality and privacy are not the same thing. Confidentiality refers to limits on the dissemination of information disclosed by a person in a special professional relationship, such as the doctor-patient relationship or the participant-researcher relationship (Beauchamp and Childress, 2001). *The Institutional Review Board Guidebook* defines confidentiality as "pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure" (U.S. HHS, 1993). Emanuel et al. (2000) state that one way to respect the privacy of the participants is "by managing the information in accordance with confidentiality

rules." Confidentiality in research also may extend to limiting dissemination of the knowledge that an individual is participating in a research study.

As part of the research planning process, researchers are responsible for developing procedures to protect confidentiality and to define limits on the researcher's ability to provide or protect confidentiality. Explaining plans or procedures for protecting confidentiality and their limits[14] to prospective research participants is an integral part of the informed consent process.

### *4.2.1 Confidentiality of Information*

Many types of information may be collected in observational human exposure studies. Information may be collected through questionnaires, staff observations of residential or other environments, diaries, personal sample collection, environmental or residential sample collection, and collection of biological specimens. Measurement data from the collected samples become part of the information for a participant. The specific information to be obtained to address the research questions should be determined in the development of the study design and research protocol.

Disclosure of information that can be linked to an individual may cause harm or distress to that individual. Researchers are responsible for developing safeguards to protect the confidentiality of information and physical samples collected from research participants (see, for example, Guideline 18, CIOMS, 2002). [15]

Researchers also should be aware that certain combinations of information from a study may sometimes lead to the *indirect* identification of the individual. Certain combinations of demographic information, for example, may make it relatively simple to identify an individual. Precise geographic location information may be sufficient to pinpoint a residence. Researchers may use several strategies to reduce the likelihood of indirect identification when study results are reported (see, also, Text Box 4-3).

- Redact from publications, reports, or public data sets information that might be used to indirectly identify a research participant.
- Generalize exact information; for example, replace birth date with age or year of birth or classify age as part of a range.
- Aggregate information across individuals; for example, only report data in cells of sufficient size to make individual linkages unlikely.
- Reduce the specificity of geographic coordinate information to a level that a specific residence or other location can not be identified.

**Text Box 4-3. Approaches for Protecting Personally Identifiable Information**

- Developing procedures for safeguarding information prior to collecting the information
- Ensuring that data or samples are anonymous by not collecting or by destroying identifying information or linkages
- Restricting access to identifying information to only those requiring access
- Assigning codes to participants, data, and samples rather than using identifiers
- Physically separating identifying information and linkage files from other study information
- Securing identifying information in locked files with limited access
- Restricting identifying information from computers that are networked with other computers or electronic systems
- Restricting identifying information from computers that are not kept in secure locations with limited access
- Training research staff members on human subject protection and on information security procedures

Another step that can help protect confidentiality is to obtain a Certificate of Confidentiality. Certificates of Confidentiality are issued by NIH (2002) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being

[14] Beauchamp and Childress (2001) discuss when one may be ethically justified in infringing on an individual's privacy and confidentiality—for example, because of risks to others evidenced by biomarkers of infectious disease. They also discuss similar ethical issues that may arise in regard to genetic data. CIOMS (2002) Guideline 18 provides suggestions for safeguarding or disclosing genetic information. If exposure scientists collaborate with medical researchers or epidemiologists and obtain such information, they need to be cognizant of the relevant ethical issues and of the CIOMS guidelines.

[15] Guideline 18 states, "The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality." Additional CIOMS commentary on the confidentiality guideline states, "Prospective subjects should be informed of limits to the ability of researchers to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. . . . These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects."

compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants. Any research project that collects sensitive, personally identifiable information and that has been approved by an IRB is eligible for a certificate. Identifying information is broadly defined as any item or combination of items in the research data that could lead directly or indirectly to the identification of a research subject.

Federal funding is not a prerequisite for a certificate. A Certificate of Confidentiality does not diminish, however, the investigator's need to protect the personally identifiable information as described above.

### *4.2.2 Confidentiality of Participation*

In some types of research, the knowledge that a person is participating in a particular research study could, potentially, put the participant at risk for harm or distress. This topic is discussed in *The Institutional Review Board Guidebook*, with special emphasis on behavioral and social research that deals with sensitive topics (U.S. HHS, 1993). The guidebook describes the need for additional safeguards to protect and prevent disclosure of the identity of participants, including the use of Certificates of Confidentiality for sensitive matters.

Observational human exposure studies often pose particular challenges with regard to limiting dissemination of the knowledge of an individual's participation in the study. Visiting the research participant's residence to collect samples or to make observations will necessitate informing other family members or occupants about the visit and study procedures. Research participants may be asked to wear personal monitors over time periods ranging from a day to a week or more. Wearing these devices in public places, schools, or workplaces may identify them as a study participant or generate questions regarding the activity. Field staff visits to the participant's home or setting up outdoor sample collection devices around the home also might disclose their participation. And, in some cases, third parties outside of the home have to be asked for permission or be informed that monitoring activities are taking place.

Researchers and IRBs should consider whether knowledge of an individual's participation by others might create potential for harm or distress in an observational human exposure study. Such risks might be limited to possible discomfort in attracting unwanted attention; this may be particularly true for adolescents. However, in some cases, the potential risks could be greater, for example, in cases where participation could provoke an adverse reaction from a landlord or employer. Oftentimes study protocols can be structured to minimize these potential risks. Through the informed consent process, prospective participants should be made aware of the limits of the researcher's ability to protect knowledge of their participation in the study and of the possible risks of disclosure.

## 4.3 Collateral Observations

In the course of conducting an observational human exposure study, research staff may observe potentially unsafe conditions or situations that are unrelated to the research study. Such "collateral observations" may involve physical hazards in the study participant's residential environment or evidence of situations, such as child abuse, that have to be reported to proper authorities. In preparing for the research study, it is recommended that researchers carefully plan for possible collateral observations, including their identification, staff training, and hazard communication and reporting. This may be a major element in the data and safety monitoring and oversight for the study. The informed consent process should reflect procedures used to manage collateral observations. Potential participants should be informed of situations in which confidentiality might be breached, such as statutory requirements for reporting abuse or imminent harm to self or others.

### *4.3.1 Potential Nonstudy Hazards in the Residence*

Research staff conducting observational human exposure studies often will spend time in and around study participant residences. In the course of visiting a residence or conducting study-related observations, research staff may observe potential hazards unrelated to the research being performed (see Text Box 4-4). Some hazards may be associated with the potential for physical injury, whereas others may be related to exposure to chemical or biological agents. Some situations may be potential hazards only for young children, whereas other conditions may present potential hazards for all residents or occupants.

The NRC & IOM recommend that researchers should consider such foreseeable observations and potential hazards in advance, develop responses to the risks, and submit the proposed plans to the IRB for review to ensure that they are appropriate "in the context of the research and the affected community." The NRC

& IOM also advise that field staff should be trained in how to assess and respond to such risks (Recommendations 7.3 and 7.4, NRC & IOM, 2005). For other behaviors and risks that have not been specifically identified in advance, procedures should be included in the data and safety monitoring and oversight provisions of the study design and research protocol to address these issues. The fundamental ethical principle of beneficence would motivate researchers who observe serious harms to take steps to try to prevent those harms, even for observations that are not directly related to the study. The steps that they may take can range from immediate action to prevent an imminent and serious danger to statutory reporting of observations (see Section 4.3.2) to reporting the observation to the data and safety monitoring and oversight authority for advice on how to respond (see Section 4.5). (The reader is also referred to pages 59-61 and 134-144 of the NRC & IOM [2005] report for a more thorough discussion of researchers' responsibilities in such cases.)

**Text Box 4-4. Potential Hazards that Might Be Encountered in a Residential Environment**

- Unsecured firearm
- Uncovered electrical outlets
- Unprotected stairways
- Missing child-protective cabinet latches
- Lack of window guards
- Missing or inoperable smoke alarm
- Housing code violations
- Chipping or flaking paint—potential for lead exposure in older homes
- Malfunctioning or unvented combustion appliances—potential for carbon monoxide exposure
- Unsecured poisons or other dangerous products
- Excessive mold growth

### *4.3.2 Collateral Observations with Mandated Reporting Requirements*

Some collateral observations may have statutory requirements for reporting to designated authorities. Examples of such observations include

- observed child or elder abuse or evidence of such abuse or neglect,
- statements or actions of intent to harm self or others, and
- certain communicable diseases.

Because different reporting statutes pertain in different states, it is necessary for researchers to learn and understand the applicable reporting requirements for the study location. In the case of abuse, it is also important to understand what actions or situations are considered abusive in a particular state. Although direct physical harm or violence might be obvious to a research staff member, there are other conditions of neglect that might be more difficult to recognize or to know when to report.

Study participants should be made aware of statutory requirements for reporting collateral observations as part of the informed consent process. Researchers should include the reporting requirements in the informed consent form (discussed in Section 5) and should ensure that the study participant fully comprehends this information and the impact on their privacy and confidentiality.

### *4.3.3 Hazard Communication*

It is difficult for researchers to determine when and how to communicate with study participants or third parties about collateral observations related to potential hazards. A hazard might present such an imminent threat to health or safety that staff would need to communicate immediately with the participant or take action to mitigate the threat. In some cases, such as instances of abuse with attendant statutory reporting requirements, it may be necessary to breach confidentiality. More often, however, a potential hazard identified as a result of collateral observation may not be an imminent threat or pose a potential risk that is situation dependent or is related to third parties. A number of considerations in hazard communication come into play regarding confidentiality, privacy, the ability of the researcher to provide accurate and effective information regarding the hazard and hazard mitigation, and the ability of the study participant or others to effectively mitigate the hazard without unintended adverse consequences. The National Academy of Sciences Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children, Youth, and Families discussed many of these issues in depth (NRC & IOM, 2005).

Different communities, cultures, or demographic groups can have different risk perceptions, which may affect how collateral observations are assessed and reported from one study location to the next. The AAP Committee on Environmental Health has prepared information regarding perception, identification, and communication of environmental health risks (AAP, 2003). Researchers likely will benefit from including community members on the research team in developing the study design and research protocol or from consultation with community boards regarding identification of hazards and hazard communication.

It is important that any advice that the researcher might provide to study participants regarding hazard mitigation should be carefully considered. Considerations in recommending an action may include whether the mitigation approach has been shown to be effective, whether the study participant can understand and effectively implement the action, and whether unintended adverse consequences might result from taking an action. In some cases, it may be reasonable to refer the participant to another organization that can provide expert advice or assistance.

### *4.3.4 Planning and Staff Training*

As part of the study planning process and protocol development, it is important that researchers be cognizant of the kinds of collateral observations that might occur in the implementation of the study protocol and to develop plans as to how such observations would be handled. Researchers may choose to include a systematic approach in hazard identification, such as using a home-hazard checklist that becomes an ancillary part of the study protocol. Alternatively, collateral observations could be handled on a case-by-case basis.

Staff experience and training is a critical consideration for managing collateral observations. Staff members that visit study participant residences may not have expertise or experience in identifying many of the potential hazards without adequate training. All staff involved in a study, particularly those responsible for field data collection, should be trained on identification and reporting of collateral observations. This training should be study specific and likely will include, but not be limited to

(1) identification of actions (e.g., child abuse) that have (state-specific) statutory reporting requirements,
(2) conditions of neglect that may adversely impact study participants or third parties,
(3) environmental hazards and situations that may be associated with imminent harm (e.g., combustible materials near an open flame, unsecured firearms accessible to very young children),
(4) policies and procedures for reporting or intervention by members of the research team, and
(5) local and state reporting requirements.

It is advisable that this training be developed in consultation with community representatives who can provide input on potential hazards and situations that may be encountered in the study community, local norms and attitudes about potential interventions and reporting, and local agencies available to assist on these types of issues. It is also especially important to consider staff experience and training in hazard communication. Consistency in communication is very important, and researchers may decide to use materials prepared by other organizations that have expertise regarding a particular hazard.

Another important element of planning for field data collection and training of research staff is on hazards and situations that the field staff may encounter during their field work. Although the previous discussion highlights the need to be prepared to report potentially negligent or illegal behaviors, these same behaviors may place the research staff in imminent danger during the conduct of their work in residences and communities. The research team should develop a plan for identifying potential situations, hazards, and dangers that may place the research team at risk of imminent harm. This should generally involve working with community representatives to identify the hazards and situations that may be of concern. For example, a researcher's observation of illegal drugs in a study residence may place the researcher in potential danger. Similarly, if studies are conducted in areas with high crime rates, researchers need to be aware of the potential dangers and have a plan for addressing them. In some cases, situations may arise because of to inadvertent actions. For example, if an area has a high rate of daytime break-ins, the presence of researchers in the area may trigger calls to local authorities when the researchers, who are strangers, are observed in the neighborhood. Feedback from the community representatives should be solicited when developing a plan for responding to situations such as these. Comprehensive training should be developed for research field staff to assist them in identifying potentially dangerous situations and in responding to such situations.

## 4.4 Third-Party Issues

Third-party issues can arise in observational human exposure studies in two ways. First, the study may collect limited information about or related to individuals other than the study participants. Second, study activities may affect or involve people or organizations other than the study participants.

Examples of activities that may involve or affect third parties in observational human exposure studies could include, but are not limited to the following types.

- Asking the participant about demographic, occupational, smoking, or product use information for other household members
- Collecting residential environmental samples in multiperson households

- Collecting environmental samples in common areas of multifamily housing units
- Collecting personal or environmental samples in a day care, school, health care, or occupational setting
- Measuring chemical occurrences or concentrations that may be of interest or import to other household members or to the community
- Collecting activity or dietary information about a community

It is important for researchers and research staff to understand whether and to what extent the research involves or affects third parties, and how third-party involvement might affect the study participants. Several examples of possible third-parties are listed in Text Box 4-5. Study planning; IRB review; and communication before, during, and after the study should take third-party issues into account.

**Text Box 4-5. Possible Third-Parties in Exposure Studies**

- Household members not enrolled in the study
- Relatives
- Care givers for children or elders
- School staff
- Employers
- Other members of the community
- Building managers or facility operators
- Landlords

### *4.4.1 Determining Whether a Third Party Is a Human Subject*

It is up to the IRB to determine whether a third party is a human subject afforded human subject protections under the Common Rule. A third party would meet the Common Rule definition of a human subject [40 CFR 26.102(f)] if individually identifiable private information about them is collected (CFR, 2006). When this occurs, the informed consent of the third party must be obtained, or, if certain criteria are met, the IRB may determine that informed consent may be waived. It can be difficult to determine whether information about a third party is both individually identifiable and private. Discussions of this issue and recommendations for determining whether third-party information is identifiable and private have been submitted to the HHS Office of Human Research Protections by NIH (2001) and by the National Human Research Protections Advisory Committee (NHRPAC, 2002).

Whether or not a third party is determined to be a human subject, the researcher should treat research information about a third party as confidential.

### *4.4.2 Informing Third Parties of Research Activities*

Obtaining permission from or informing third parties of certain types of activities may be needed in some observational human exposure studies. For example, household members living with a study participant need to be informed about home study visits and residential sample collection activities. Study activities that occur outside of the participant's home or yard may require informing or gaining permission from third parties. A study may include collection of environmental samples (i.e., ambient air, dust, soil) from outdoor common areas of multifamily housing where the study participant lives. Issues regarding privacy, permission, and payments for third parties in housing-related studies have been discussed in the NRC & IOM (2005) report.

Observational human exposure studies also may include cases when study participants are asked to collect personal samples (i.e., wearing a personal air monitor) over a time period that includes time they spend in a school, day care, or workplace. Such monitoring might require informing or gaining permission from an organization's staff or an employer. In each case, the researcher and IRB have to consider whether obtaining permission from or informing a third party is appropriate and, if so, to define the procedures for doing so. The researcher and IRB have to also consider the potential impact of third-party knowledge of research activities on confidentiality and risk for the study participant and have to ensure that it is clearly and fully explained in the informed consent process.

### *4.4.3 Research Results and Third Parties*

Prior to initiating a research study, researchers should consider whether research results may be provided to third parties. In some studies, there may be reasons to inform household members living with a study participant about specific residential measurement results. In community research studies, aggregated or summary research results may provide a benefit to the community. In this case, it would be beneficial to seek out the advice of community representatives regarding results reporting prior to the study. Researchers also should determine whether there are State or local reporting requirements for some types of measurement results above specified action levels (i.e., blood-lead levels, heavy metal concentration in soil). It is important that the researcher and IRB ensure that confidentiality and privacy of study participants are carefully

considered in any case where reporting study results to third parties is contemplated or may be required. Ideally, the informed consent process would make clear whether, under what conditions, and how research results might be provided to third parties.

## 4.5 Data and Safety Monitoring and Oversight

The Common Rule requires for IRB approval that, "When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects." [40 CFR 26.111(a)(6)].

Data and safety monitoring plans (DSMPs) are developed and applied in all clinical trial research studies. Clinical trials are prospective studies designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions. The DSMPs are used to insure the safety of participants, the validity of data, and appropriate termination of studies for which significant risks or benefits have been uncovered or when it appears that the trial cannot be concluded successfully (NIH, 1998; NCI, 2001; U.S. FDA, 2001). Depending on the study scope and potential risks and benefits, a data safety monitoring board (DSMB) may be created to assess procedures for data and safety monitoring and to independently assess safety and outcomes on an ongoing basis during the study.

Formal independent monitoring boards or committees, like DSMBs, have not seen widespread use in observational human exposure studies, although much of the information included in DSMPs often has been captured in the research protocols. Researchers and IRBs may, however, consider using monitoring and oversight boards to help assure participant safety and research integrity in observational human exposure studies, particularly in complex longitudinal studies and in studies that include vulnerable subjects.

At least two NIH institutes have developed guidelines for monitoring and oversight in the observational research that they sponsor.

(1) The National Heart, Lung, and Blood Institute (NHLBI) has developed an interim policy on the creation and role of observational study monitoring boards (OSMBs) for observational research sponsored by that institute (NHLBI, 2007). OSMBs may be established for large or complex studies on a case-by-case basis. The role of the OSMB is "to help assure the integrity of the study by closely monitoring data acquisition for comprehensiveness, accuracy, and timeliness; and monitoring other concerns such as participant confidentiality."

(2) The National Eye Institute (NEI) has developed guidelines for data monitoring and oversight committees (DMOCs) for observational research (NEI, 2001). The role of the DMOC is to "assist the NEI and the study investigators in protecting the interests of study participants and in preserving the integrity and credibility of the study."

When appropriate, formal procedures for routine monitoring of scientific and ethical issues will need to be incorporated into observational research and approved by the IRB to ensure participant safety and the integrity of the research. Even though most observational human exposure studies are considered low-risk, there is often a need to determine whether appropriate threshold values for biological or environmental levels of chemicals exist or can be determined that, if the threshold value is exceeded, it would trigger reporting or other actions. The safety of measurement procedures and equipment also has to be considered. Unanticipated adverse events also may be encountered in observational research. Participant consent and understanding of the research effort, participant recruitment, participant retention, and data accuracy and quality should all be monitored to ensure the scientific integrity of research results.

The authors already have discussed (Section 2.8) the needs (1) to establish, in advance, criteria and standards for monitoring the research program in regard to both scientific and ethical issues; (2) to establish who will monitor and oversee the research progress (the monitoring and oversight authority, be it an individual, team, or review committee); and (3) to establish the roles, responsibilities, and authorities of the researchers and of the monitoring and oversight authority. The planning also should include steps to meet the IOM recommendations that researchers should "anticipate risks and behaviors that may be observed in the home… [and] develop anticipatory plans that specify how to assess and respond to risks when they are identified, and educate their staffs about the plan" (Recommendation 7.3, p. 144, NRC & IOM, 2005).

Once the procedures and organization for monitoring and oversight of the observational study are approved by the IRB, it is the responsibility of the researchers and of the monitoring and oversight authority to ensure that the planned actions are implemented. Implementation of the monitoring and oversight function may include the following items.

- Ensuring that procedures for identifying, reporting, and responding to anticipated or unanticipated adverse events and safety issues are in place and are being followed

- Assessing and responding to risks when they are identified
- Evaluating the performance and knowledge of the staff regarding identification of potential risks and the actions they should take
- Implementing procedures for monitoring the informed consent process, participant behaviors, participant recruitment, participant retention, procedures to protect privacy and confidentiality, and other human requirements for adherence to the research protocol and compliance with ethical standards and with EPA's human subjects rules
- Ensuring that measurements and samples are collected as planned, and that data are reported on a timely basis
- Evaluating whether the observed measurements exceed the pre-established threshold values and, if so, ensuring that reporting procedures and plans to respond to the potential risks are completed on a timely basis
- Ensuring that quality assurance plans that define procedures for assessing and ensuring study protocol compliance are being met
- Ensuring data quality targets are met through independent internal or external auditing requirements
- Taking all warranted oversight actions to ensure the safety of the participants and the integrity of the study, including terminating the research study if appropriate

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## SECTION 5

# Creating an Appropriate Relationship Between the Participant and Researcher

In observational human exposure studies, the researcher and the participant routinely interact with each other, often in the participant's home or other private setting and often repeatedly over a number of days. The nature and setting of the interactions mean that exposure researchers should give special consideration to the many scientific and ethical issues that shape the relationship between participants and the researchers. In these studies, it is recommended that a strong relationship, built on openness and trust, should be developed between the researcher and participant. The nature of that relationship and the ethical principles underpinning an appropriate relationship are the focuses of this section of the document.

This relationship should be established on the ethical values of respect for the participant's autonomy and respect for their welfare. Emanuel and his co-authors find that these two ethical values translate into specific responsibilities for an ethical researcher in regard to informed consent and respect for potential and enrolled subjects (Emanuel et al., 2000). They describe the ethical principles for these responsible actions thusly, "Respect for potential and enrolled subjects is justified by multiple principles including beneficence, nonmaleficence, and respect for persons. Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy. Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and nonmaleficence." Section 4 already has described some of the particular concerns regarding privacy, confidentiality, and other issues related to observational human exposure studies. This section further describes elements of the relationship between researchers and participants that are important to consider and address during design and implementation of a study.

Of course, the relationship between the researchers and the individual participants does not exist in isolation. The researcher-participant relationship may influence and be influenced by the relationship with the community in which the participant lives. Good, two-way communications are critical for the development and nourishment of an appropriate researcher-participant relationship. Although those two topics are the subject of the next sections of this document, elements from those topics unavoidably will color the discussions in this section as well.

Researcher training is a key component for conducting research that incorporates human subject protections and fosters appropriate researcher-participant relationships. Most organizations require basic human subjects training on the essential elements for processes and procedures for research with human subjects. More in-depth training will improve researcher understanding in areas of the informed consent process, observational techniques, community-based research, and other topic areas. Such training will benefit principal investigators throughout the research study from the design stage through communication of research results. Training is also important for staff that will work directly or indirectly with research participants or their samples and data. This document can be used as both a training tool for researchers as well as a resource for designing training courses. There are a number of sources of training on human subjects protection. The Collaborative Institutional Training Initiative (CITI, http://www.citiprogram.org/) is a subscription service providing research ethics education to many institutions. Other training, such as that provided by the National Cancer Institute (http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp) and the U.S. Department of Health and Human Services

(http://www.hrsa.gov/humansubjects/default.htm), are available on-line.

## 5.1 Informed Consent

In observational human exposure studies, informed consent ensures that the participant accurately understands the range of risks and benefits (if any) associated with participation; emphasizes the voluntary nature of their participation; and provides essential protections to the participant. The three "pillars" of the informed consent process are (1) information; (2) comprehension; and (3) voluntary participation, or "voluntariness" (U.S. DHEW, 1979). Informed consent requires "provision of information to subjects about the purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate" (Emanuel et al., 2000).

The NRC & IOM document *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children* (NRC & IOM, 2005) contains a comprehensive and very useful discussion of informed consent procedures and requirements in Chapter 6. The IOM report, *Responsible Research: A Systems Approach to Protecting Research Participants*, also includes a thoughtful discussion of participant-investigator interactions and the informed consent process (IOM, 2002). CIOMS also includes recommendations for both the process and content of informed consent (CIOMS, 2002). Some of the important points from those documents are summarized in Text Box 5-1, but the reader should refer to those documents for additional information about this topic.

Federal regulations governing research that is either Federally conducted or Federally funded (i.e., all human subjects research at NERL) are codified in the Common Rule. The regulations set forth requirements for both the content of an informed consent and the process for obtaining and documenting an individual's informed consent (see Text Box 5-2).[16] General regulatory requirements for the elements of informed consent are codified in the Common Rule at 40 CFR 26.116(a)(1)-(8) (CFR, 2006). The regulations also prescribe the use of a written consent form and describe how informed consent is to be documented (at 40 CFR 26.117). The regulatory requirements for informed consent highlight a number of issues that a NERL researcher needs to consider in developing and administering the informed consent process and the consent form document. The discussion of these issues, arising from regulatory requirements or identified in recent writings on ethical considerations in human subjects research, is grouped below, under the three pillars of informed consent: (1) information, (2) comprehension, and (3) voluntary participation.

**Text Box 5-1. Recommendations for Informed Consent In the United States and Internationally**

(1) **Revitalize Informed Consent** (IOM, 2002)

Informed consent is a process, not a form. It is an on-going, interactive dialogue between research staff and research participants with disclosure and exchange of relevant information, including assessment of understanding.

Ethics Review Boards should ensure that the focus of both the informed consent process and the consent forms is on informing and protecting participants, *not* the research institution.

(2) **Strengthen Process of Parental Permission and Children's Assent if Children Are Involved in Research** (NRC & IOM, 2005)

The process begins with a community-based discussion and concludes with an assurance that individual parents understand the essential elements of the research.

Educate parents on issues critical to informed decision making and assess their degree of understanding.

Use informational materials in the form that is most appropriate to convey information to potential participants.

Consult with community representatives to ensure that information is complete, clear, and understandable, and that any payment will not be exploitive.

Expand the perspective about what information about risks and benefits is needed to make an informed choice.

Ethically, it is critical to assure that participants and parents understand the crucial features of the research effort.

(3) **Informed Consent Is a Decision To Participate by an Informed, Competent Individual Without Undue Coercion, Influence, or Intimidation** (CIOMS, 2002)

Informed consent is a process that takes time and resources.

It is not a ritual recitation of text from a form but informative communication in language that suits the individual's level of understanding.

Consent is ethically obtained, considering language and cultural issues, and is documented.

Material changes in conditions or procedures require that informed consent be renewed.

Consent should explain how samples will be used in current research, and, if applicable, how samples may be used in future research.

### *5.1.1 Information*

Some items that researchers should keep in mind as they provide information to the study participants are summarized below. These items may be based on regulatory requirements or currently may be recommendations as ethical "best practices."

[16] An IRB may waive informed consent under some very limited conditions. See 40 CFR 26.116(c) and (d).

**Text Box 5-2. Common Rule Requirements: Elements of Informed Consent**

(1) An explanation of the purposes of the research
(2) The expected duration of the subject's participation
(3) A description of the procedures to be followed and identification of any experimental procedures
(4) A description of any reasonably foreseeable risks or discomforts to the subject
(5) A description of any reasonably expected benefits to the subject or others
(6) A disclosure of appropriate alternative procedures that might be advantageous to the subject
(7) A description of the extent that confidentiality will be maintained
(8) For research involving more than minimal risk, an explanation about whether compensation or medical treatments are available if injury occurs
(9) An explanation of whom to contact with questions about the research or to report a research-related injury
(10) A statement that participation is voluntary, refusal to participate will involve no penalty, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
(11*) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable
(12*) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
(13*) Any additional costs to the subject that may result from participation in the research
(14*) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
(15*) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
(16*) The approximate number of subjects in the study

* Included if appropriate [40 CFR 26.116(b)]

- The information "shall be in language understandable to the subject" (40 CFR 26.116). This may require forms to be written and administered in different languages during a study. For example, the National Children's Study (NCS) plans to produce all consent materials in English and Spanish, with other translations made available as needed (NCS, 2007). Ethically, "language understandable to the subject" goes beyond simply using the appropriate language; the researcher is compelled also to consider readability and vocabulary (e.g., avoiding jargon or terminology that may be clear to the researcher but which may confuse or intimidate the potential subject) if the information is to be understandable.
- Information may be presented orally in addition to an appropriately written document (40 CFR 26.117). Participants often find discussions with research staff more useful than written consent forms (p. 103, NRC & IOM, 2005). NCS plans to pilot test an interactive, computer-based audio/video consent tool and to compare it with traditional written informed consent approaches (NCS, 2007).
- The information being discussed, including the explanation of the purpose of the research and the description of the study procedures, should be written or discussed at a level that the participant can understand.[17] The National Institutes of Health recommends writing consent forms as "plain language documents that explain the research in an honest, straightforward way" and suggest that doing so will help enhance public trust (Recommendation 11, NIH, 2005).
- The consent form should contain sufficient information to describe the study procedures, but not so much information that it causes confusion and results in the participant not understanding the study. There is not agreement on what the appropriate level of information is. IRBs do not agree on the level of information; some require lengthy descriptions of the study, whereas others prefer concise information. Ultimately, the IRB dictates the language of the informed consent document, and the researcher will need to comply. It will benefit the researcher to discuss the consent process with their IRB when they develop the consent form document and process (p. 108, NRC & IOM, 2005).
- In observational human exposure studies, information about the risks of the hazards being studied needs to be conveyed to the participants during the consent process. Information should be provided to the study participant on what hazards pertinent to the topic of the study may be present in the participant's environment, particularly those microenvironments being studied, what hazards will continue to exist in those microenvironments after the research is completed, and how those hazards may adversely affect the participant's health (NRC & IOM, 2005).
- The informed consent process should describe whether any study results will be provided to

[17] A survey of IRBs found that their readability standards ranged from 5th- to 10th-grade level (Paasche-Orlow et al., 2003). Interestingly, the same report found that, 92% of the time, the sample consent forms provided by the IRBs did not meet their own readability standards. The NRC & IOM report (p. 107, NRC & IOM, 2005) discusses an NCI effort to simplify informed consent forms by using text targeted at 8th-grade reading level. More information about the NCI template may be found at www.nci.nih.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page2 (accessed September 12, 2007).

participants and, if so, how and when (p. 101, NRC & IOM, 2005).

- For studies involving children as participants, it generally is regarded as desirable that the informed consent process should involve both parents (assuming that there are two competent parents available), and that the consent of both parents be obtained, if possible. The IRB may decide that the permission of one parent is sufficient, but only when certain risk-benefit conditions are met.[18]
- For studies involving children as participants, it is desirable for those children with sufficient capacity to be involved in the consent process. Moreover, it is generally accepted that the child's assent be obtained whenever this is developmentally possible and otherwise appropriate. Under both the EPA Rule and the HHS Rule, the IRB is responsible for determining that adequate provisions have been made for soliciting the assent of the children when, in the judgment of the IRB, the children are capable of providing assent. Assent, however, may be waived in those restricted circumstances in which consent may be waived under the Common Rule. Those circumstances and the required IRB documentation are described in the Common Rule at 40 CFR 26.116(d).
- The consent form should clearly state that participation is voluntary and that study participants may "discontinue participation at any time without any penalty or loss of benefits to which the subject is otherwise entitled" [40 CFR 26.116(a)(8)]. If a subject chooses to withdraw from a study, the consequences of their decision and the process for orderly withdrawal should be clearly explained [40 CFR 26.116(b)(4)].
- The consent form should address any foreseeable potential future use of samples and data (CIOMS, 2002). For example, effects of environmental exposures on gene expression are potentially very important. Therefore, biologic specimens for DNA analysis may be obtained from participants in future studies. But, it is recognized that human genomic data are private, intimate, and sensitive, and they create special concerns about the potential for discrimination, stigmatization, and impact on future employment or insurance. The informed consent process needs to explain what the plans may be for such specimens and recognize the rights of the subjects to decide about any such future use, including having the material destroyed. The informed consent process needs to explicitly discuss obtaining permission from participants on behalf of themselves and their child to obtain specimens for genetic analysis.

### *5.1.2 Comprehension*

Research participants frequently fail to understand the research protocols in which they agree to participate (NRC & IOM, 2005). In considering the ethical issues raised by the *Grimes* v. *Kennedy Krieger* case, the NRC & IOM committee "realized that the crucial issue regarding consent was not what information was contained in the consent forms, but rather what the parents understood about the study and the hazards present in the home before and after the study" (p. 19, NRC & IOM, 2005). The committee laments that "IRBs place their attention on consent forms rather than on the process of providing and discussing information" (p. 103, NRC & IOM, 2005). The IOM recommends that "the informed consent process should be an on-going, interactive dialogue between research staff and research participants involving the disclosure and exchange of relevant information, discussion of that information, and assessment of the individual's understanding of the discussion" (Recommendation 4.1, IOM, 2002). These comments emphasize how important true two-way communication is to comprehension, the second pillar in the informed consent process.

The following items are a variety of issues concerning comprehension that NERL scientists should keep in mind as they develop an informed consent process in collaboration with the research team, the IRB and other peer reviewers, and EPA's HSRRO. These items may be based on regulatory requirements or may simply be recommendations as ethical "best practices."

- Researchers need to assume responsibility for developing an interactive dialogue with participants for the exchange and discussion of relevant information as a part of the informed consent process, not just for conveying information. The dialogue should be ongoing, continuing throughout the research project (IOM, 2002).
- The consent form and its content are only one part of the overall consent process. An equally important part

[18] See the EPA Rule at 40 CFR 26.406(b) for observational research with children and the HHS Rule at 45 CFR 46.408(b) for all research with children. Under the EPA Rule, greater than minimal risk observational research with children that does not hold out the prospect of direct benefit to the child is not permitted under any circumstances. Under the HHS Rule, greater than minimal risk research involving children without the prospect of direct benefit is permitted in very limited circumstances, but the consent of both parents is required in those cases (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child).

is how information is conveyed to the participant outside of the written form itself. Participant comprehension is contingent on all elements of a comprehensive consent process that involves ongoing information exchange between researchers and participants, as well as a written informed consent document (NRC & IOM, 2005).

- The most effective way to improve comprehension is by talking one-on-one with study participants. "Having a study team member or a neutral educator spend more time talking one-on-one to study participants appears to be the most effective way of improving research participants' understanding" (Flory and Emanuel, 2004).
- The information being exchanged (e.g., explanation of the purpose of the research, description of the study procedures) should be written at a level that the participant can understand (NRC & IOM, 2005).
- The researcher should describe the benefits of participation in the study [40 CFR 26.116(a)(3)], but should not promise any outputs or outcomes that he or she cannot deliver. Participants often misunderstand the purpose of the research. The researchers also should attempt to reduce the likelihood of "therapeutic misconception"[19] or related misunderstandings in which the participant anticipates a benefit that does not really exist, such as reduction of the hazard in an observational study (NRC & IOM, 2005).
- The consent procedure should include some test of the participants to demonstrate that they truly understand the information that is being conveyed (IOM, 2002).
- Tools to assess comprehension have been developed, but, as described in NRC & IOM (2005), there are no standard mechanisms for assessing comprehension. Tests for appropriate grade-level language can be performed, but additional comprehension testing should be considered as well (Flory and Emanuel, 2004).
- Researchers need to develop innovative approaches to improve comprehension. Multimedia, such as video or graphics, may be used but have had limited success in the past (NRC & IOM, 2005; Flory and Emanuel, 2004). NCS currently is developing a highly sophisticated video consent tool that may be able to serve as a model going forward. The video presentation will include embedded questions to assess the participant's understanding of the key elements of NCS and what their participation will involve (NCS, 2007).
- Development of written materials with appropriate languages and comprehension levels is only part of the communication challenge. In communities where languages other than English are spoken, it will be important that the research team be able to communicate orally with participants, often in ad hoc situations. Research protocols should address how translations will be accomplished. The use of untrained persons such as co-workers usually will not meet requirements for full understanding of human subject protections. Researchers should make plans for trained staff or trained community members, associated or affiliated with the research study, to be available for translations.

### *5.1.3 Voluntary Participation*

The third pillar of informed consent is voluntary participation. The Belmont Report emphasizes that participants "should understand clearly the range of risk and the *voluntary nature* of participation" [emphasis added]. The ethical principles of respect for persons and their autonomous decisions morally obligate the researcher to ensure that an individual's decision to participate in a human research study is truly voluntary and uncoerced (Emanuel et al., 2000). A number of study characteristics may affect whether the participant's actions are truly voluntary.

- Access to study-dependent benefits or care that would otherwise not normally be received may impair voluntariness.
- Voluntary participation also may be compromised when there is an existing relationship between the researcher and participants, such as employer and employee or teacher and student.
- Restricted voluntariness may be an intrinsic part of belonging to certain vulnerable groups, including children, prisoners, handicapped persons, mentally disabled persons, and economically or educationally disadvantaged persons, or members of the military, for example. When research participants come from such groups, additional protections to insure voluntariness in the context of the research may be required (see also 40 CFR 26, Subparts B, C, and D).
- Payments as incentives may have undue influence and are discussed below.

[19] Therapeutic misconception is a term that refers to an inaccurate understanding on the part of a research participant that a direct therapeutic benefit will be provided by virtue of participation in a clinical trial. Researchers performing observational human exposure studies should be aware of the potential for misunderstandings to arise that are analogous to the misunderstanding represented by the therapeutic misconception. Ensuring comprehension of the study and its expected results is important to this issue.

- Whether payments will lead to a coerced decision to participate often is difficult to determine without input from people from similar socioeconomic backgrounds as the participants (p. 111, NRC & IOM, 2005). Researchers should work with community representatives to develop a consent process that will be maximally effective in providing information, ensuring and documenting comprehension, and ensuring that participation is voluntary (also see Section 6).

Researchers should remember that obtaining informed consent should be "an on-going, interactive dialogue . . . involving the disclosure and exchange of relevant information" (IOM, 2002): it is not simply having a consent form signed. The process is most effective when the researcher spends time with potential participants to discuss the study and to answer questions.

## 5.2 Payments to Research Participants

The decision whether to pay research participants, including the appropriate level of payment,[20] is a complex ethical issue. Monetary or nonmonetary payments are not ethical if they constitute an undue inducement for participants to assume research risks that they would not otherwise accept. On the other hand, it may be ethically appropriate to offer reasonable payments in some research studies. Indeed, payment of human subjects for their participation in scientific research is a common practice in the United States, with a history of well over 100 years (Grady, 2005). The difficulty for researchers and IRBs is that there is often little clear and uniform guidance for determining what constitutes "undue inducement" or "reasonable" payment for any particular research study, population, and level of risk. Additional considerations regarding payment to participants arise when working with vulnerable populations, including children.

### *5.2.1 Types and Amounts of Payments Offered in Research Studies*

Payments have been offered in a wide variety of research studies, ranging from clinical trials to behavioral and social research to observational human exposure studies. Payments can take various forms, including monetary payments (e.g., cash, gift certificates, reimbursement for expenses), nonmonetary payments (e.g., gifts, valuable information), or nothing at all (e.g., for a sense of altruism). Grady (2005) has described payment for the participation of research subjects as serving from one to four purposes: (1) an incentive, (2) compensation, (3) reimbursement, or (4) reward. Text Box 5-3 describes the roles that payments may serve, together with potential advantages and disadvantages or ethical concerns. The text comes mostly from Grady (2005) but builds also on the NRC & IOM document and other writings. (A number of authors have addressed issues associated with payments, including Ackerman, 1989; Dickert et al., 2002; Emanuel 2004; Erlen et al., 1999; Fry et al., 2005; Grady, 2005; Grady et al., 2005; Iltis et al., 2006; IOM, 2004; NRC & IOM, 2005; Russell et al., 2000; VanderWalde, 2005; Weise et al., 2002; Wendler et al., 2002). A number of specific issues or concerns regarding participant payments have been identified. Many researchers and ethicists argue that it is often appropriate to provide reasonable payment and have done so for many years. In the view of an NRC expert panel, the principles of "justice, fairness, and gratitude support payment to those who bear the burdens of research on behalf of society" (NRC, 2004).

Direct reimbursement may be made to participants for out-of-pocket expenses for costs directly associated with participation in a study. These might include transportation costs, parking fees, or child care costs. When payment for time and burden is provided, it is often in the form of monetary payments. Different approaches may be considered for determining reasonable amounts for payment, including a set payment for each visit, a small daily payment, payment at the prevailing minimum hourly wage, or payment at some other hourly rate appropriate for the community—perhaps a prevailing rate for unskilled labor (Emanuel, 2004). Incentives to encourage enrollment are sometimes used when participants will receive little or no direct benefit from the research and can take the form of monetary or non-monetary payments. Incentives are kept modest so as not to impart undue influence. Researchers need to consider the possible effects of incentive payments on the potential

[20] There are many terms that may be found in the literature to describe both monetary and nonmonetary payments, like payment, remuneration, compensation, recompense, incentive, inducement, reimbursement, and reward. Each of these words has its own definition, and each word also may carry specific connotations. In general, these terms refer to money or other items that "are often given to acknowledge the time and inconvenience of participating in research or to reimburse participants for any costs they incur. The term compensation is often used in the context of compensation for research-related injuries" (p. 112, NRC & IOM, 2005). The authors have chosen to use "payment" as the general term for monetary and nonmonetary items provided to research subjects for their participation in the research. They may occasionally refer to compensation for research-related injuries, but the text should make it clear when they do.

**Text Box 5-3. Payments for Participation of Research Subjects**
(based on Grady, 2005)

| Payment Serves As | Amount Determined By | Potential Advantages | Potential Disadvantages |
|---|---|---|---|
| Incentive | Supply and demand; market rates | (a) More rapid recruitment<br>(b) Completion bonuses encourage subject retention and high completion rate<br>(c) Possibility of profit for participants<br>(d) Little or no financial sacrifice by subject | (a) Undue inducement possibly resulting in incomplete assessment of risks and benefits by subject; subject concealing information to ensure enrollment and retention<br>(b) Competition between studies; better funded studies more likely to meet recruitment goals<br>(c) Different levels of payment at different locations for multicenter research because of supply and demand |
| Compensation | Standardized "wage" for time and effort, suggested to be commensurate with wages for unskilled, but essential jobs; additional payment for extra burdens such as endurance of uncomfortable procedures | (a) Recognizes contributions of participants<br>(b) Uniform payment across studies<br>(c) Equal pay for equal work<br>(d) Less risk of undue inducement | (a) May have little impact on recruitment<br>(b) Might undercompensate some subjects in relation to regular wage and preferentially attract others |
| | Provide "wage" for time and effort; base level of payment on some small fraction of participant's or the community's income, or on an appropriate hourly rate for the location, or on community-input about the appropriate level of payment | (a) Recognizes contributions of participants<br>(b) Decreases potential that payment would be undue inducement in some communities or locations and insufficient in others<br>(c) Provides equivalent payment for participation across communities and locations (markets)<br>(d) Less risk of undue inducement across study | (a) Different levels of payment at different locations in multicenter research or in different communities<br>(b) Unequal pay for equal work may violate one's sense of justice |
| Reimbursement | Actual out-of-pocket cost to participant related to participation, such as parking, transportation, child care, cost of food samples, etc. | (a) Lowers barriers to participation<br>(b) Reduces burden and impact of research on participants | (a) Few disadvantages<br>(b) Possible differences in costs experienced by different participants |
| Reward | Token of appreciation at end of study | (a) Expresses gratitude for contribution made<br>(b) Not market dependent<br>(c) Avoids undue inducement | (a) Probably no impact on recruitment<br>(b) No basis for consistency |

for differential recruitment that could result in bias in the study sample.

Determining appropriate level of payments or incentives for participants in a research study is complex. "No bright line distinguishes proper and reasonable payments to parents and children from payments that are inappropriate" (p. 214, IOM, 2004). The ethical issue is at what level might a payment change from being an incentive (an encouragement) to participate and become an inducement (the cause or reason) for participation. Many research organizations and IRBs do not have written policies or guidelines regarding the determination of reasonable payment. Decisions often are made based on the level of discomfort and burden, costs to participants, and population characteristics. However, large differences in payment levels have been found even in multisite studies in which the same protocol is administered across all sites.

Grady et al. (2005) performed a survey of practices for paying research participants in the United States in Phase 1 to 4 clinical trials and physiologic, behavioral, and other types of research. Across 467 studies of varying complexity that included payments, the median

payment was $155 (mean $266, range $5 to $2,000). The basis for dollar amounts was infrequently described, with 19% of the payments based on time, and 12% based on the procedures. In a model of payment factors, studies with some prospect of therapeutic benefit, studies having at least one invasive procedure, and studies with greater numbers of clinic visits were significantly associated with higher dollar amounts. About 9.5% of the studies offered completion bonuses, and a similar percentage offered escalating payments for followup study visits.

### *5.2.2 Regulations and Guidance Regarding Payment to Research Participants*

There is little specific guidance regarding payments in Federal human research regulations. The Common Rule and additional human subjects protections do not directly address payments to research participants, but the regulations do discuss providing additional safeguards for subjects vulnerable to coercion or undue influence [40 CFR 26.111(b)]. The NIH IRB guidebook advises IRBs to determine whether the rewards offered for participation in research constitute undue influence (U.S. HHS, 1993). According to the IRB guidebook undue inducement might blind prospective subjects to risks, impair their ability to exercise proper judgment, or may cause people to lie or to withhold information that would make them ineligible to enroll or continue participation.

The U.S. Food and Drug Administration (FDA) has provided guidance for investigators and IRBs for clinical research studies (FDA, 1998). The guidance states that "payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive." FDA expects payments to accrue as the study progresses and not to be contingent on completing the study, although a "small proportion as an incentive for completion of the study is acceptable." The guidance is concerned with the issue of coercion or undue influence, and it recognizes the IRB as the responsible party for deciding what is or is not acceptable.

The U.S. Office of Management and Budget (OMB) develops standards and guidelines for statistical surveys performed by the Federal government. Under Guideline 2.3.2, OMB states that, while incentives are not typically used in Federal surveys, agencies may consider use of respondent incentives if they believe incentives would be necessary to use for a particular survey to achieve data of sufficient quality for their intended use (OMB, 2006a). OMB requires that agencies provide a justification for giving incentives to respondents. Some of the factors cited by OMB to be addressed include those particularly relevant to observational human exposure studies, including unusual reporting burdens (keeping data logs for extended periods, coordinating study team visits, participating in a medical examination, etc.), complex study designs (such as studies requiring ongoing participation of respondents), and past experience, especially when there is evidence of attrition or poor response rates (OMB, 2006b). Although OMB primarily considers incentives with regard to survey response rates and data quality, researchers need to consider payments to participants, including participation incentives, in the broader context discussed in this section.

CIOMS also provides guidance and commentary on this issue in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002). Guideline 7 and the associated commentary emphasize that payments to subjects for expenses incurred because of their participating in a research study are legitimate. The guideline also allows payment for inconvenience and time spent, so long as the payments or other direct benefits are not "so extensive as to induce prospective subjects to consent to participate in research against their better judgment."

The approaches of HHS, FDA, and CIOMS above are consistent in not considering payments to be a benefit to research participants when considering risks versus benefits. All of the guidelines recognize the legitimacy of some recompense, but they all are concerned with the issue of undue influence. "Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent" (CIOMS, 2002), and voluntariness is a pillar of legitimate informed consent.

Text Box 5-4 lists some of the concerns about, and the reasons for, payment of participants.

IRBs have considerable discretion with regard to payments and consider payments with regard to the specific circumstances of the research and of the population being studied. The issue of recompense can be a difficult but legitimate ethical issue involving weighing the different ethical principles of justice and fairness against the concerns about undue influence and the invalidation of consent. Ethical review committees, including IRBs, need to consider many factors when determining when it is appropriate to offer payments to research participants and the level and form of payments when they are appropriate. Review committees also should consider how and when information on payments is communicated to prospective study participants.

**Text Box 5-4. Weighing the Ethical Issues About Payments**

| Concerns about Payments | Reasons for Payments |
|---|---|
| • Payments may compromise voluntary participation.<br>• Participants may accept risks they would not otherwise accept.<br>• Participants may continue in a research study beyond a point they might ordinarily have withdrawn.<br>• Payments may differentially encourage research participation by economically disadvantaged people.<br>• The offer of payments may cause guardians or parents to not act in the best interests of incompetent persons or children in their care.<br>• Persons in different circumstances may view the same amount of payment quite differently.<br>• Payments may alter the composition of the study sample and potentially could compromise study integrity. | • Recognizing participant contributions to the research and knowledge gained<br>• Providing reimbursement for direct and indirect participant costs<br>• Providing reasonable payment for the time and effort associated with participation in research<br>• Providing incentives for participation in studies with low risk but no or few direct benefits<br>• It is the just and fair thing to do for those who bear burdens of research on behalf of society. |

### *5.2.3 Payments When Children or Other Vulnerable Populations Are Involved*

It is essential that special care be taken with regard to payments when members of vulnerable populations are included in research studies. Vulnerable populations may include children and adolescents, those with cognitive impairments because of medical conditions or age, economically disadvantaged persons, and prisoners. These populations often are not capable of making autonomous, fully informed decisions regarding risks and benefits, or they may be particularly vulnerable to undue influence resulting from the offer of a payment for research participation. In addition, payments made directly to parents or guardians could alter judgment regarding the best interests of minor or incompetent persons in their care.

The ethical concern is that too high a payment may "undermine free and informed consent by leading parents to expose their children to unacceptable risks" (NRC & IOM, 2005). The NRC & IOM committee recognized that some commentators argued that children should never be paid, and that parents ought not to be paid to enroll their children in research. Yet, on balance, the committee felt that "reimbursement for expenses and some modest payment for time spent in research activities is thus justified on the grounds of fairness" (p. 112, NRC & IOM, 2005).

Similarly, the IOM Committee on Clinical Research Involving Children found that "certain types of payments to parents or adolescents are usually if not always acceptable, for example, reimbursement for reasonable expenses that are necessary for research participation. The specifics may vary, but examples of reasonable expenses are costs of transportation to the research site, parking, lodging, meals, and babysitting. Other payments are never appropriate in pediatric research, for example, paying parents for the use of their child in research" (pp. 225-6, IOM, 2004).[21]

The IOM committee recommends establishing policies on acceptable and unacceptable types of payments. They also recommend that the policies disclose any recompense in a full and open process,[22] while not overemphasizing any recompense.

Although the NRC & IOM Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children and the IOM Committee on Clinical Research Involving Children both concluded that it is appropriate to reimburse expenses or compensate for time or inconvenience, neither committee endorsed incentive payments to parents. In Europe, too, incentive payments to induce parents to allow their children to

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[21] The IOM Recommendation 6.2 states, "In addition to offering small gifts or payments to parents and children as gestures of appreciation, investigators may also—if they minimize the potential for undue influence—act ethically to reduce certain barriers to research participation when they

- reimburse reasonable expenses directly related to a child's participation in research
- provide reasonable, age-appropriate compensation for children based on the time involved in research that does not offer the prospect of direct benefit, and
- offer evening or weekend hours, on-site child care, and other reasonable accommodations for parental work and family commitments."

[22] In recommending an open process, the IOM committee chose to reject the arguments from the American Academy of Pediatrics that "any token payment to children for participating in research should not be discussed with them until after research is completed for fear of unduly influencing their decisions (AAP, 2003)…. On balance, the committee agrees that it is best to mention token or other payments during the permission and assent processes" (p. 215, IOM, 2004).

The IOM Recommendation 6.1 states, "Institutional review boards, research institutions, and sponsors of research that includes children and adolescents should adopt explicit written policies on acceptable and unacceptable types and amounts of payments related to research participation. These policies should specify that investigators

- Disclose the amount, the recipient, the timing, and the purpose (e.g., an expense reimbursement or a token of appreciation to a child) of any payments as part of the process of seeking parents' permission, and, as appropriate, children's assent to research participation;
- Avoid emphasis on payments or descriptions of payments as benefits of participating in research during the permission or assent procedures; and
- Obtain institutional review board approval for the disclosure of information about payments in advertisements and in permission and assent forms and procedures."

participate in research are unacceptable. The European Union requires that clinical trials on minors be undertaken only if "no incentives or financial inducements are given except compensation" (European Parliament, 2001).

Payment for participation of children in research also is discussed in the literature. Diekema (2005) emphasizes the need to ensure that payments do not distort parental decisionmaking and do not tempt parents to consider other issues than the welfare of their child. Similarly, Menikoff (2005) suggested that there need to be relatively robust protections in place to ensure that families do not change their behaviors to participate in a study. He suggested that these may include determining payment as a percentage of a family's income and developing criteria for documenting that behaviors have not changed to be eligible for participation in a study. He suggested that, for a study of pesticides, potential study participants provide documentation (such as receipts) that they routinely have been using a commercial pesticide service. This may be difficult for potential participants to do if they do not save receipts, and it would exclude all potential participants who purchase products and apply pesticides themselves. This likely would affect the study objectives and generalizability of the data collected. A survey of investigators (Iltis et al., 2006) found that payments were made in 52% of the pediatric research studies surveyed, and that payment practices varied, as did the reasons for decisions regarding payments. They found a range of payment values separated across cash, gifts, items, vouchers, and other categories. A survey of IRBs (Weise et al., 2002) found that payment for participation in research was allowed by 66% of responding institutions, but that many IRBs did not have specific policies, and that there was considerable variability regarding the basis for decisions on payments in studies with children. The types of payments included money, certificates, and bonds with large ranges in the amounts of payments for approved pediatric research. This research shows a lack of consistency and the need for guidance and institutional policies that describe acceptable and unacceptable payments and the basis for the amount of any payments.

The NRC & IOM Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children described many of the ethical considerations, practices, and policies regarding payments (NRC & IOM, 2005) for research conducted in the participants' homes, rather than in a clinical facility. The research setting is similar to the setting of most observational human exposure studies, and the committee's commentary and recommendations are also relevant. The committee notes that it would be unfair to expect families to make considerable sacrifices to participate in a time-consuming activity designed to advance generalizable scientific knowledge, rather than benefit themselves directly, and that payment for reimbursement of expenses and modest payment for time spent in research activities is justified on the grounds of fairness. But the committee then warns that if payments are too high, they may distort parents' decisions about enrolling their children. The committee also found that "*how* the payment is made may also result in undue influence. For example, if payment for a long-term follow-up study is made in a lump sum and only if the subjects complete the entire study, then it could constitute an undue influence to stay in the study. If, on the other hand, the money is paid weekly, the effect would not constitute an undue influence."

The NRC & IOM committee recognizes that the issue of payment for participation in research is controversial. They also discuss how "countervailing ethical guidelines" may complicate the issues even more. Citing Wendler et al. (2002), the NRC & IOM committee points out that payments that are trivial for some families may be substantial for low-income or disadvantaged families. "Yet to pay economically disadvantaged families less than more affluent families for participating in the research is unfair because it requires similar sacrifices of time and inconvenience from both" (p. 113, NRC & IOM, 2005). Similar ethical quandaries can arise in multisite studies with differing costs for living. If the same payment is used in high-cost cities as in low-cost areas, the payment may be inadequate to gain sufficient enrollment in the high-cost area, whereas the same dollar amount may be "coercive" in the low-cost area. The NRC & IOM committee notes that a similar situation can arise when a study enrolls participants from diverse socioeconomic backgrounds. There are social justice concerns that poorer people might incur a disproportionate share of research risk and burden if payments induce unequal participation rates in the population. Decisions regarding payment for research participation will require careful consideration by IRBs when economically disadvantaged people may be enrolled. Community advisory boards (CABs) can be very important in helping researchers and IRBs determine what is appropriate with regard to payments within their community.

### *5.2.4 Payments in Observational Human Exposure Studies*

Observational human exposure studies most often involve minimal risks to study participants and few direct benefits, but may require considerable time and burden for participation. Study requirements can include multiple in-home visits; the burden of wearing personal air monitors for one or more 24-hour period; preparing and providing duplicate diet samples; collection of environmental samples inside and outside the home; completing questionnaires, food diaries, and time-activity diaries; and providing urine, blood, saliva, or hair samples. Monetary payments often have been included in these studies, with the level of payment related to the number of study days or visits or the specific kinds of environmental and biological samples and information that are collected or provided. Payment for direct participant costs has been included in some studies, such as a reasonable payment for providing researchers with duplicate diet samples.

NERL scientists should review the commentary and recommendations in the literature before devising a payment program as part of a research protocol, especially the two recent National Academies of Science documents, *Ethical Issues in Housing-Related Health Hazard Research Involving Children* (NRC and IOM, 2005) and *Ethical Conduct of Clinical Research Involving Children* (IOM, 2004). They should seek guidance from EPA's HSRRO to determine EPA's latest policies and guidance in this regard. Input also should be sought from community representatives to ensure that any payment is adequate to compensate for expenses and reward participation, but that the payment is not so high as to constitute undue influence or coercion in the community. If the study includes several followup visits over a long term, NERL researchers should ensure that payment is made incrementally as the NRC & IOM committee suggested. NERL scientists also should adopt the IOM Recommendations 6.1 and 6.2, including ensuring that any payment should be for appropriate purposes and age-appropriate, and that the process should be open and fully disclosed, while not overly emphasizing payments during the recruiting or informed consent phases. The final decisions about the ethics of payments rest with the IRB, which will review, modify as needed, and approve the research protocol, and with the EPA HSRRO, who has final authority to approve, modify, or disapprove all of NERL's human subjects research efforts.

## 5.3 Research Rights and Grievance Procedures

Protecting the research rights of participants and providing independent access to information regarding those rights and to grievance procedures is an important element in developing and maintaining appropriate participant-investigator relationships. As part of the informed consent process, the Common Rule requires "An explanation of whom to contact for answers to pertinent questions about the research and human subjects' rights, and whom to contact in the event of a research-related injury to the subject" [40 CFR 26.116(a)(7)].

Information about the research often best can be answered by the researcher. However, it may benefit researchers and participants if information about the research can be obtained from or confirmed by a trusted independent person or organization. Participants also need to know how they can contact someone, independent from the researcher, who can answer questions concerning the rights of research participants and provide information on grievance procedures and research-related injuries. These questions could be addressed to the IRB, an ombudsman, an ethics committee, or other knowledgeable administrative body. Consent documents are expected to have at least two names with appropriate telephone contact information—one that can provide information regarding the research and another that can provide information regarding their rights as research participants. Grievance procedures should be structured so that grievances reach the approving IRBs and sponsoring organizations.

### *5.3.1 Ombudsman*

An ombudsman is a neutral independent advocate for research participants (and their families or guardians, where applicable). Institutions and IRBs may recommend or require the use of an ombudsman in certain types of research studies, particularly those seeking to study vulnerable populations. Ombudsmen can fill several roles as participant advocates. They may be an independent source of information regarding the study. They may be present during the informed consent process to ensure that risks, benefits, and study requirements are communicated correctly and understood by potential participants or their guardians. An ombudsman may be used in studies involving prisoners or military personnel to ensure that there is no coercion to participate. And the ombudsman may

communicate problems or grievances raised by research participants to the IRB and sponsoring organization.

### *5.3.2 Community Advisory Board*

CABs can help ensure that participant rights are considered and addressed during the study design and can play an important role in monitoring the research process. Community members may choose to seek information about the study from the advisory panel, as an independent entity, before deciding whether to enroll. Representatives from such advisory boards can be included in the research team that designs the study (see Section 2.3). The role of CABs is more fully discussed in Section 6.

## 5.4 Creating a Supportive Environment for Research and Interaction

It is recommended that researchers and institutions strive to create a supportive environment for research and interaction with research participants and communities. At the personal level, this means researchers building trust with individuals and treating them with respect. Following the IOM recommendations about the informed consent process—that it "should be an on-going, interactive dialogue between research staff and research participants involving the disclosure and exchange of relevant information, discussion of that information, and assessment of the individual's understanding of the discussion" (Recommendation 4.1, IOM, 2002)—should go a long way in establishing a supportive environment with the individual participants. At the community level, engagement of the community throughout the design, conduct of the study, and follow-up will support trust-building and positive interactions. Developing and providing this kind of support can be challenging in large-scale studies, and particularly those that cross communities or are conducted across large geographic areas. Institutions need to recognize the need for, and value of creating supportive research environments by providing adequate funding because effective interaction takes considerable time and effort.

Many of the factors that create a supportive environment for research participants are described in the *Report and Recommendations on Public Trust in Clinical Research for the NIH Director from the Director's Council of Public Representatives (COPR)* (NIH, 2005). Although the advice from this workshop was developed in the context of NIH-supported clinical research, many of the recommendations are applicable to observational human exposure studies and human subject research in general. A summary of recommendations from the report for enhancing public trust is provided in Appendix D. The recommendations are focused on the following areas.

- Building trust through community partnerships
- Building relationships with patients (participants) (True partnerships with patients may not be possible, but bidirectional relationships must be enhanced.)
- Building partnerships with community providers
- Building trust in scientists
- Building trust in the (EPA) and scientific research.

## 5.5 Recruitment Strategies

Many strategies are used to select and recruit people into research studies requiring human participation. The IRB is responsible for reviewing the selection process to ensure that it is, above all, equitable. The requirement for IRB review is stated in 40 CFR 26.111(a)3.

> Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB guidebook is an excellent resource for consideration of concerns and elements for equitable participant selection (U.S. HHS, 1993). It states that "Defining the appropriate group of subjects for a research project involves a variety of factors—requirements of scientific design, susceptibility to risk, likelihood of benefit, practicability, and considerations of fairness." The IRB guidebook raises a number of points to consider in the process for selection of human participants (see Text Box 5-5).

Various participant recruitment strategies may be used depending on the type of research being performed and the population of interest. This section addresses the strategies and approaches for identifying and contacting people and subsequent recruitment into a research study. Sampling design approaches and issues, such as statistical issues regarding representative and nonrandom sampling designs, oversampling of subpopulations, and environmental justice considerations are part of the study design process described in Section 2 and are critical for deciding which recruitment approaches will be used.

**Text Box 5-5. IRB Guidebook Issues on Identifying Subjects**

1. Who will bear the burden? Who will reap the benefits?
2. Is there a disproportionate burden on any single group?
3. Is the proposed subject population required or justified?
4. Are there susceptible groups of people who should be excluded from the research?
5. Are anticipated benefits distributed fairly? Do others have a greater need to receive any of the anticipated benefits?
6. Are the research burdens distributed fairly?
7. Will any special physiological, psychological, or social characteristics of the subject group pose special risks for them?
8. Would it be possible to conduct the study with other, less vulnerable subjects?
9. Has the selection process overprotected potential subjects who are considered vulnerable (e.g., children, cognitively impaired, economically or educationally disadvantaged persons, patients of researchers, seriously ill persons), so that they are denied opportunities to participate in research?
10. If the subjects are susceptible to pressures, are there mechanisms to reduce the pressures or minimize their impact?

Some of the common approaches for identifying and making initial contact with potential participants include, but are not limited to

- direct telephone or in-person contact with a person selected through a statistical sampling process to obtain a representative sample of the population being studied;
- use of print or other media advertisements, often used to recruit people in a community with specific characteristics;
- advertisement or word-of-mouth contacts through community groups, civic organizations, or other types of organizations; and
- recruitment at physicians' offices, hospitals, and clinics or at churches, schools, or other social institutions, either in person or through the use of advertisements or study brochures.

CABs can be consulted regarding proposed approaches for recruitment in community-based research. All procedures and materials for participant recruitment are reviewed and approved by the IRB prior to implementation. Some of the materials prepared for recruitment might include the following.

- Recruitment scripts—prepared scripts used for in-person or telephone study information and recruitment contacts
- Printed materials—brochures, flyers, newspaper advertisements, letters, and information articles
- Audio/visual materials—radio and television scripts, video segments, public service announcements
- Internet postings—study announcements and information, links to study materials, links to related information.

The IRB reviews all recruitment material to ensure that it does not adversely affect the informed consent process, is consistent with the study protocol, and is likely to result in equitable participant selection. IRBs will carefully consider how information regarding payment for participation is presented to potential participants so as not to create undue influence.

Participant recruitment may be performed directly by the researcher or staff members of the researcher's organization, or other individuals or organizations may be asked to recruit or make initial informational contacts with potential participants. All persons involved in recruiting must adhere to the procedures and materials approved by the IRB. It is recommended that sponsoring organizations should not pay recruiters on a per-individual basis to minimize the likelihood that individual recruiters will put undue pressure on potential participants to enroll.

## 5.6 Retention Strategies

Some observational human exposure studies require only a single visit or a single set of visits with a participant over a relatively short time period (e.g., 24 hours or 1 week). Other studies may involve repeated interaction with participants over longer periods of time. Longitudinal study designs require retention strategies that ensure that adequate sample sizes are maintained for meeting study objectives. It is recommended that researchers and IRBs evaluate the level of burden in longitudinal studies and ensure that retention strategies are not likely to create conditions of coercion or undue influence.

Some of the common strategies for maintaining high retention rates in longitudinal studies are listed in Text Box 5-6.

**Text Box 5-6. Common Strategies for Maintaining High Retention Rates in Longitudinal Studies**

- Developing and maintaining a strong study identity
- Building participant trust
- Communicating regularly with participants
- Providing feedback that is of use to participants
- Maintaining confidentiality
- Incorporating active participant tracking mechanisms
- Maintaining reasonable levels of burden
- Providing periodic tokens of appreciation
- Providing reasonable levels of payment at each time point, sometimes including escalating payments or a higher final payment for completion of all study activities

It is important that strategies that use payments to encourage retention should be carefully scrutinized against the possibility that they will result in undue influence or diminish voluntary participation. Payments that cover expenses and for time and burden at each visit have to be reasonable, and researchers and IRBs should consider whether the cumulative level of payments over time or the use of escalating payments or final bonus payments might present undue influence on decisionmaking regarding participation. Participants have to feel capable of withdrawing from participation at any time, and escalating payments or completion bonuses can impact decisions to withdraw. Withholding all payment until all study visits are completed or making payment contingent on completing all activities is not an acceptable practice in most longitudinal studies because it can diminish the capacity for voluntary participation. (See the discussion about payment issues in long-term studies in Section 5.2.3.)

People are more likely to continue active participation in longitudinal studies when they believe that the research is important, and that they are making a valuable contribution, are receiving regular feedback, and are treated with courtesy and respect by researchers. Observational human exposure studies sometimes involve substantial burdens of time and effort. Over long periods, this level of burden can reduce retention. It may be necessary to develop novel methods that reduce participant time and effort or to focus the study design so that fewer study procedures are implemented at any time point. Because the time needed to analyze samples, verify results, and perform data analyses can be long, it may be difficult to provide timely feedback to participants in observational human exposure studies. Researchers might consider including simple measures that can provide immediate and useful information of value to participants to encourage continued participation. Effective use of these strategies will reduce the need for higher payments to encourage retention.

## 5.7 Ensuring Recruitment or Retention Methods Will Not Lead to Unacceptable Risk

Researchers and IRBs need to ensure that the procedures and materials used to recruit and retain study participants in observational human exposure studies do not "undermine free and informed consent by leading parents to expose their children to unacceptable risks. (NRC and IOM, 2005)" Payments in these studies should not be so high that they would cause an undue inducement for a participant to use a product they would not normally use or to perform an activity that they would not normally perform. Not only would this bias the study results but may lead to higher than normal levels of exposure. Alternatively, the act of studying one set of conditions or activities in an observational human exposure study could lead participants to assume that those conditions or activities involve substantial risk. In response, they subsequently may change their activities in ways that could lead to possibly higher risks. The potential for such unintentional outcomes is difficult for researchers to gauge but requires researcher caution in how information and results are conveyed. However, if the informed consent process is truly "an on-going, interactive dialogue . . . involving the disclosure and exchange of relevant information," then such misunderstandings should be minimized.

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## SECTION 6

# Building and Maintaining Appropriate Community and Stakeholder Relationships

Community engagement promotes active community involvement in the processes that shape research strategies and the conduct of research studies. In developing this document, NERL held an expert panel workshop to identify the content and organization of this document (ERG, 2007). That panel of experts concluded that the need to engage the community in observational research was based on the ethical principles of (1) respect for persons, which manifests itself in both a respect for the individual and, through respect for the community, their culture; (2) fairness, resulting in efforts to assure equity in resources, burden, and benefits; and (3) beneficence, including "empowering the community to endure."

Involving the community in the research effort can improve the research both scientifically and ethically. In the document, *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children*, the joint NRC-IOM committee found that community involvement was a "guiding theme" of their findings (NRC & IOM, 2005). Because the researchers were working in the homes and communities of the participants, they faced issues that were different from a clinical setting. They were challenged to think about the fundamental ethical principles in the context of the research setting and about how those ethical principles should be interpreted in that setting. "When researchers discuss a planned study with community representatives, understand their concerns and needs, and respond to them, protocols can be strengthened both scientifically and ethically" (p. xii, NRC & IOM, 2005). Just as was described in Section 5, where the informed consent process was described as needing to be "an on-going, interactive dialogue between research staff and research participants involving the disclosure and exchange of relevant information, discussion of that information, and assessment of the individual's understanding of the discussion" (Recommendation 4.1, IOM, 2004), so, too, the process of community involvement should be a process of effective two-way communication. These NRC & IOM comments emphasize how critical effective, bidirectional communication is to the scientific and ethical foundation of a research study in such a setting.

EPA has established a public involvement policy to "improve the content of the Agency's decisions and enhance the deliberative process" (U.S. EPA, 2003) (see Text Box 6-1). The policy is focused largely on Agency decisionmaking processes (e.g., rulemaking, permit issuance, Superfund remediation, etc.), whereas observational human exposure studies are intended to provide data to inform those decisionmaking efforts. Nonetheless, the Agency policy may be helpful in planning for community involvement in observational human exposure studies. The policy is intended to promote mutual trust and openness between EPA and the public, to improve the quality of the Agency's actions, and to promote the public's involvement in the Agency's mission of promoting human health and the environment. The policy identifies seven basic steps for effective public involvement and offers guidance for implementing public involvement at EPA.

**Text Box 6-1. Seven Basic Steps for Public Involvement at EPA**

1. Plan and budget for public involvement activities.
2. Identify the interested and affected public.
3. Consider providing technical or financial assistance to facilitate involvement.
4. Provide information and outreach to the public.
5. Conduct public consultation and involvement activities.
6. Review and use input, and provide feedback to the public.
7. Evaluate public involvement activities .

## 6.1 Approaches to Community Involvement

Community involvement can take many forms. The forms of community involvement are not mutually exclusive, and researchers may use several approaches for seeking community involvement. The nature and extent of community involvement reasonably would depend on the nature of the research itself and the affected community. In Section 2, the authors discussed some reasons for involving the community early in the research planning and scoping process and the benefits that community involvement may bring to the research effort. "Community residents can be involved in the research process as research staff, through community consultation and review, membership on community advisory boards, and involvement in a community-based participatory research process" if that is used (p. 83, NRC & IOM, 2005). In addition, IRBs may seek additional community representation on the IRB panel.

The Centers for Disease Control and Prevention (CDC) recommends nine governing principles for engaging communities in health-related research (see Text Box 6-2). Health research is a "privileged and empowered activity in that the researchers have special access to resources and sensitive information about people and, through the analysis and presentation of findings, are able to influence the way people think and have considerable influence on decisions regarding the allocation of resources" (CDC, 1997). Regardless of the approach utilized to involve the community in research, whether the process employs community-based participatory research (CBPR) or another community engagement method, researchers should guide their interactions with community members using these underlying principles to promote the aforementioned ethical principles of respect of persons, fairness, and beneficence.

One form of community involvement is to include qualified members of the community on the research staff. Section 2 advocates community representatives as part of the research team. Paid research staff members from the community could serve as valuable consultants for protocol development and research design, including how to collect the data, how to recruit and retain participants, and how to interpret and disseminate the results. However, including paid research staff from the community may introduce a conflict of interest among community members: community representatives may feel a greater allegiance to the researchers providing the payment and be less inclined to uphold the interests of the community. In addition, the community may come to view the paid research staff from the community as "outsiders." To help alleviate these potential issues, researchers should ensure an equitable distribution of paid research work among different communities within the larger community as to not promote a perceived bias among community members. Additionally, when possible, researchers should make efforts to provide payments to community members employed as research staff through community partner organizations to prevent conflict of interest issues. Refer to Section 5 for further discussion on remuneration of community members as research participants.

**Text Box 6-2. Community Engagement Principles for Researchers**
(From CDC, 1997)

| Requirement | Explanation |
|---|---|
| Clarity | Clear communication of the study objectives, research goals, and the populations or communities of interest. |
| Knowledge of the Community | Familiarity with the economic conditions, political structures, demographics, history, past research experiences, and research perceptions of the community. |
| Visibility | Travel to the community, interact with formal and informal leadership, and establish relationships to build trust. |
| Acceptance | Acknowledge, without judging, the assets and deficits of the community. |
| Partnership | Balanced discussion and shared decisionmaking among participants concerning risks, responsibilities, expectations, benefits, and investment. |
| Respect | Value the diversity of culture, history, beliefs and opinions within the community for improved understanding. |
| Asset Utilization | Identify and mobilize community assets to improve scientific credibility of the interpretation and dissemination of results. |
| Flexibility | Anticipate changes within the community in regard to perceived benefits of research and stakeholder interest and additional time and resource needs. |
| Commitment | Prepare to engage the community beyond the constraints of the research projects, before and after, to promote longevity of the relationship for future research . |

Furthermore, institutional and community partners need to ensure that anyone involved as part of the research team has the requisite research and social skills. Researchers often place a greater emphasis on scientific over social skills and may, in turn, assume that they have

the necessary expertise to conduct research in community settings. Likewise, research staff from the community should have knowledge of research fundamentals. Education and training targeted at both the institutional researcher and the community researcher may, respectively, improve the competence of researchers to work with communities and the scientific literacy of the public.

A recent NERL study, the Detroit Exposure and Aerosol Research Study (DEARS), included community members as paid members of the research team. The community researchers were instrumental in recruiting study participants from the seven study neighborhoods in Detroit that required multiple door-to-door visits to the homes of potential participants to discuss the DEARS study. The success of DEARS was dependent on researchers developing strong relations with community leaders and State and local organizations.

A second approach to community involvement is to seek community consultation and review. Researchers may periodically meet with community residents in a process of "engagement, dialogue, and feedback" (Dula, 1994) to discuss research plans, research progress, and results. The objective is to seek a dialogue with community residents to promote co-learning and asset sharing between the researchers and the community. Effective communication—open, honest, jargon free—is imperative to the successful use of this approach. Effective communication ensures that the community has a voice in the research process for the expressed purpose of increasing the community's trust and engagement in the research, the applicability of the research to the community's needs, and the benefit of the research to the community. Authentic community consultation embraces the "experiential knowledge of the average citizen" (Leung et al., 2004). When developing research budgets and timescales, researchers who plan to incorporate community consultation and review in the research process should take into account the additional expenses and time necessary for community marketing efforts and travel.

Corburn (2002) describes a successful community participation in an EPA exposure assessment in Brooklyn, NY. He explains how a shift of focus from risk assessment to exposure assessment may provide an opportunity for community engagement to improve the technical assessment. Listed among the specific factors integral to the assessment's success are the incorporation of local, nonexpert information by community groups during the consultation and review process that was used to modify the conventional risk assessment process and the inclusion of community-based organizations on the scientific research team as contributors to the data collection, modeling, and interpretation processes, where they provided data and expertise not available through traditional research frameworks (Corburn, 2002).

Community advisory boards (CABs) also have been used as an approach for getting the community involved in the research effort. A CAB could be formed to serve as a liaison between participants and researchers. In particular, CABs can advise the researchers about community concerns and assist in the development of materials to explain the study to potential participants. CABs should be sufficiently large to ensure a diversity of community views, perspectives, and attitudes. Representatives from the board may be selected for participation on the research team. In Section 5, it was noted by the authors that such a board could function as an oversight committee in case of any participant grievances. According to Quinn (2004), the success of CABs "lies in the ability of the researchers and CABs to form a true partnership, enabling their different voices to be heard equally." Creating a CAB may be perceived as "window dressing" and, in fact, harm relationships with the community if researchers are not truly open to working with the CAB.

O'Fallon and Dearry (2002) describe how the Tribal Efforts Against Lead (TEAL) partnership collaborated with EPA to clean up and minimize exposure to toxins from a Superfund site in Ottowa County, OK. The TEAL project utilized the services of a CAB, which included representatives from several local tribes, to ensure that the research would be responsive to the needs and concerns of the tribal residents. The CAB facilitated the researchers interactions with the target communities "by helping the investigators interpret data and distribute information to the communities" and "developing and conducting the training" of the community members on risk reduction strategies. The value of the research to the TEAL target communities would have been diminished had a CAB not been formed to assist the researchers with specific best practices to use when engaging the tribal members and the appropriate tribal leadership structures.

Another potential approach to involve the community is to use a CBPR approach, wherein the community is actively involved in each step of the research process, including sharing of decisionmaking power and resources. This will impact decisions about study design, study methods, dissemination of findings, and resulting actions. "Under the principles of community-based participatory research, research must

address the concerns, needs, and priorities of the communities where it is conducted and lead to actions and changes that benefit the community" (p. 86, NRC & IOM, 2005). Information about CBPR approaches can be found online at the HHS Web sites http://www.ahrq.gov/clinic/epcsums/cbprsum.htm and http://www.ahrq.gov/research/cbprrole.htm.

Israel et al. (2005a) reviewed the results of CBPR efforts at six Children's Centers co-funded by EPA and the National Institute of Environment Health Sciences. They found that considerable commitment of resources and time are needed for the approach to be successful, and the translation of research findings into interventions and policies is of the utmost importance. Community partners played little role in defining the research topics and data analysis, but were vital to disseminating the findings to the community. Keeler et al. (2002) describe using CBPR methods to evaluate personal and community-level exposures to particulate matter among asthmatic children in Detroit. The research partnership, Community Action Against Asthma (CAAA), consisted of representatives from local health organizations, community environmental advocacy groups, State and local governmental agencies, and academia. The CAAA partnership credits community involvement as active research partners in the research process with the success of the project to acquire "more relevant exposure data for the study of children in urban neighborhoods" and to provide "immediate knowledge and understanding of the outcomes and results of the combined environmental health analysis to the communities" (Keeler et al., 2002).

There are, however, several drawbacks to utilizing CBPR methods that researchers should consider before developing a CBPR project. CBPR is time consuming (develop partnership, establish and agree on research aims and objectives, disseminate results to the community using appropriate methods, and review manuscripts and presentations) and not conducive to situations where rapid decisions are necessary given a tight timeline. Weighing the research need versus the community's desire for an intervention is the greatest source of tension in conducting CBPR (Israel et al., 2005b).

One additional opportunity for community input may involve participation on an IRB. IRBs are required by the Common Rule to have members who are sensitive to "community attitudes" [40 CFR 26.107(a)]. How they meet this obligation is totally at their discretion, and NERL researchers have no influence. There have been a number of recent articles in the literature about IRBs that have envisioned a need for more regulatory reform (Ledford, 2007). Ideally, the IRB should take into account the views of the community. Quinn (2004) argues for extending protections now reserved for individuals to groups (populations and communities) through CABs. Her argument is that there are "ethical issues related to research with communities that are distinctly different from the ethical issues related to research with individuals." CAB members have to be educated on human subjects' protections, should represent their communities honestly, and need to be willing to interact with researchers on complex research issues.

Gilbert (2006) goes even further. He suggests supplementing or even replacing traditional IRBs with environmental health and community review boards (EHCRBs). He argues that traditional IRBs are inadequate for the review of community-based research because they were developed to address issues related to individuals involved in research projects, not communities. He proposes EHCRBs that combine the fundamental and ethical concept of traditional IRBs with an expanded ethical construct of dignity, veracity, sustainability, and justice, with added emphasis on community. He envisions that an EHCRB would function as an IRB with the requirements and responsibilities for review for the protection of human subjects, plus the additional role for review of community issues associated with the research project.

Gilbert's recommendation for EHCRBs is consistent with the recommendations of the authors of the NRC & IOM report who recommended that "Institutional review boards that review housing health hazards research involving children should ensure that those boards have the necessary expertise to conduct a complete and adequate review, including expertise on research involving children and community perspectives" (NRC & IOM, 2005).

Involving community representatives in the IRB process is challenging for IRBs, however. One challenge could be the need to provide sufficient training to community members about the IRB process and the regulations governing IRBs. This can be significant if members sit on an IRB for a limited time to review specific community-based studies. In some cases, IRBs may invite community members to participate in the IRB process as nonvoting members to solicit the community perspective. This approach, which would be totally at the discretion of the IRB, might reduce the burden on the community representative by reducing training requirements.

## 6.2 Issues in Community Involvement

There are a number of issues that need to be addressed in any efforts to ensure community involvement. The Expert Panel that was convened to advise NERL about scientific and ethical issues in observational human exposure studies discussed a number of challenges (ERG, 2007). The topics that the expert panel identified as issues are discussed below.

### *6.2.1 Defining "Community"*

"Community" refers to a group of people united by a shared attribute, and the attributes can be wide-ranging, such as geography, culture, social characteristics, values, interests, traditions, or experiences (ERG, 2007). *Community* can be defined broadly (as a system of interrelated groups operating to meet the needs of its members) or more narrowly (as the population from which study participants are selected). For observational field studies, the Expert Panel from the workshop suggested the narrow definition. A narrow definition allows social and cultural factors to be included but excludes government agencies, industry, and others who do not necessarily represent the interests of the participants (ERG, 2007).

Central to the definition of a community is a sense of "who is included and who is excluded from membership" (NRC & IOM, 2005). A person may be a member of a community by choice, as with voluntary associations, or by virtue of their innate personal characteristics, such as age, gender, race, or ethnicity (NRC & IOM, 2005). As a result, individuals may belong to multiple communities at any one time. When initiating community engagement efforts, one should be aware of these complex associations in deciding which individuals to work with in the targeted community.

Quandt et al. (2001) discuss a CBPR research project, Preventing Agricultural Chemical Exposure in North Carolina Farmworkers, where the process of defining a community was complicated by language, ethnic and racial stereotypes, and lack of organization. Many of the affected farmworkers originated outside the United States from several different Spanish-speaking countries and possessed contradicting viewpoints on research and the utility of community organization. Moreover, the community organization tailored for this farmworker demographic did not include enough members to adequately populate the study. The researchers utilized multiple approaches, including community forums, community advisory councils, and public presentations, to identify a diverse, yet viable, community within the broader farmworker population. Through this process of using multiple participatory strategies to define the community, a sense of community was nurtured among the farmworkers collectively (O'Fallon and Dearry, 2002).

Understanding and describing a community (CDC, 1997) involves exploring factors related to

- people (including socioeconomics and demographics, health status, and cultural and ethnic characteristics),
- location (geographic boundaries),
- commonalities (including shared values, interests, and motivating forces), and
- power relationships (including formal and informal lines of authority and influence, stakeholder relationships, and resource flows).

It is important to distinguish between stakeholders and the community, but both should be engaged at some point in the course of a study. Stakeholders are groups or organizations that may affect, be affected by, or perceive themselves to be affected by a decision or activity. Stakeholders may have a direct or indirect interest in the "matter" of interest. They may include individuals; environmental, social, or community nongovernment organizations (NGOs); government entities; businesses; and industry. Stakeholders include business, industry, and various levels of government. A critical difference between the community and stakeholders is that the community has a right to speak for its own interests, but stakeholders cannot represent or speak for the community. Although relationships with stakeholders can, at times, be confrontational, stakeholders often provide useful information and expertise. When stakeholders and the community members overlap in particular individuals, it is important to distinguish the role in which the individual is acting (ERG, 2007).

### *6.2.2 Identifying Who Represents the Community*

To sufficiently represent the community, an individual has to have not only the right to speak for the community's interests (a right afforded by legitimate membership in the group) but also should be able to describe those interests on behalf of the community. Identifying those who represent the community is not simply a matter of identifying the most vocal activists because those individuals do not necessarily represent the interests of the entire community. In fact, several individuals may be necessary to adequately represent the diversity of viewpoints within a community; in such cases, a CAB may be appropriate (ERG, 2007). One of the researcher's first steps should be asking the potential participants from the community who they see as a

legitimate representative (i.e., someone who can speak for them). Corburn cites an example of a locale in Brooklyn, NY, that contained individuals with widely different backgrounds. It was impossible to identify appropriate spokespeople, or even to define the nature of the community, without talking with community members (Corburn, 2007).

The NRC & IOM (2005) Report also discusses the issue of who can represent the identified community. Some communities may have a formal governmental structure and a recognized political authority (e.g., Native American tribes). Other communities may have clearly identifiable leaders (e.g., religious communities), whereas still other communities have no formal leadership structure at all. Whether there is a legitimate political authority or some other hierarchal leadership structure, the goal is to seek community input as to who best represents the interests of the community with regard to the proposed research project, rather than selecting those who are favorable to the research project. The NRC & IOM report cautions against the ethically questionable practice of seeking out population spokespeople and research participants whose positive response to a research plan can be predicted in advance and refers the reader to an article on this topic by Juengst (2000).

With multiple sources of leadership and authority in many communities, careful consideration should be given to what aspect of the community a particular person will represent, and what efforts may be needed to ensure that the entire range of views in a community are obtained. Researchers should consider reaching out to multiple organizations such as churches, social service agencies, community-based organizations, and tenant and other community advocacy groups.

### *6.2.3 Building Relationships and Trust*

A key first step in developing trust is to establish a relationship with the community before the study. Trust must be built; it cannot be assumed. This relationship involves not only listening to community input but actually taking it into consideration (ERG, 2007). A long history of research with no direct benefits and no feedback of results to the community, however, has contributed to a general mistrust of researchers by community members (Israel et al., 1998). Moreover, the recurring abuse of trust in communities is a reality that researchers should be aware of when attempting to build a long-term relationship (Minkler and Wallerstein, 2003). Past ethical failures have created distrust among some communities and have produced great challenges for current community organizers. Although it may seem self-evident, researchers need to remember that ethical action, during all phases of the research, is necessary for developing and maintaining the trust of communities (Perkins and Wandersman, 1990; CDC, 1997).

Developing trust is a difficult and time-consuming process. Israel et al. (2005b) suggest a number of ways partners can gain each other's trust. First, partners can *show respect* by seriously considering the ideas and opinions of others. Second, trustworthiness can be demonstrated by *following through* with those things that each partner commits to. Third, partners have to *respect confidentiality*. Fourth, they recommend *attending to each other's interests and needs* by participating in activities beyond the specific work of the partnership.[23] A history of prior positive working relationships is also beneficial (Israel et al., 1998).

Trust cannot be separated from respect. Potential participants need to see researchers fostering respect for community members and leaders to gain trust. For example, meeting with key community leaders and groups in their surroundings helps to build trust for a true partnership. Such meetings provide organizers of engagement activities with more information about the community, its concerns, and factors that will facilitate and constrain participation. Once a successful rapport is established, the meetings and exchanges with community members can become an ongoing and substantive partnership (ERG, 2007).

One mechanism for helping to build trust may be a contract with the community. A community contract outlines the roles and expectations of both the researcher and the community. Living up to these agreements builds trust with all partners, and the establishment of the agreement helps reduce misunderstandings. Contracts or memorandums of understanding that outline the roles and expectations of the researcher and the community are discussed in both Minkler and Wallerstein (2003) and Israel et al. (2005b). An example outlining expectations in a partnership with tribal communities is presented in Appendix E of Minkler and Wallerstein (2003), whereas an example discussing access to data and authorship issues is presented in Appendix I of Israel et al. (2005b). An example of a memorandum of understanding between the University of Michigan School of Public Health, Detroiter's Working for Environmental Justice, the Detroit Hispanic

[23] For a more detailed description of each of the suggestions for enhancing trust, please see Chapter 3 of Israel et al. (2005).

Development Corporation, and the Warren Conner Development Coalition for a study investigating asthma is available at http://depts.washington.edu/ccph/pdf_files/MOU10.pdf.

Work within communities involves a considerable investment of researchers' and residents' time. It should be an ongoing, interactive exchange of information and ideas between the researchers and the community members, where voices are both heard and honored. Trust is fostered when all interested parties feel that they have influence, and that their input contributes to the community effort. The collaborations should be inclusive of the entire community, including those members with incompatible interests and perceptions. If participation, influence, and benefits are limited only to some of the partners, then distrust is likely, and the potential benefits of community involvement may be lost. Being inclusive can create some organizing challenges, but the benefit of effective community involvement "has the potential to lead to greater understanding of community perspectives of the risk and benefits of research, improve informed consent, increase study enrollment, enhance data validity and quality, and build trust for research" (NRC & IOM, 2005).

### *6.2.4 Importance of Language and Communications with the Community*

Even when all partners and community members are speaking the same language, some terms are not necessarily understood by all. Communications with participants should be reviewed by all partners to ensure that the language used will be appropriate for all participants. At times, one method to communicate research findings will not fit all community members and partners. Even among the partners, understanding each other's meanings is essential, so that all partners can move forward with a common understanding (Israel et al., 2005b).

Furthermore, Minkler and Wallerstein (2003) note that "research must be produced, interpreted, and disseminated to community members in clear, useful, and respectful language." Researchers, and especially researchers in a government agency, may have their own distinct lexicon. Researchers should be careful to avoid acronyms, jargon, or technical terms that may obscure the meaning or intimidate participants who are not familiar with the terms. Communicating in "plain language" to "explain the research in an honest, straightforward way" will help build a strong relationship with the community and the participants and also help enhance public trust (Recommendation 11, NIH, 2005).

Culturally sensitive communication is necessary to developing effective research partnerships with communities. To develop effective communications, researchers must understand key aspects of the cultures influencing the intended audience and build that understanding into the communication strategy (Tillman, 2002). The symbols, metaphors, visuals (including clothing, jewelry, and hairstyles), types of actors, language, and music used in communication materials all convey culture. Discussions with community members can assist researchers in identifying messages and images that resonate across groups or suggesting situations in which different messages or images are likely to work best.

As discussed above and in Sections 5 and 7, communication materials must be tailored for each individual community and must be written in a language and at a reading level that will ensure comprehension. Many IRBs require materials to be prepared at a 5th grade reading level. Researchers should evaluate the reading level of all data collection instruments and study communication materials and should objectively measure comprehension in pretests prior to use in the study. Similarly, if translations of materials are required, certified translating services should be used to ensure accuracy and comprehension.

### *6.2.5 Recognizing and Addressing Cultural Differences*

Building and maintaining appropriate community and stakeholder relationships requires acknowledgment of the diversity within communities with regard to many factors, including, but not limited to, race/ethnicity, religious beliefs, heritage, and lifestyles. Different groups in the study area may have different cultural norms and practices. The researchers should take these issues into consideration as they work in the community. Community partners can help researchers design the study to be attentive to the increasing heterogeneity of community groups (Minkler and Wallerstein, 2003, Chapter 4) and to the different boundaries of privacy (crucial when designing sampling strategies) of different groups (Israel et al., 2005b, Chapter 11).

Vega (1992) provides a thorough discussion of the theoretical and pragmatic implications of cultural diversity for community research and explains that researchers should interact with communities using methods that promote understanding and demonstrate sensitivity and competence in working with diverse

cultures (e.g., with respect to class, gender, ethnicity, race, age, and sexual orientation). To aid in this process, researchers should include sufficient time in their project timeline to interact and dialogue with the community before the study begins to understand the cultural issues that may affect the research. Researchers and the results of their work are expected to promote a strengthening of the community; however, it should be recognized that, given the heterogeneity and the diverse views within a community, the study findings potentially may conflict with the desires of the community or may promote feelings of anger or distrust among members of the community with each other. Enlisting the services of a third-party evaluator/mediator may be useful for sustaining positive relations between all research participants and the community at large.

The Research Triangle Park Particulate Matter Panel Study (Williams et al., 2003), a NERL investigation of PM and related pollutants involving African-Americans in North Carolina, demonstrated an effective strategy for using communication to address cultural differences between the community and research personnel. Before beginning the research, the study design included time and a budget for building collaborations with organizations having close ties with the African-American community to establish trust between the community and research team. Using input from the community partner organizations, the researchers developed a systematic communication plan to establish rapport with the community and to guide interaction between study participants and the key study personnel. A well-designed and culturally sensitive communication plan was integral to the success of the study. Eighty percent of the original participants completed the four-season study (Williams et al., 2003).

### 6.2.6 Honesty, Power Relationships, and Partnerships

The NRC & IOM report (NRC & IOM, 2005) describes a relational paradigm that acknowledges that research is part of a broader societal context, with the conduct of research often mirroring a system in which power is unequally and perhaps unfairly distributed. The trust and mutual commitment required from the researchers and the community are subject to the overall power relations in society.[24] The Expert Panel convened to discuss the content of this document recognized that the researchers have a variety of forms of power that needed to be understood and acted on ethically (ERG, 2007). One form of power is resources, both funds and access to resources and decisionmakers. Other forms of power may be more subtle, including expertise, which can intimidate or limit a participant's choices. Peer pressure, fear of intimidation, expectations of benefits from the research, and power to stigmatize the community all, whether real or perceived, can influence the relationship between the researcher and the community. Many forms of power may be tipped toward the researcher, but the community often has power in the form of knowledge about the community that can impact the quality of the research effort. An ethical balance of power can lead to benefits for all partners (ERG, 2007).

In describing principles in *Methods in Community-Based Participatory Research for Health*, Israel et al. (2005b) describe CBPR as facilitating "a collaborative, equitable partnership in all phases of research, involving an empowering and power-sharing process that attends to social inequalities." One way to address the inequities is to ensure that the roles and responsibilities are mutually acceptable to all parties. Researchers involved in CBPR should recognize and address the inequalities, thereby promoting trust, mutual respect, open communication, information sharing, collaborative decisionmaking, and resource sharing.

It is important that researchers recognize that partnerships with the community are ongoing processes that need to be monitored and maintained. As a study progresses, the dynamics of the partnership may change as roles and responsibilities for the partners change. All partners need to be willing to make the investment of time and resources necessary to maintain an effective partnership.

### 6.2.7 Building a Lasting Infrastructure

*Infrastructure* is anything that builds the capacity of the community by providing its members with skills and resources. Infrastructure building ideally occurs throughout the project and should be included in the overall plan (ERG, 2007). When involving the community in the planning process, investigators need to be forthright regarding funding limitations and research expectations, such as publication and dissemination of results. The community needs to be made aware of the ephemeral nature of funding, even if it results in apprehension toward involvement.

Researchers should communicate early on those issues that will become important once the research has been completed, such as sustainability. Frankness is

[24] A discussion of the evolution of theories on power relations, including the contribution of feminism, poststructuralism, and postcolonialism, can be found in Minker and Wallerstein (2003, Chapter 2).

required to cultivate the community's confidence and expertise over time. Because so much time and investment is involved in building an appropriate relationship with the community, researchers may wish to continue their relationship with the community even after the study has ended. Researchers should remain accessible for technical support related to the subject of the research. Helping community members identify new funding opportunities and assisting with the writing of grant applications are two examples of potential continued relationships. Many private sponsoring institutions already recognize the importance of enduring commitment and have used a variety of approaches, often involving funding, to ensure that these relationships are able to continue (ERG, 2007). The challenge will be for universities and Federal agencies to be able to establish similar funding mechanisms.

The objective of capacity building is to involve members of the community in certain roles (e.g., performing interventions), training them to perform some of the functions initially performed by the research team. Certain research grants specifically support this type of training. Training can be reciprocal, and allowing the community to train the researchers (for example, in cultural sensitivity) not only fosters respect but also can lead to important new understanding.

Another important step is to formalize the relationship between the community and the institution conducting or sponsoring the research, not just between the community and the individual researcher. Institutional relationships can survive even if individual researchers leave. Institutions may be reluctant to build enduring relationships with communities if they do not see long-term financial value in this investment. Researchers may be able to get more support from their institutions if they can document their successes (ERG, 2007).

## 6.3 Community Involvement in Observational Human Exposure Studies

Observational human exposure studies, like those conducted by NERL, benefit from community involvement. Scientific rigor apart from ethical considerations fails as good science. Community involvement in research ensures that ethical standards are a priority in the study design and are pursued by the researchers throughout the study. The form and extent of community involvement will vary, depending on the scope and utility of the research effort. The nature of the community—the population from which the participants are selected—often will vary considerably from one study to the next, ranging from a small group involved in a pilot study to a randomized, representative sample of the whole population. As a result, the nature of the community involvement also will depend on the particulars of the study. The typical lack of direct benefit from observational human exposure studies may mean that many research efforts cannot meet all of the principles of CBPR. Nonetheless, community involvement should be included in observational human exposure research efforts to the fullest extent possible. As the NRC & IOM committee observes (p. 98, NRC & IOM, 2005):

> Community involvement, though time and resource intensive, is a necessary and useful component of… research with the potential to enhance trust and increase the relevance of research to affected communities. Thus, attention to the issues raised by the community and consideration of the most appropriate method of community involvement for a given research project is warranted.

NERL researchers also should consider the recommendations set forth in the NRC & IOM report (Recommendation 5.1, p. 98, NRC & IOM, 2005) as they develop their research plans and protocol.

> Researchers…should describe in their protocols and IRB submissions how they have involved and will continue to involve the affected community in the research project, justify the lack of such involvement, and report how they have responded to any community concerns.

Researchers and the members of the communities in which they work should recognize, however that the primary role of the researcher is to be an advocate for the science, not an advocate for the community. Although being an advocate for the community is desirable, and in many projects achievable, it should be recognized that resource constraints and potential conflicts of interest may impact the researcher's ability to advocate for the community, particularly if it involves regulatory activities of the Agency.

## 6.4 Identifying and Interacting with Other Stakeholders

Like community involvement, stakeholder involvement in a research study can take many forms. Also like community involvement, researchers should engage stakeholders in their studies early in the planning stages. The relationship between the researchers and various stakeholders should be maintained during the study. How this relationship is maintained can be expected to vary with different stakeholders and may

change as the study progresses. Stakeholders can provide useful information and perspective during the planning and implementation of observational human exposure studies.

Stakeholders may include individuals, NGOs, businesses, industry, and various government entities or agencies with jurisdiction over or interest in the community. Stakeholders are a separate entity apart from the community, although they may conduct business or operate within the community or have a direct or indirect interest in the community's activities. Even though they are not able to speak for the community, stakeholders may have knowledge of impacts and ideas about how to interpret and use the results of proposed research studies. Such knowledge may prove very helpful as part of the research planning and scoping (ERG, 2007). Including a variety of stakeholders in the planning process provides insight that comes from reconciling the disparate perspectives of different stakeholders.

Observational human exposure studies conducted or supported by NERL may have many potential stakeholders, both internally in EPA and outside of the Agency. Internal stakeholders include the ORD Office of the Science Advisor, the Office of Science Policy, other laboratories and centers in ORD that may be interested in the study and its results, program offices, and the regional offices. Outside of the Agency, other Federal, State, and local agencies may be stakeholders. For example, CDC may be interested in biomonitoring studies. State agencies will be stakeholders when research is done in their state. Examples of NGOs that may be external stakeholders include the Natural Resources Defense Council, Environmental Defense, American Lung Association, American Academy of Pediatrics, American Chemistry Council, and literally hundreds of other organizations with interests in environmental or public health issues. Researchers should identify potential stakeholders and communicate with them early in the planning stages of a study if they are determined to be appropriate. Identifying the appropriate stakeholders who have a legitimate interest in the study will be done on a study-by-study basis and should be done in consultation with the research team, the community representatives, and senior management. In EPA, the Office of Public Affairs can assist in identifying contacts in stakeholder groups.

The concept of "stakeholder" has been discussed in management literature since the 1980s. Mitchell et al. (1997) have developed an approach for identifying the relevant stakeholders through an assessment of their power, legitimacy, and urgency. Such an approach may be useful for identifying stakeholders to be involved in the research studies. In describing CBPR, Israel et al. (2005b) discuss the need to examine the advantages and disadvantages of extending membership beyond the "community of identity" at the outset. For example, they discuss the relative merits of including representatives of the agricultural industry in a study of farmworkers because of industry's possible role in policy change and weigh their inclusion against the concerns that the true voice of the farmworkers may not be heard under such conditions. They also describe a possible solution of creating separate partnership groups. O'Fallon and Dearry (2002) explain the benefits of including diverse stakeholders for the dissemination of results.

Successful interactions with stakeholders will require effective communication strategies and materials, as is discussed in the following section. After relevant stakeholders have been identified, they should be contacted to inform them of the proposed research study and to determine their interest in the study. If the stakeholders express an interest in participating, the research team should develop a plan for interacting with the stakeholders that includes roles and responsibilities, activities, and timelines that are mutually agreeable to the team, community representatives, and the stakeholders. There needs to be a clear agreement on the plan with all parties involved. Failure to have such an agreement may lead to misunderstandings of the roles of the stakeholders. As planning for the study proceeds, the plan for stakeholder involvement should be updated to reflect activities and timelines for longer term engagement.

When developing relationships with stakeholders, researchers also should ensure that participation of the stakeholder in the study, regardless of level of participation, does not result in actual or perceived conflicts of interest. This should be addressed in the plan and agreement for stakeholder involvement.

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## SECTION 7

# Designing and Implementing Strategies for Effective Communication

Successful implementation of observational human exposure studies requires effective communications between the researchers, study participants, community representatives, community members, stakeholders, and the public. The previous two sections established the need for communications that are "on-going, interactive dialogue…involving the disclosure and exchange of relevant information, discussion of that information, and assessment of the individual's understanding of the discussion" (Recommendation 4.1, IOM, 2002). NIH advocates "plain language" that explains the research "in an honest, straightforward way" (Recommendation 11, NIH, 2005). Indeed, strong relationships can be built with participants, the community, and stakeholders only if there are clear and effective communications between the researchers and the community. The previous section illustrates, also, that effective communication is bidirectional; it involves listening as well as "speaking." The ethical value of respect for persons, including respect for one another's autonomy and welfare, demands that researchers, participants, community members, and stakeholders strive to establish effective communications and to foster a relationship of trust and respect. The researchers should make a commitment to effective communications and make the appropriate investment of time and resources to ensure that the communications are at an appropriate level and are truly effective. Researchers should regard communications as intrinsic to the ethical basis for the study.

With the ethical basis for bidirectional communication assumed as a given, and the need for open and honest bidirectional communications having been well established in the previous sections that discussed relationships between the researchers and the participant (Section 5) and the researchers and the community (Section 6), this section discusses strategies and tools that researchers may find useful in developing effective communications. The focus in this section is primarily from the perspective of "getting the word out," because that is the aspect of communication most under the control of the researchers. Nonetheless, effective communications will be bidirectional and involve effective listening. Researchers should keep in mind that it is as important to listen to the participants, community, and other stakeholders as it is for the researchers to provide them with information using the approaches described in this section.

## 7.1 Communication Strategy and Implementation Plan

Fundamental to achieving effective communications are a communications strategy and implementation plan. In general, the goal of the communication strategy and plan is to clearly define how effective bidirectional communications will be achieved in the study. Specific goals should be developed based on the specifics of the study design, the study population, the community, and the stakeholders. The plan will describe who will be involved in the communications, what communications are required, and how the communications will be performed. The communication strategy and implementation plan should be developed early in the planning stages of a study. The communication plan, however, needs to be dynamic, with revisions and updates occurring throughout the study and in collaboration with the community and stakeholders.

Text Box 7-1 lists elements that should be included in a communication plan. The communication strategy should be developed based on the goals of the study and an understanding of the background, education, attitudes, and opinions of the stakeholders and the community that will be involved in the many different aspects of the study from the initial conceptualization to the final reporting of the study results.

**Text Box 7-1. Elements in a Communication Plan**

- Background information description (overview) of the study, relevant historical background information, statement of communication needs, and identification of communication opportunities and issues
- Purpose and goals of the communication strategy
- List of individuals and groups involved in the communications, plus relevant demographics and other information to profile the groups
- Strategy and approach for achieving the goals, including a statement of the primary message to be conveyed and descriptions of the communication channels
- Activities and materials to achieve the goals of specific elements of the plan to be performed
- Timetable
- Roles and responsibilities
- Resources needed (budget)
- Measures of effectiveness

Careful planning is required to develop a communication plan that will be effective. The research team has to invest the time and resources necessary to develop and implement the plan. They also should recognize that the communication plan is essential for conducting the study and is just as important as the study design, human subjects research protocol, or QAPP. The observational study, if properly justified as described earlier, provides a social and scientific value and brings benefit to society (and perhaps the participants); it should be a program that the researchers want to discuss and explore with the public. The communication plan and strategy provide the researchers with an opportunity to create effective bidirectional communications with the participants, community, and stakeholders. They are not simply a way to "avoid problems" with the community, stakeholders or the media nor only a plan for reacting to "negative" feedback.

Recognizing that the communication strategy must address the bidirectional nature of communications with the study participants and the community to be effective, it is important that the communication strategy and implementation plan be developed in collaboration with the community and other stakeholders. As discussed in previous sections, members of the community in which the study will be performed will provide valuable input into the development of the communication strategy by providing information about the community culture, norms, attitudes, perceptions, etc. They will provide, not only expertise about the community, but also experiences and lessons learned about previous communications activities in the community. It is important to engage community representatives and stakeholders early in the process of development of the communication strategy, the implementation plan, and the communication tools.

Researchers also may find it helpful to seek guidance on how to communicate more effectively, especially because that is not a routine part of their training or experience. They may consult and learn from communications specialists in their organization. In addition, a wide variety of resources are available. For example, the Federal Communicators Network (FCN) (www.fcn.gov) has prepared a "communicators guide" that offers advice on how to communicate—in plain language, in easily digestible "chunks," and in a form that will be used. They emphasize that "good communication is difficult because it requires a lot of effort, time, and patience" (FCN, 2001). Some tips from the guide to help federal communicators get their point across are listed in Text Box 7-2.

**Text Box 7-2. Tips for Getting Your Point Across**

- Be prepared.
- Be confident.
- Stay focused on your conversation and your listener.
- Maintain eye contact with your listeners.
- Make sure your listeners are following you by asking them for questions or feedback.
- Do not lose your temper or get over-emotional.
- Speak slowly and calmly; don't raise your voice.
- Speak clearly and concisely.
- Get to the point; do not ramble.
- Be kind, compassionate, and empathetic.
- Be honest; do not play games.
- Be assertive but tactful

## 7.2 Individuals and Groups Involved in the Communications

An effective communication plan will identify and involve all of the individuals and relevant groups that should be included in the communications efforts. When conducting observational human exposure studies, this list may be quite long. Although researchers may desire to limit the number of individuals and groups involved to keep the effort as simple and focused as possible, they need to ensure that all potential stakeholders are identified. The communication plan should identify all groups, including community organizations and stakeholders, involved in a study, their roles and responsibilities in the study, how communications will be developed with each group, and the timing of the communications. It is likely that most studies will involve the individuals, community groups and stakeholders shown in Text Box 7-3.

**Text Box 7-3. Individuals and Groups Involved in Communications**

- Principal investigator—the researcher with ultimate responsibility for the study
- Research team
- Study participants
- Third parties associated with study participants (e.g., spouse, children, landlords)
- Community representatives
- Community members
- Governments (local, State, and Federal)
- Study institution management
- Study sponsors or funding organization
- Organizations with interest in the participants, the community, or the research question
- Stakeholders that may be impacted by the results of the study
- The scientific community
- Media
- The general public

The study participants are a key group involved in communications during a study and are easily identified. Similarly, it is generally not difficult to identify the third parties associated with the study participants, because these groups must be identified when considering ethical issues in the study and when developing the human subjects research protocol. Research teams should ensure that the communication strategy includes the strategy and approach for third-party communications.

As discussed in Section 6, it is critical that community representatives are identified early in the scoping and planning phase of the study. It is important that researchers are informed about the community in which they will conduct the study and understand the unique characteristics and culture of the community and the potential study participants to develop effective bidirectional communications. When possible, researchers should identify other research organizations who have worked in the community and attempt to gather information from them on the nature of the community, who represents the community, and what communication strategies have been used previously in the community. Understanding how the community defines itself or thinks of itself is critical to establishing effective communications.

Identification of all relevant stakeholder groups may be more difficult. As defined in Section 6, the term stakeholder is used here to identify a person or group who has a valid interest in an activity or decision, but who does not speak directly for the community or the participants. There may be many organizations who consider themselves as stakeholders that represent the interests of the community, the participants, or the research problem. For example, there are many nonprofit organizations that advocate for the protection of children's health. When conducting an observational study involving children, the research team should identify those groups that could have an interest in the study. They need to be identified in the communication plan, and an approach needs to be developed for communicating with them about the study. There are many sources of information on potentially interested stakeholder groups. This information can be obtained from the research team based on similar studies, the participants, the community representatives, sponsoring organizations, and "umbrella" organizations for various advocacy groups. The Internet has made identification of the various stakeholder groups easier and is a source of information on goals of the groups and contact information. Approaches for communications with these and other groups on the list are discussed further in the following subsections.

Researchers should recognize that identifying and involving all pertinent community and stakeholder groups in their observational human exposure studies is important for effective communications and the potential success of the study, but that there is the potential for the group to become so large that it becomes difficult to manage. Large groups not only have the potential for impeding progress on a research effort simply because of the logistics of the interactions within the group, but, also, because of the potential for conflict between the groups. It is essential, therefore, that researchers attempt to maintain stakeholder groups of manageable size and be prepared to deal with potential conflict within the groups. There is extensive literature available on conflict management, but it is outside of the scope of this document to recommend specific approaches or literature references.

## 7.3 Communications Timetables—When To Communicate

Communications begin with the initial conceptualization of the study and continue through the reporting of the study results and beyond. Even after a study has ended, followup communications may continue with the study participants, the community, the scientific community, and the public. It is beyond the scope of this document to lay out timetables for communications in observational human exposure studies because timing will differ with each study. The following discussion highlights a few of the issues associated with the timing of communications to ensure

that they are effective. This section also does not discuss communications among the research team, research organization, or study sponsors.

Researchers should begin the dialogue with the community as soon as possible during study conceptualization and planning. Once the community in which the study will be performed is identified, community representatives should be identified and contacted to discuss the potential study and to get input on how the study may be designed. As discussed in Section 6, the observational human exposure studies discussed in this document are generally not CBPR. Although the study objectives or hypotheses have been defined and the general approach has been developed, the community still can provide valuable input about their environmental or public health concerns. Again, as discussed earlier, the planning for the study should be flexible enough to incorporate community concerns where feasible. Recognizing that many observational human exposure studies will not be able to address all of the community's concerns, it is important that the communications with the community accurately convey the value, merit, and benefits from the study that will be relevant to the community.

Press releases can serve as useful tools for informing communities about upcoming studies and for identifying stakeholders. Assuming that community representatives have been identified early in the development of the study design and communications strategy, and that community buy-in for the study has been gained, researchers can work with community leaders and community members to develop press releases and other communication tools. Press releases can serve multiple purposes. They provide information to potential community representatives who may not have been identified by the researchers as potential collaborators in the study. They provide publicity that will inform community members about potential contacts by the research team (e.g., in a random sample design). They provide information to public interest and advocacy groups who may feel that they are stakeholders who should be involved in the study. Press releases also provide the transparency for the study and the research team that is essential for building trust.

Studies also should be announced to stakeholders and the public (via the media, community interactions, or other means) well in advance of study implementation. Large grants expected to have significant impact in communities often are announced by EPA at the research institution receiving the grant and in press releases to the local media. These studies, therefore, are publicized at a very early stage. Cooperative agreements, which are another mechanism by which the government funds some research projects, are announced in the same way. Cooperative agreements and studies performed by EPA researchers receive additional public notice when they are reviewed by the Office of Management and Budget (OMB) under the Paperwork Reduction Act. All studies involving collection of survey information from more than nine people are reviewed by OMB. This involves submission of an Information Collection Request (ICR) to OMB, announcement of the ICR in the *Federal Register*, and an opportunity for public comment. A docket is established specifically to facilitate public comment. This process results in widespread publication of upcoming government research studies through scrutiny by concerned stakeholder groups who routinely review the announcements in the *Federal Register*.

Prior to the start of data collection in a community, relatively large-scale communications may be required. These communications may involve notifications to public safety officials about the presence of the research team in the community, press releases to local media outlets about the study, and meetings with community groups to provide details about data collection activities.

It is essential that the research team fosters continuing bidirectional communications with the participants, community, and stakeholder groups throughout the study to maintain transparency, trust, and interest in the study. This can be aided by providing project progress reports and interim results to the participants and the community through community meetings, mailings, or Web sites. In observational human exposure studies with repeated measurements over seasons or years, routinely meeting with participants can serve as a mechanism for providing study information to the participants and receiving feedback from the participants and the community about the study and their roles in it. Effective bidirectional communication with participants can be expected to improve their participation in the study (e.g., in completing surveys and collecting personal samples) and for improving retention in longitudinal studies. However, it is essential that the researcher recognize the implications of such meetings on privacy and confidentiality issues for the participants and develop communications to advise the participants of these issues.

Community meetings also are effective for maintaining communications throughout a study. They provide the opportunity to disseminate information to

community representatives and to obtain feedback. They also provide an opportune setting for news releases to the media to maintain or increase interest in the study.

## 7.4 Communicating at Different Levels

The diversity of interested people and groups often means that communications materials should be developed at different levels of scientific literacy. In any case, the materials should all be written in "plain language" that is honest and straightforward. Stableford and Mettger (2007) state that "plain language embodies clear communication." Many researchers mistakenly believe that the term means just using simple words, or worse, ''dumbing things down.'' It actually refers to communications that engage and are accessible to the intended audience.

A 1998 Presidential memorandum required that "plain language" be used in all governmental communications with the public. That memorandum stated, "By using plain language, we send a clear message about what the Government is doing, what it requires and what services it offers. Plain language saves the Government and the private sector time, effort, and money." Plain language is reader friendly and designed to increase the participant's understanding of the communication material. It serves as a means by which lay audiences can access and understand scientific information. Researchers desiring to use plain language in their verbal and written communications with communities must decide on key messages to include and delete unnecessary descriptive, bureaucratic, or jargon-filled language. Researchers should use words that commonly are understood, rather than difficult abstract terms and concepts. A friendly, conversational tone is used to engage the lay audience, rather than a formal, scholarly tone that distances the community. Stableford and Mettger (2007) argue that proficiency in creating appropriate plain language materials is an acquired skill that requires knowledge and experience. "It is both an art and a science, requiring the ability to simultaneously think about the cognitive, emotional, and visual appeal of the piece as well as applying research-based strategies to ensure a truly easy-to-read and understand print material."

The Department of Health and Human Services (HHS) has developed a Web site that specifically address the issues related to "plain language" (see http://www.health.gov/communication/literacy/plainlanguage/PlainLanguage.htm). The site includes a list of references and other helpful resources.

To maintain community engagement through the research process, it is critical that communications are at the appropriate level, and that materials are written at a reading level that is appropriate to the audience. For the nonscientist, many IRBs and other groups target materials to be used with participants and communities at a reading level no higher than the 8th grade to improve the likelihood of comprehension. In some communities, however, other factors, like primary languages other than English, educational disadvantages, etc., may require communications materials to be written in alternate languages and at different reading levels. The issue is comprehension, as was discussed in Section 5.1.2. Empirical testing of communication methods and content is essential to ensure comprehension (Health Canada, 2006).

Researchers also should recognize that in this information age, dissemination of informational materials may be rapid and widespread. Therefore, even documents intended for scientific peers may benefit by including summary information in an executive summary or preface that a lay reader can understand.

## 7.5 Communications Materials

Researchers need to communicate clearly with the many groups listed in Section 7.2 to develop their relationship with the participants in the study, to develop their partnership with the community, to gain support from stakeholders, and to inform the public. To achieve the multiple purposes of communications during a research study and to communicate with many diverse groups, a variety of communications materials may need to be developed. Different materials have different purposes and different types of information to be communicated. Because of diversity in interested individuals and groups with respect to education, cultures, information needs, etc., the format and content of communication materials likely will need to be diverse. Text Box 7-4 list activities and materials that may be helpful in facilitating communications.

By definition, communication is an exchange of information. This has to be the primary goal of communication activities. The accuracy and completeness of the information transferred is important. There are many different ways to communicate, the effectiveness of which varies substantially. The way in which the information is conveyed is as important as the information itself. Effective communication should promote trust and credibility. Peters et al. (1997) found that three determinants, namely, (1) knowledge and expertise, (2) openness and honesty, and (3) concern and

care, were important factors determining perceptions of trust and credibility. Therefore, the approach to communication in observational human exposure studies should consider these factors, and communication materials should be developed with these factors in mind.

**Text Box 7-4. Activities and Materials That May Be Useful in a Communication Plan**

- Flyers
- Web sites
- Brochures
- Interviews
- Newsletters
- Focus groups
- Presentations
- Direct mailings
- Press releases
- Questions and answers
- Desk statements (government)
- Abstracts
- Study reports
- Talking points
- Community meetings
- Stakeholder meetings
- Technical presentations
- Study participant meetings
- Scientific meeting presentations
- Peer-reviewed scientific journal manuscripts
- Final reports describing the total research effort

When developing communication materials, the researcher should consider the needs of the reader, listener, or viewer with respect to content, scope, style, and the level at which the materials are written. There are many sources of information on design of informational materials, such as flyers or brochures. For example, Alderson (1995) provides an example of the recommended content and style for information leaflets (that also may be flyers or brochures) for pediatric medical research. She suggests that leaflets be provided to parents of children who will be study participants that can be read to the children. She recommends that these be provided at the time that the parent is being informed of the study, prior to requesting the informed consent. The content of the leaflet would include the following topics.

- Nature and purpose of the research
- Anticipated benefits of the research
- Risks, harms, costs, and inconvenience to the participant
- Assurance that the participant freely can refuse to participate in or withdraw from the study
- Details about remuneration
- Names of the project sponsors and the researchers
- Contact information for the researchers
- Respect for privacy and confidentiality

Leaflets and brochures that contain this information provide a tool for communication with study participants. However, these materials need to be written carefully using everyday terms that the average nonresearcher can understand. The brochure should be written in a friendly style that conveys the intent of the researcher to engage the reader as a collaborator on the study, not as a study "subject," who will be told to do a series of tasks while participating in the study.

These same leaflets and brochures can be used to inform other groups that either may be involved or interested in the study, such as community representatives, stakeholder organizations, the media, and the general public. The researcher should ensure that any brochure developed for the study includes accurate and complete information that is less likely to be misinterpreted by anyone who might pick up the brochure. Brochures and flyers that are used to announce a study or are used as recruiting tools should be carefully written in plain language to ensure that there is not a perception of activities that are unethical. For example, if flyers announcing a study state that study participants will be compensated, the flyer needs to ensure that the compensation is not the focus of the flyer, and that the payment does not appear to be excessive and coercive (see Section 5.2). Flyers announcing a study generally do not include the dollar amounts of payment.

Researchers need to have similar concerns about all of the communication materials that are developed, regardless of the type of material, whether it is a direct mailing, a Web site, a news release, or a set of questions and answers (Q&As) used to respond to media or stakeholder inquiries. In developing the communication materials, the research staff should seek the assistance, advice, and input of people in their organization and community groups with experience in developing such materials. With all of these materials, the researchers should be concerned with how the materials could be misinterpreted, and whether there could be a perception that the study would not meet the highest scientific and ethical standards. In this age of rapid communications and increased accessibility to information, it is essential that communication materials are well developed, accurate, and understandable to all audiences that may read them.

Research study Web sites are especially useful for communicating information about observational human

exposure studies. Web sites should be developed early in the study to disseminate information to stakeholders and the community. Additionally, the sites can be set up with participant-only pages to provide more detailed information to study participants, including information on study protocols that require participant assistance (e.g., protocols for collecting urine samples, time/activity log entries). However, researchers need to ensure that Internet access is available to their intended audience and be prepared to provide alternative communication tools for those without such access.

The plan for disseminating information from the study should be developed in the early design phases of the study and should be included in the study design document. Sufficient resources, both time and funding, need to be budgeted for this activity.

## 7.6 Informing the Study Participants and Communities

Effective communications require that all parties, researchers and participants alike, involved in the communication understand the content and context of the information being exchanged. "When researchers discuss a planned study with community representatives, understand their concerns and needs, and respond to them, protocols can be strengthened both scientifically and ethically" (p. xii, NRC & IOM, 2005). Comprehension is one of the key pillars of informed consent, and it means that participants understand the key elements of the research. The most effective way to improve comprehension is by talking one-on-one with study participants.

To accomplish that, the researchers need to make a commitment to communicating with both the study participants and the community to inform them of the study and provide training as appropriate. This can require a substantial investment of time and resources, but it is critical to the success of the study.

Working with study participants to inform them about the study and the scientific basis of the study will have many benefits. The more educated the participant is about the purpose of the study and the activities to be performed during the study, the more likely the participant will be to develop a beneficial researcher-participant relationship. By taking the time to inform the participant, the researcher demonstrates his or her commitment to the participant and conveys the importance or value of their participation in the study. If the researcher-participant relationship is well developed, the participant will have a higher level of trust in the researcher and will be likely to have more interest in the study and a positive outcome. If such a relationship is developed and the participant is informed about the study goals, the participant will take part more readily and effectively in the specific study activities. For example, a study participant who understands why time/activity information is critical to understanding exposure is likely to do a better job completing a time/activity log than a participant with no interest in the outcome of the study. In addition, an informed participant may have good suggestions for improving the study and the interactions with the participants and the community that the researchers should listen to and adopt. Developing the researcher-participant relationship and informing the participants also should improve retention in longitudinal, repeated measures studies because the participant feels that he or she is collaborating with the researcher and is not merely a study "subject."

Similarly, providing information on the research study to the community should provide significant benefits in terms of support to the research team and working with the team to facilitate the study in their community to address both the scientific issues and the community's concerns. If community leaders understand the research problem, the study goals, and the study activities, they can more effectively articulate the community's concerns to the researchers and integrate those issues into the study design. This will enhance their work with the research team during the design phase and will enable them to more effectively advise and assist during the implementation of the study.

## 7.7 Reporting Study Results to the Participant and Community

Researchers need to develop the approach for reporting results to the participants, community, stakeholders, media, and others during the initial planning of the study. There are not well-developed guidelines for when and how to report study results (Parkin, 2004). In her systematic review of guidelines and frameworks for reporting study results, Parkin determined that locating guidance may be difficult and time consuming for researchers. She found agreement on the importance of disseminating study results to produce public health benefits, but there is not a consensus on when and how results should be reported to either communities or study participants. Although she did not identify well-developed guidance documents, she did identify some common themes. The first was that researchers are becoming aware of the importance of systematic planning of the research communications,

planning that needs to be done early in the study. Second, organizations are recognizing the importance of communicating with communities. And, third, research professions are recognizing the importance of research communication and their responsibilities.

There is a large body of literature on processes for risk communication (e.g., see Covello et al., 1989, 2007; U.S. HHS, 2002; ASTDR, 2007). Processes for risk communication are highly relevant to reporting results from observational human exposure studies, even though they may not include measurements of health outcomes or risk assessments.

HHS has prepared a useful document entitled *Communication in a Crisis: Risk Communication Guidelines for Public Officials, 2002*. It is available online and in hard copy and includes a chapter on communicating complex, scientific, and technical information (U.S. HHS, 2002). They recommend using clear, nontechnical language, avoiding jargon, and putting technical terms into frames of reference that the public or other listeners can understand.

Covello and Allen (1988) described seven cardinal rules for risk communication (Text Box 7-5) that are still quite applicable today. More recently, Covello et al. (2007) have developed a "message mapping" approach for risk communication. Message mapping is a process to anticipate the questions likely to be asked after an incident and to prepare clear and concise answers to the anticipated questions in advance. The approach builds on an understanding of current communications practices (e.g., short messages averaging 27 words, soundbites of around 9 seconds, the most frequently asked questions after an incident) and typical human responses to crisis. The report lays out a series of steps to develop short, clear key messages to address stakeholder concerns in advance.

**Text Box 7-5. Seven Cardinal Rules of Risk Communication**
(Covello and Allen, 1988)

1. Accept and involve the public as a partner.
2. Plan carefully and evaluate your efforts.
3. Listen to the public's specific concerns.
4. Be honest, frank, and open.
5. Work with other credible sources.
6. Meet the needs of the media.
7. Speak clearly and with compassion.

The report also provides useful approaches for effectively communicating the messages in times of crisis. It emphasizes that during a crisis, "people judge the messenger before the message and they base their judgment in terms of trust." In times of crises, opinions about trustworthiness hinge largely on perceptions of caring and empathy, whereas competence and expertise are key factors when there is little or no stress. Figure 7-1 is taken from the Covello et al. (2007) report and represents the relative importance of various factors in influencing whether or not people trust a speaker in times of crisis. Many of the principles and processes for crisis communications are applicable for communication of research results from observational human exposure studies, and the reader should consult the risk communication literature.


**Figure 7-1. Factors Influencing Trust in Times of Crisis**
*EPA, 2007*

ATSDR (2007) has *A Primer on Health Risk Communication Principles and Practices* available online. Because ATSDR generally responds to environmental issues identified by individuals or communities, their guidance focuses on communicating with individuals and communities that perceive an imminent or significant health risk because of a problem in the community. Because ATSDR often enters a community after a potential problem has been identified, ATSDR communications are often reactive, by necessity, rather than proactive.

Health Canada (2006) has recently published *The Strategic Risk Communications Framework*. The focus of the effort is always the stakeholders. Health Canada's

process aims to involve the interested and affected parties at all points in a "dialogue-based" communication process. (See Text Box 7-6).

**Text Box 7-6. Steps in Health Canada's Risk Communication Framework**

1. Identify the issue and its context—define the opportunity and characterize the situation.
2. Assess the risks and benefits—assess stakeholder perception of the risks, benefits, and tradeoffs.
3. Identify and analyze options—assess how stakeholders perceive the options.
4. Select a strategy—develop and pretest strategies, risk communications plans, and messages.
5. Implement the strategy—implement risk communications.
6. Monitor and evaluate results—evaluate risk communications effectiveness.

Guidance on risk communication strategies and practices consistently stresses the importance of obtaining input and feedback from community representatives, who can assist in developing approaches that place the results in relevant contexts for the community and the participant.

One of the difficulties in reporting results to participants and communities is timely reporting because it generally takes a long time to complete both the chemical and data analyses in large studies. Researchers desire to report fully validated and analyzed data to study participants and to the community. But, delay in reporting data can create a number of difficulties. Participants may move before they receive results. They also may lose interest in the study, or more importantly, lose trust in the researchers and the scientific research community if they do not receive their results in a timely manner. Similar problems may occur in the community as community leaders and representatives change. Community representatives may have expectations for data and information that researchers cannot achieve. Therefore, it is important that researchers clearly communicate with the participants and the community about what results will be provided and when they will be delivered so that expectations do not differ from "reality."

Reporting study results from observational human exposure studies can be particularly challenging because data on exposure concentrations and the factors impacting exposure may be difficult to relate to a health outcome that is relevant to the study participant. Health effects data is often lacking for the concentrations at which chemicals or their metabolites are measured in environmental or biological media. This is especially true for studies of many chemicals for which acceptable occupational exposure levels have been established, but for which there are not environmentally relevant standards for low-level exposures. Williams (2004) describes an approach for communication using comparative risk analyses. She describes intrachemical comparisons, interchemical comparisons, comparisons to background levels of risk, comparisons to theoretical risk or safety levels, and risk comparisons to other actions or activities. Williams also includes an extensive list of references for guidelines and other information on risk communication. Readers of this document should refer to her manuscript to determine which approach may be applicable to their particular study.

During longitudinal studies with repeated measurements over months, seasons, or years, it is important that researchers commit to providing interim and ongoing results to participants and the community as the study proceeds. It is important to maintain the researcher-participant relationship throughout the study. This can be facilitated by keeping study participants informed of the study progress and of the interim results

Researchers also should recognize that there may be potential risks to the study participants, third parties, or the community because of results generated from a study (refer to Text Box 7-7). Therefore, providing information to communities has to be done thoughtfully and with appropriate preparation. Processes should be developed that provide participants with the option to receive, or decline, study results. Researchers should work with community groups to determine how study results should be disseminated to the community and what communications strategies should be used.

**Text Box 7-7. Potential Harms of Sharing Research Results with Participants**
(Fernandez, Kodish, and Weijer, 2003)

- Incorrect or harmful decisions based on uncertain or unreliable results
- Causing distress for those participants who did not benefit from the research
- Rekindling old memories and emotions, especially in the setting of serious illness
- Emotional distress among community members
- Possible discrimination in obtaining employment or insurance for a participant identified by the research to be at high risk of developing complications
- Financial costs to participants and to researchers

There are a variety of methods for providing study results to participants and the community. Fact sheets can be used to describe the study and provide general

study findings to the community and stakeholders. Individualized fact sheets can be used to disseminate results to the individual participants. Meetings with study participants have been used to disseminate study information. Community meetings also can be used to provide updates on study progress and general results.

Examples of the processes and the materials used for dissemination of information are included in case studies described by Israel et al. (2005) and others conducting CBPR studies.

Overall study results generally are disseminated in peer-reviewed journal manuscripts and study reports. The availability of results published in manuscripts and reports has been greatly enhanced by posting them on Internet Web sites. For example, all EPA reports are now available electronically via EPA's National Service Center for Environmental Publications Web site (http://www.epa.gov/ncepihom/).

## 7.8 Reporting Unanticipated Results or Observations

The previous subsection discussed reporting of routine results from observational human exposure studies. The communication plan should include processes and procedures for the dissemination of the study results. Additionally, the communication plan needs to integrate with the data and safety monitoring and oversight plans for the study and include a plan for reporting unanticipated results or observations. Unanticipated results may include measurements of a chemical at a concentration that exceeds what is considered to be an "acceptable" level in environmental media or biological fluids. Unanticipated observations might include observation of the use of a chemical not approved for indoor use, storage of chemicals in inappropriate containers, storage of chemicals in places accessible by children, etc. Unanticipated results or observations may be directly related to the research question being addressed in the study (e.g., measurements of pesticide residues in a home) or nonstudy hazards (e.g., frayed electrical cords that may pose a hazard to young children and residences). Section 4 discusses issues that may affect privacy and confidentiality. Section 4.3 covers collateral observations of nonstudy-related hazards, including those that States may mandate must be reported. Section 4.5 discusses the need for data and safety monitoring and oversight, including the development of plans to report and react to anticipated or unanticipated adverse events or conditions.

As part of the study implementation plan and the communication plan, researchers should develop a protocol for how to identify contaminant measurements and exposures of "concern" that should be reported to the study participant as quickly as possible because of the potential risk associated with the exposure (see Section 4.5, Data and Safety Monitoring and Oversight, and also Section 2.7.1, Establishing Criteria and Standards for Monitoring Scientific and Ethical Issues During a Study.) The plan needs to include the protocol for making the determination and the criteria that will be used as the threshold or "trigger" for reporting. The plans should describe how the results will be reported to the participants and what additional action will be undertaken to assist the participant in reducing their exposures. The first step in developing the protocol is to identify what measurement will be used to identify exposures of concern. In observational human exposure studies, this will generally be the chemical measurement in either environmental or biological samples. For example, measurement of lead concentration in blood would be an appropriate exposure metric if the research question being addressed involves lead exposure. The measurement is relatively simple and can be performed with a short turnaround time. Similarly, measurements of chemicals in blood may be appropriate for other persistent chemicals that have relatively long half-lives in blood. For nonpersistent chemicals, biomarkers of exposure measured in urine or saliva may be appropriate metrics to identify exposures of concern. For some chemicals (e.g., PM, volatile organic compounds [VOCs], ozone), biomarkers of exposure either are not available or difficult to measure or interpret. In these cases, measurements in environmental media may be the best exposure metric. Whatever metric is chosen, it is important that the chemical analyses can be performed relatively quickly to reduce such exposures as quickly as possible.

The second, and more difficult, step in developing the reporting protocol is to determine the level of concern that triggers reporting of the concentration to the study participant. For some environmental media, such as drinking water, EPA (2007) has established maximum contaminant levels that can be used as triggers for reporting. For example, if the researcher measures a level of arsenic in drinking water above 0.010 mg/L, he or she would be expected to report the level to the study participant. For other environmental media, such as air, there are few applicable standards. The National Ambient Air Quality Standards might be used for the criteria pollutants. Guidelines for occupational exposures, such as threshold limit values (TLVs) and

biological exposure indices (BEIs) published by the American Conference of Governmental Industrial Hygienists (ACGIH, 2008) also may be used. TLVs are not standards; ACGIH formulates a conclusion on the level of exposure that the typical worker can experience without adverse health effects. Many people would argue that the TLVs are not conservative enough for the average population, particularly not for vulnerable lifestages (e.g., children, the elderly) and TLVs are only for exposure by inhalation. WHO (2005) also publishes air quality guidelines. These types of guidelines can be used to advise study participants if their exposures are high relative to the guidelines. Reporting levels should be conservative, but not so low that reporting the level to the participant causes unwarranted concern and stress. For other environmental media measured in observational human exposure studies, such as house dust or surface wipes, the measurement results cannot be used easily to estimate exposures, and they are a poor metric if used alone.

An alternative approach to comparison of measurement results against available guidelines and standards is the comparison of measurements in biological fluids to measurement data available from the National Health and Nutrition Examination Survey (NHANES). For example, results of measurements of chemicals or their metabolites in urine or blood can be compared to different percentiles (e.g., the 95th) reported in the NHANES national reports (CDC, 2005). This type of comparison shows that the participant's measurements are at the high end of the distribution of the NHANES data, suggesting that action *may* need to be taken to mitigate exposures. However, researchers need to be judicious in the selection of the exposure metric. Biomarkers in blood and biomarkers in urine can be very different exposure metrics and may represent different aspects of the exposure event. A similar approach could be taken with measurements of chemicals in environmental media if there are sufficiently large databases available for comparison. For many chemicals and many media such databases are not available. In some NERL studies, one comparison approach that has been used is to compare an individual's environmental media measurements to the 50th, 75th, or 95th percentile concentrations for the entire study population, so that the participant can evaluate his or her measurement results relative to those of the other study participants.

A more complex approach than using simple data comparisons is to calculate a reporting level defined as a chemical or metabolite concentration indicative of an absorbed dose greater than that of a target level (for example one-tenth) of a lifetime reference dose (RfD) level. For a pesticide, the absorbed dose could be estimated from the urinary pesticide metabolite level using an approach similar to the methodology published by Fenske et al. (2000). This deterministic approach to dose estimation allows direct back-calculation of doses from urinary metabolite concentrations using few assumptions and is consistent with current pesticide regulatory procedures for risk assessment. When using this approach, the research team will need to determine how conservative the reporting level should be, as there are no guidelines available for using this approach. If the concentrations of a metabolite measured in a study participants' urine level are indicative of elevated exposures (i.e., above the reporting level), the researchers would be expected to report the information to the participants and provide information or local contacts that could assist in helping the participants identify sources of exposure and reduce their exposures. Although this would seem to be a reasonable approach for some classes of chemicals, the authors are not aware of reports of the use of this approach in the scientific literature.

## 7.9 Anticipating and Responding to Criticism

As discussed in other parts of this document, in spite of researchers best intentions, there may be situations that arise in which people's perceptions of the study design or implementation plan are not accurate, or their opinions and beliefs about the ethical issues associated with a study may not be in agreement with those of the research team and others involved in the study (e.g., the peer review panel, the IRB). Just as it is not unreasonable to expect differences in opinion on scientific approaches to an observational study, it is not unreasonable to expect differences of opinion on ethical approaches. The researchers, therefore, should be prepared to respond to criticism. The implementation plan and the communication plan should address how the research team should anticipate study elements that may be criticized. During study conceptualization, the research team should develop a list of potentially controversial study elements (many of which are discussed in this document). For each study element, the research team should describe how the ethical approaches to the study element were evaluated and selected. Both the process and the rationale for selection of a particular approach should be documented. At each step in the study planning and review process, the

research team should document discussions related to the specific element, considerations that were made, actions taken, and justification for the actions. Input from research team members, internal reviewers, external reviewers, community members, and others involved in the study should be documented for these controversial study elements. Similarly, for potentially controversial study elements, the review and actions by the IRB should be documented. All of this information should be compiled for potential use to prepare a set of Q&As that can be used by the research team and sponsoring organization to respond to criticism. When responding to criticism, establishing trust and credibility are essential, as discussed previously. The public's perception of trust and credibility is determined by the public's perceptions of the researchers' knowledge and expertise, openness and honesty, and concern and care (Peters et al., 1997). These factors are important to consider in developing the information and approach that will be used to respond to criticism.

There is a large volume of information available on "crisis communication" that the reader can use to develop a plan for anticipating and responding to criticism (e.g., FCN, 2001; ATSDR, 2007; U.S. HHS, 2002). The key is to be proactive and have a plan before any criticism is raised.

## 7.10 Responding to the Media, Public Inquiries, and Other Stakeholders

Like crisis communications, the communication plan should include detailed plans for how to interact with the stakeholders, the media, and the public. Standard approaches have been developed for effective communications (e.g., the Federal Communicators Network's *Communicators Guide* [FCN, 2001]) with the media and will not be included in this document. A proactive plan, open and transparent communications, and easily to comprehend information will ensure effective communications with stakeholders and the public.

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# Appendix A

# Additional Discussion of Observational and Exposure Terminology and Examples of Previous NERL Observational Human Exposure Studies

The authors recognize that the words "observational human exposure studies" may convey a variety of meanings to different people. The word *exposure* is often interpreted differently by different people; similarly, the word *observational* may have a variety of interpretations. The following discussion regards potential meanings of those terms and describes what the authors of this document mean when they use the term *observational human exposure studies*.

## Exposure

*Exposure*, as it is used throughout this document, is a technical term that is defined as the "contact of a chemical, physical, or biological agent with the outer boundary of an organism (e.g., a person) (U.S. EPA, 1992). Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact."

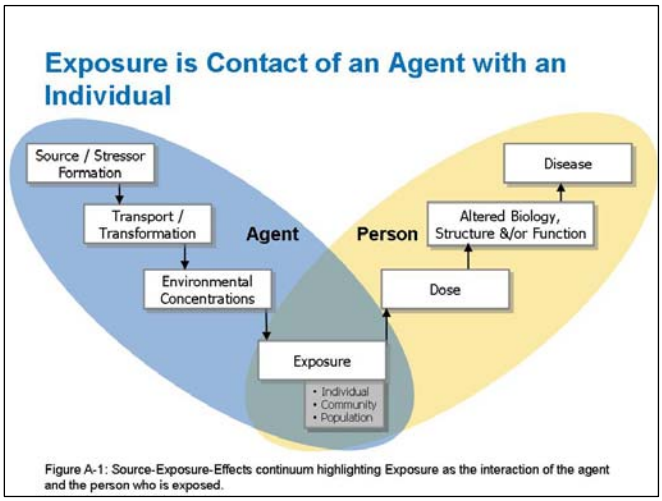

Figure A-1: Source-Exposure-Effects continuum highlighting Exposure as the interaction of the agent and the person who is exposed.

As the authors use the term, *exposure* is only the quantification of the "contact" as defined above. The word itself carries no connotation of intent, and it is *not* equivalent to *intentional exposure*, *dose (dosing)*, or *intentional dosing*. A review of the dictionary definition of exposure shows that the word has many different meanings, and shades of meaning, in common, everyday English. However, when the authors use the word in this text it is being used in the technical sense that is defined above.

The authors' understanding of the word *exposure* is illustrated in Figure A-1. This graphic is a paradigm that ORD uses in formulating its human health research program. The graphic illustrates that exposure occurs at the intersection of both the chemical, physical, or biological agent and the person who is exposed. To understand exposure, one must understand the distribution of the "agent" throughout the environment over time and combine that understanding with knowledge about the location and activities of people that bring them into contact with the agent. Knowledge about the distribution of the agent in space and time generally involves measurements and data collection about environmental conditions external to the person. Knowledge about the person's behaviors requires collection of personal information or observations of their location and activities. Understanding exposure, including the pathways, routes, duration, frequency, and magnitude of the exposure, requires combing both types of information.

See the Glossary, Appendix F, for more information and the definition of additional and related terms.

## Observational

Observational human exposure studies, as used in the context of this document, involve only the collection of environmental or biological samples and information for the purpose of quantifying the contact between the participant and the agent being studied. Observational human exposure studies are inherently the process of watching people in context—in their natural environment, doing routine activities—and collecting the

samples and relevant information from them and from their surroundings to measure and calculate the exposures that occurred in the same context.

***Scientific Study Design:*** From a scientific study design perspective, an *observational study* of the sort being considered in this document is one where the researcher does not control the variables but, rather, observes both the variable and the outcome and tries to infer the relationship between the variable and the outcome. This contrasts with a *controlled study* where the researcher isolates and controls one or more variables in a systematic way to assess the impact of changes in the variables on an outcome measure. Consider the intervention study examples cited in the section on regulatory distinctions below (cleaning a house to reduce exposure in the residence and wearing a particle mask to reduce exposure to smoke from forest fires). In those cases, participants would be assigned either to receive the intervention (treatment) or not (the control group). The outcomes (exposures) would be measured and compared between the two groups to assess the effectiveness of the intervention. Similarly, drug trials would randomly assign participants to receive either a test medication or a placebo. The medical outcome (e.g., pain relief, blood pressure, cholesterol levels in blood) would then be measured for all participants, and the outcomes compared between the treated group (getting the test medication) and the control group (receiving the placebo).

Controlled studies are often desirable in science because, when properly designed, they provide unambiguous estimates of the impact of unique variables on the outcome (even if the impact of one variable could normally be overwhelmed by other factors) and eliminate the need for alternate explanations of the experimental results (because other factors are held constant). However, controlled studies are not always possible. They may be unethical (e.g., to "treat" a group of women with abortions to test if there is a linkage between having had an abortion and breast cancer), impractical (e.g., to follow a cohort large enough to yield statistically significant results in a test of rare side effects to a medication), or just impossible to accomplish (e.g., to measure nutritional levels of a population in the middle of a war zone).

As a consequence, much medical research is observational in the scientific sense being considered here. Public health data represent observations of health outcomes, but the factors that may have led to or influenced those outcomes are not under the control of any researcher. Observational techniques long have been used in medical studies to infer information about the impacts of certain factors on health outcomes. Commonly used techniques include cohort studies, case-control studies, cross-sectional studies, case reports, case series, and descriptive studies (NEAC, 2006; Vandenbroucke et al., 2007).

*Observational human exposure studies* as used in this document are considered to be observational from a scientific study design perspective because the variables leading to exposure are not controlled by the researchers. Most of the observational human exposure studies conducted by NERL to date have been cross-sectional studies (sometimes repeated several times). While a particular variable may not be controlled by the researcher, the study design (e.g., selection of the population to be studied, location of the research, data selection to exclude confounding factors) can sometimes influence the range of values over which a variable may be observed. For example, NERL's observational human exposure studies to understand exposure to PM (see www.epa.gov/heasd/sources/projects_completed/pm_panel_studies.htm and www.epa.gov/heasd/sources/projects/a3a_understanding_airshed_sources.htm) have traditionally excluded homes with smokers from the study population to avoid cigarette smoke as a confounding factor in the studies.

***Observational Studies in Market Research, Ethnography, and the Common Vernacular:*** Observational market research can involve covert observation, overt observation, or researcher participation. Covert observation is said to have a "key advantage" that "the respondent or consumer is unaware that they are being observed, allowing their behavior to be observed naturally" (see http://www.asiamarketresearch.com/glossary/observational-research.htm). This means that the subject's behavior will be natural and uncontaminated by the researcher's presence. On the other hand, covert observation may be construed to be deceitful and ethically questionable. Overt observations involve sampling surveys, polls, interviews, focus groups, etc. Validity of the data obtained this way may be shaded by people's natural tendency to behave or respond ideally when they know they are being watched. Motorists routinely slow down when they think they are being observed by the police. Finally, the researcher may participate in the activity being observed. Ethnography is a long-term investigation of a group (often a culture) that is based on observations made while immersed in and, useually, participating in that group. "Ethnography provides a detailed exploration of group activity and may include

literature about and/ or by the group." (See http://writing.colostate.edu/guides/research/observe/com3a1.cfm). One obvious problem with immersion techniques is that the researcher may lose his or her objectivity.

In the common language use of the term *observational research*, it appears to the authors that some people understand the term to imply that the observations are both benign and often covert, that is, without interaction with the persons being studied. That is not the case in NERL's observational human exposure studies. The research often takes place in and around the homes of the participants. Often, the research involves asking the participant to answer a questionnaire and to provide personal samples (e.g., urine, blood). Collection of survey information and personal urine and blood samples cannot be done covertly, and collecting a blood sample is not considered to be benign.

***Observational Research in NERL:*** NERL's observational human exposure studies entail the collection of environmental or biological samples, data, and information from study participants and their surroundings in their everyday environments, as they go about their normal activities, for the purpose of quantifying the contact between the participant and the agent being studied. As such, the studies are designed to meet the regulatory definition of observational research in the CFR. NERL's studies also meet the scientific definition of an observational study, because the variable being studied, exposure to some agent, is not controlled by the NERL scientists. The observations are not covert, and they may or may not be noninvasive (e.g., sometimes blood samples may be collected).

Because NERL's observational human exposure studies meet the definition of human subjects research as set forth in the Common Rule, there is also a regulatory requirement to meet the ethical and scientific standards set forth in EPA's human subjects regulations and in Agency rules. The research protocol must be evaluated and approved by an IRB and by EPA's Human Studies Research Review Official (HSRRO) before any human subjects research effort can take place. But, even more compelling to NERL managers and scientists is the fact that NERL cannot conduct observational human exposure studies without the participation of willing individuals. Indeed, without the research participants, NERL's human exposure research would be nothing. This intimate involvement of research subjects in NERL's research imposes moral and ethical obligations to deal with participants respectfully and to ensure their safety, protection, and well-being.

## Regulatory Distinction Between Intentional Exposure and Observational Research

***Intentional Exposure:*** The CFR states, "Research involving *intentional exposure of a human subject* means 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" [40 CFR 26.202(a)]. This definition sets forth two requirements regarding an intentional exposure: (1) the exposure has to be to a substance that is being studied, and (2) at least one aspect of the exposure to the substance being studied has to be attributable to the subject's participation in the study.

The first requirement means the objective of the study must be to understand the impact or exposure of the substance being studied. In observational human exposure studies, like those that NERL conducts, the research protocol may require the use of isopropyl alcohol or some other chemical to collect a personal sample (e.g., to sterilize the puncture site immediately prior to collection of a personal sample of blood drawn by a trained phlebotomist). Indeed, it would be both unethical and bad medical practice not to sterilize the puncture site before drawing blood. But this requirement does not constitute intentional exposure because the research is not the study of isopropyl alcohol but of some other agent. Incidental exposures to chemicals like isopropyl alcohol still must be considered from a safety perspective, pass both scientific and ethical review, and be approved by the IRB, but such incidental exposures do not constitute intentional exposure.

The second requirement is that the exposure as experienced by the subject "would not have occurred but for the human subject's participation in the study." The two primary ways in which intentional exposure studies commonly meet this definition are by the direct introduction of the study substance into the research environment under the control of the research protocol or by scripting the participants' activities in such a way that their contact with the study substance is determined by the research. Although either would be sufficient to meet the regulatory definition, many, if not most, intentional exposure studies attempt to control both. Because "exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact," intentional exposure studies are usually more scientifically robust if both the concentration of the agent and the duration of the exposure are controlled by the research.

***Observational Research:*** In the language of the Code of Federal Regulations, "*observational research* means any human research that does not meet the definition of *research involving intentional exposure of a human subject*" (40 CFR 26.302).

By this definition, *observational research* encompasses *all* human research that does not meet the definition of *intentional exposure*. As a consequence, it is a broad regulatory category that includes a variety of research domains, including human research that does not involve the study of exposures at all. This regulatory definition of *observational* is sufficiently broad, moreover, that it encompasses study types that this document is not intended to address. For example, it may be possible to design an intervention study that does not bring about or script in any way the participants' exposure to a substance, but rather reduces or mitigates it. (Consider a study to test whether professional cleaning of the carpets, floors, walls, and other surfaces in a home might lead to a lower exposure to a residential contaminant or a study to determine if wearing a particle mask would reduce an individual's exposure to smoke from forest fires.) Such a study might meet the regulatory definition of *observational research* (Note: The final decision in regard to whether any EPA study meets the definition of *observational research* resides with the Agency's HSRRO), but it would not meet the authors' intentions regarding "observational human exposure studies" as they are defined in this document. An intervention study, such as described in these two examples, does not involve observing people's exposures in their everyday environments, as they go about their normal activities. In an intervention study, either the participant's environment (cleaning of the household surfaces) or their behavior (wearing a particle mask) has been manipulated by the researcher. Secondly, the objective of these studies is not to understand exposures in everyday environments but would use changes in exposure to test the effectiveness of an intervention strategy. Such a study is not addressed in this document.

Observational human exposure studies, as used by the authors of this document, generally meet the regulatory definition of observational research. But, not all studies meeting the CFR definition of observational research would be considered by the authors to be observational human exposure studies.

## Examples of NERL Observational Human Exposure Studies

NERL and its predecessor organizations have conducted observational human exposure studies since 1980. Table A-1 lists many of those that NERL has conducted, supported, or participated in since 1980. The table gives the name of the study, dates, sample size, then type of study, a brief explanation of the research, and NERL's role therein. The table represents a variety of first-party or second-party research efforts. In many cases, NERL staff would design, oversee, and, if possible, participate directly in the study (first-party), but often contractor support would be needed to accomplish the field sampling or some of the sample analysis. In other cases, NERL researchers would solicit proposals for exposure research to be conducted to address specific exposure issues and then would fund researchers in academia or at nonprofit institutions to design and conduct the research (second-party research). In a few cases, grants might already be in place with research institutions, and NERL simply would augment the pre-existing funding to expand the exposure component (second-party). Some other cases involve research efforts initiated by other Federal agencies with which NERL would collaborate and participate in directly (first-party).

An examination of the entries in the table shows that most of the agents being studied were chemicals, often air pollutants or pesticides. A few of the entries indicate that other agents, for example, molds and fungi or other microbes, were the subject of the study. The largest number of the studies involved small numbers of participants and often were designed to determine whether or not a method for collecting exposure-related data or samples was feasible or burdensome. Most of the smaller studies used convenience samples. Studies, like DEARS, CTEPP, NHEXAS, and TEAM, which involved large numbers of participants, employed randomized or probability-based approaches for selecting participants.

Table A-2 shows the types of samples that often have been collected in NERL's observational human exposure studies. Some of the samples, like air concentrations or surface wipes, allow NERL staff to determine the concentration of the studied chemicals in the environmental media with which the participants may come into contact. Other items, like time activity diaries or videotaping children to measure the amount of hand-to-mouth activity, allow NERL researchers to understand how people may come into contact with the agent and to estimate the duration or frequency of a

potential exposure. Still other measures, like personal samplers or biological samples, represent an attempt to determine a time-integrated measure of exposure. NERL staff put all of this information together to estimate an individual participant's exposure, either through relatively direct measures of exposure or through algorithms that combine the media concentrations measurements and the activity data.

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| Table A-1. Examples of Observational Human Exposure Studies Conducted or Funded by NERL or Its Predecessor Organizations | | | | | |
|---|---|---|---|---|---|
| **Study** | **Date** | **Size** | **Type** | **Brief Description** | **NERL Role** |
| Total Exposure Assessment Methodology (TEAM) Studies | 1980-1984 | 400 Households | Three-stage stratified probability selection, cross-sectional | The TEAM study was designed to develop and demonstrate methods to measure human exposure to toxic substances in air and drinking water. The goals were to develop methods to measure individual total exposure (from air, food, and water) and the resulting body burden of toxic and carcinogenic chemicals and to apply these methods within a probability-based sampling framework to estimate exposures and body burdens of urban populations in several U.S. cities. Air sampling measured personal exposure to airborne toxic chemicals in indoor air and in exhaled breath. Related objectives were to determine the relationships between personal, indoor, and outdoor, and blood, urine, and exhaled breath concentrations; determine the variability of VOC concentrations within a home; and determine seasonal and multiyear variability. The study was conducted in New Jersey, North Carolina, and North Dakota in three phases. | EPA designed and run, contractor conducted |
| Additional TEAM Studies | 1987 | 51 in LA area, 17 in NJ, and 75 in Baltimore | Convenience sample | A separate VOC TEAM study was carried out in Baltimore, MD: Baltimore lacks the petroleum and chemical manufacturing plants present in most of the previous TEAM study sites and is more representative of many U.S. cities. Focused studies were also conducted in New Jersey and Los Angeles to further explore the sources and factors contributing to personal VOC exposures identified in the earlier TEAM studies. | EPA designed and run, contractor conducted |
| Nonoccupational Pesticides Exposure Study (NOPES) | 1986-1988 | 259 | Probability selection, mainly cross-sectional, partly longitudinal | First attempt to develop a methodology for measuring the potential exposure of the general population to common household pesticides using probability-based sampling; questionnaire data collection; and personal monitoring of air, drinking water, food, and dermal contact. Conducted in Jacksonville, FL, and Springfield and Chicopee, MA, to capture high- and low-pesticide-use areas, respectively. | EPA designed and run, contractor conducted |
| Nine-Home Children's Pilot Study | 1990 | 9 | Convenience pilot study to test methodology | A 9-home pilot study was conducted to evaluate monitoring methods in the field that may be used to assess the potential exposures of children aged 6 months to 5 years to pesticides found in the home environment. Newly developed methods were tested for measuring pesticide residues in indoor air, carpet dust, outdoor soil, and on children's hands. Information also was collected on household characteristics, pesticides used and stored at the residence, and children's activities. | EPA designed and run, contractor conducted |
| Particle Total Exposure Assessment Methodology (PTEAM) Study | 1990 | 178 | Probability | A study of nonsmokers age 10 years and older in Riverside, CA, in which indoor, outdoor, and personal monitoring of integrated particle mass over 12-hour day and night periods was conducted for $PM_{10}$ and $PM_{2.5}$. Polycyclic aromatic hydrocarbon and phthalate measurements were collected indoors and outdoors at a subset of 125 homes. A separate monitoring site provided ongoing 12-hour measurements of ambient particles throughout the study (48 days). Reference $PM_{10}$ and dichotomous samplers were used at this site in addition to personal and stationary monitors identical to those used for participant monitoring. Nighttime and daytime recall time-activity questionnaires, as well as household questionnaires, were administered to each selected subject and household, respectively, and meteorological and air exchange rate data were recorded for each monitored home. | EPA designed and run, contractor conducted |
| National Human Activity Pattern Study (NHAPS) | 1992-1994 | 9,386 | Probability (national random dialing) | This survey collected 24-hour activity diaries and other questionnaire data from participants from 48 states. It was conducted as a next-day telephone recall interview. | EPA designed and run, contractor conducted |

| Table A-1. (Continued) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Date** | **Size** | **Type** | **Brief Description** | **NERL Role** |
| Agricultural Health Study (AHS) | 1993-present; PES 1999-2003 | 84 applicators and a subset of family members in PES | AHS survey is a longitudinal study of pesticide applicators in two states. PES, led by NERL, was a cross-sectional study. | A large-scale, long-term ongoing study of Iowa and North Carolina pesticide applicators and farm families. This collaborative effort involving the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), the National Institute for Occupational Safety and Health (NIOSH), and the U.S. Environmental Protection Agency (EPA) examines how lifestyle habits, genetic factors, and agricultural exposures contribute to the risk of disease using questionnaire survey data from 89,658 participants. This is the largest, most comprehensive study of agricultural health ever conducted in the United States. The interagency exposure assessment study (Pesticide Exposure Study (PES)), led by NERL, was performed to assess exposures and exposure classification procedures used in the epidemiological study. | Collaboration with other agencies; NERL led a contractor-conducted substudy called the Pesticide Exposure Study. |
| The National Human Exposure Assessment Survey (NHEXAS)—Overview | 1995-1998 | See specifics in entries below. | | A Federal interagency research effort coordinated by EPA and consisting of four demonstration studies using probability-based sampling designs conducted in partnership with other Federal agencies (CDC, FDA, and NIST), universities, and research institutions. Household environmental and personal samples were collected and questionnaires were administered. Biological media, including blood and urine, also were sampled and monitored for parent contaminants or their metabolites. The studies were undertaken to evaluate total human exposure to multiple chemicals on a community and regional scale with the following aims: provide a baseline of the normal range of exposure to chemicals in the general population; identify subgroups of the general population that are likely to be highly exposed; and evaluate and improve the accuracy of models developed to predict exposure to chemicals. | EPA oversaw general design for the research, then solicited, evaluated and funded the individual studies (see below). Details of research were established by recipients. |
| NHEXAS-Arizona | 1995-1998 | 179 Households | Probability, cross-sectional | The NHEXAS-Arizona study sampled residences determined by a population-based probability research design for the total population of Arizona and measured metals, pesticides, and volatile organic compounds (VOCs). The study was conducted by a consortium composed of the University of Arizona, Battelle Columbus, and the Illinois Institute of Technology. | Designed and conducted by award recipient (see above). |
| NHEXAS-Maryland | 1995-1996 | 80 Households | Probability, longitudinal | The study sampled residences of Baltimore and four adjacent counties and measured metals, pesticides, and polycyclic aromatic hydrocarbons (PAHs). Data collection occurred up to 6 times over 1 year for each of the participating households. The study was conducted by Harvard University, Emory University, Johns Hopkins University, and Westat. The study investigated temporal variability in multimedia, multipollutant exposures. | Designed and conducted by award recipient (see above). |
| NHEXAS-Region 5 | 1995-1997 | 250 Households | Probability, cross-sectional | The Region 5 study was conducted in EPA's Region 5 (Ohio, Michigan, Illinois, Indiana, Wisconsin, and Minnesota), and included personal exposure, residential concentration, and biomarker measurements of metals and VOCs. The study was conducted by the Research Triangle Institute (RTI) and the Environmental and Occupational Health Sciences Institute (EOHSI). | Designed and conducted by award recipient (see above). |
| Minnesota Children's Pesticide Exposure Study (MNCPES) | 1997 | 102 Children | Probability, cross-sectional | Multimedia study of children 3-13 years conducted in Minnesota to evaluate children's pesticide exposure in urban and rural areas. The study provides exposure, environmental, and biologic data relating to multipathway exposures of children for four primary pesticides (chlorpyrifos, malathion, diazinon, and atrazine), 14 secondary pesticides, and 13 polynuclear aromatic hydrocarbons (PAHs). This study complements and extends the populations and chemicals included in the NHEXAS-Region 5 study. | Designed and conducted by award recipient (see above). |

| Table A-1. (Continued) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Date** | **Size** | **Type** | **Brief Description** | **NERL Role** |
| Particulate Matter (PM) Panel Studies | 1998-2001 | 200 Individuals (5 to 63 per study) | Longitudinal | A series of longitudinal studies in a number of U.S. cities conducted by EPA or by organizations sponsored through the National Exposure Research Laboratory (NERL). A primary goal was to determine the relationships between personal exposures to particles and associated gases relative to stationary outdoor monitor concentrations in high-risk subpopulations and to identify human activity patterns that might contribute to personal exposure. The investigators varied study locations, monitoring seasons, and study populations. Susceptible subpopulations of interest included chronic obstructive pulmonary disease (COPD) patients, individuals with cardiovascular disease, the elderly, asthmatics, and African Americans with hypertension. Panels of healthy individuals also were included. Because the elderly is the subpopulation most sensitive to health effects associated with PM exposures, the majority of subjects were over age 65. | NERL conducted one panel study with contractor support; funded and collaborated on others with Harvard School of Public Health, University. of Washington, and NYU. |
| Dietary Intake of Young Children (DIYC) | 1999-2000 | 3 Homes | Convenience | Performed in the Raleigh, NC, area in homes with children 1 to 3 years old. Homeowners reported either professional or self applications of diazinon. Goals of the study were to evaluate methods to measure excess dietary exposures resulting from food-handling activities by young children during eating and to assess whether the Children's Dietary Intake Model (CDIM) accurately represents total dietary exposures of children. Study resulted in refinements of model parameters for transfer and activity. | NERL designed, contractor conducted |
| Children's Pesticide Post-Application Exposure Study (CPPAES) | 1999-2001 | 10 Homes | Convenience, multiday pilot study to test methodology | Observational measurement study of exposure to chlorpyrifos among children 2-5 years of age in urban New Jersey homes following crack and crevice treatment by a professional applicator. Study investigated decay of pesticide levels over time, transfer of pesticide from microenvironmental media to child, and factors that affect transfer. Dermal transfer evaluated with surface wipes, hand wipes, dermal wipes, cotton garments, and videotaping. | NERL funded the Environmental and Occupational Health Sciences Institute (EOHSI). |
| Develop Risk Assessment and Define Some Risk Management Options for Exposure of Children to Toxic Mold Using *Stachybotrys chartarum* as an Example | 2000 | 8 cases and 8 controls | Case control study | Physicians at Case-Western Reserve treating children with idiopathic pulmonary hemorrhage evaluated the nature of the fungus found in homes of the afflicted and control children to determine if *Stachybotrys* was a potential factor in the illness. Three of the 8 cases, and none of the controls, had *Stachybotrys* strains that potentially were implicated. | NERL staff collaborated with Case-Western Reserve University by conducting lab analysis for *Stachybotrys*. |
| Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) | 2000-2001 | 257 Households | Randomized, cross-sectional | The largest children's exposure study undertaken to date. It examines aggregate exposures of children 18 months to 5 years to pollutants commonly found in everyday environments. The major objectives were to quantify children's aggregate exposures, apportion exposure pathways, and identify important exposure media. Participants were recruited from 12 urban and rural counties in North Carolina and Ohio using a random digit dialing method. Monitoring was performed at both daycare centers and homes. Samples collected include food, beverages, indoor air, outdoor air, hand wipes, dust, soil, transferable residues, floor and surface wipes, and urine. The samples were analyzed for more than 40 pollutants, including insecticides, phthalate esters, phenols, polychlorinated biphenyls, and PAHs. | NERL designed, contractor conducted |
| Car-Related Occupational PM and Air Toxics Exposure to Patrolmen Study (COPP) | 2001 | 9 | Convenience, longitudinal | Scientists monitored air pollutants inside and outside vehicles of healthy highway patrol officers in North Carolina while troopers were on patrol for 9-hour shifts and examined cardiovascular effects. The findings indicated that people driving in motor vehicles are exposed to $PM_{2.5}$ and other pollutants generated from motor vehicles, and that these exposures appear to cause cardiovascular changes. | EPA designed and conducted with contractor support |

| Table A-1. (Continued) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Date** | **Size** | **Type** | **Brief Description** | **NERL Role** |
| First National Environmental Health Survey of Child Care Centers (CCC) | 2001 | 168 Child care centers | Probability-based selection on national scale | A collaborative study with the Department of Housing and Urban Development (HUD) and the Consumer Product Safety Commission (CPSC) of pesticide use and young children's (less than 6 years old) potential exposure to pesticides and other pollutants in institutional childcare centers. This national study used multistage sampling with clustering. Indoor wipe and outdoor soil samples were analyzed for pesticides, lead, and allergens (mold/fungi). Pesticide use practices and application information were obtained from the commercial pest control applicators serving the centers. | HUD and CPSC study. NERL collaborated and conducted analysis of molds/fungi and helped with lead and pesticide measurements. |
| A Pilot Study Examining Translocation Pathways Following a Granular Application of Diazinon to Residential Lawns (PET) | 2001 | 6 Households | Convenience, multiday pilot study to test methodology for exposure measure-ments | Observational pilot exposure measurement study of residential exposures after homeowner had routinely applied granular formulation diazinon-containing turf treatment to residential lawns. Study was performed near Raleigh, NC, and was preceded by a 1-home methodology feasibility study. Purpose was to evaluate methods for assessing pet-borne transfer, translocation and exposure pathways, and decay rates. | EPA conducted with contractor support |
| Biological and Environmental Monitoring for Organo-phosphate and Pyrethroid Pesticide Exposures in Children Living in Jacksonville, FL (JAX) | 2001 | 9 Households in NERL exposure component | Convenience, cross-sectional | The objectives of this investigation in Jacksonville, FL, were to (1) assess organophosphate (OP) and pyrethroid pesticide exposures in a group of 4- to 6-year-old children from Jacksonville by measuring the urine metabolite levels, (2) identify possible sources of these pesticides through screening measurements and pesticide inventories, and (3) examine the relationship between environmental and biological levels. The Duval County Health Department (DCHD) collected urine samples for CDC from 200 children visiting six public health clinics in Jacksonville, and collected environmental screening samples at approximately 25% of these children's homes. A detailed aggregate exposure assessment at 9 homes was overseen by NERL and involved collection of surface wipes, transferable residues, air, duplicate diet, cotton garment samples, and urine samples. A time-activity diary of the children's activities was included. | Multiagency effort; NERL was a participant and led the 9-home exposure component. |
| Exposure Assessment for Community-Acquired Legionnaires Disease | 2001 | 21 | Case-control | Work with Veteran's Administration hospital staff. Cases of Legionnaires Disease were evaluated for potential for exposure from residential drinking water taps. In about 24% of the tested cases, homes were found to have Legionella bacteria in water taps at home, compared to their absence in other cases and in controls | NERL funded IAG with VA to conduct study. |
| Center for the Health Assessment of Mothers and Children of Salinas Quantitative Exposure Assessment Study (CHAMACOS) | 2002 | 20 Children | Convenience | Incidental pesticide exposure measurement study of farmworkers' children ages 5 to 35 mo. Purpose is the evaluation of methods for aggregate exposure measurements and the evaluation of pathways of exposure and important factors that affect exposure. Measurements include pesticide distributions in microenvironments where children spend time, transfer of pesticides from microenvironmental media to child, and factors that affect transfer. | EPA grant to UC Berkeley; NERL augmented the existing research effort. |
| Feasibility of Macroactivity Approach To Assess Dermal Exposure (Daycare) | 2002 | 9 Daycare centers | Convenience | Study identified daycare centers with previously established contracts for routine monthly pesticide applications and conducted screening sampling in each to evaluate the distributions of transferable pesticide residues on floor surfaces where children spend time. One daycare was selected for intensive measurements, and children from different age groups volunteered to wear full-body cotton suits for short time periods while their activities were videotaped. | NERL designed, contractor conducted |

| Table A-1. (Continued) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Date** | **Size** | **Type** | **Brief Description** | **NERL Role** |
| Tampa Asthmatic Children's Study (TACS) | 2002 | 9 Residences | Convenience sample, pilot study to test methods. | Pilot study on methods for measuring personal, indoor residential, outdoor residential, and ambient combustion-related products, particulate matter, and air toxics. The study identified microenvironmental factors affecting penetration of pollutants into homes and reduction of exposures to pollutants for asthmatic children (0-5 years of age). | NERL designed, contractor conducted |
| Pilot Study To Evaluate Data Collection Methods for Young Children's and Household Activities | 2004 | 3 Homes | Convenience, pilot study to test methodology | Pilot aggregate exposure study of three homes to assess burden of alternative exposure sample collection methods. | NERL designed, contractor conducted |
| Detroit Exposure and Aerosol Research Study (DEARS) | 2004-2007 | 150 | Randomized household selection with qualification criteria; longitudinal | Recruitment from seven distinct neighborhoods in Detroit required strong community relations and partnership with State and local organizations. This study monitored for air pollutants at the personal level and evaluates how well centrally located (ambient) monitors represent exposure at the residential and personal level. Sampling is for 5 days duration in summer and again in winter. | NERL designed and run; with contractor support and collaborators such as the University of Michigan |
| Accelerometer Pilot Study | 2004 | 9 | Convenience, pilot study to test methodology | Nine children <24 months old and their primary caregivers participated in this study to (a) determine if very young children will wear an accelerometer for relatively long periods of time and comply with the protocol for its use, (b) evaluate how well a caregiver can estimate the activity level of his/her infant or toddler when completing an exposure-oriented time-activity diary, and (c) compare accelerometer count output with caregiver-provided estimates of children's activity level. | NERL designed and run, with contractor support |
| Pilot Study of Waterborne Infections | 2005 | 1296 | Convenience, all volunteers from community using public water supply | Measure antibodies in people's saliva for antibodies to *Cryptosporidium*, Noroviruses, Rotaviruses, *Helicobacter pylori*, and *Toxoplasma gondii* before and after installation of an ultraviolet treatment system for a public water supply. Also served as test of methodology for detecting people's prior exposure to infectious agents. | EPA planned research (NERL is a collaborator), contractor conducted |

| Table A-2. Types of Samples Collected in NERL Observational Human Exposure Studies | |
|---|---|
| **Samples or Data** | **Exposure Concern and Typical Type of Analysis** |
| **Environmental Media** | |
| Air pollutants | Air pollutants being inhaled. Collect samples from central site, outside residence, and inside residence to assess pollutants in various locales. Measure gaseous and particle-bound pollutants. |
| Soil | Estimate track in and subsequent dermal or inhalation contact. Analyze for metals, pesticides, etc. |
| House dust | Dust from carpets and floors that may result in dermal contact or reentrainment and inhalation. Analyze for pesticides, metals, and tracers of outdoor sources. |
| Surface wipes | Dermal contact, children's hand to mouth, and contact with food and subsequent ingestion. Analyze for metals and pesticides. Examine eating and food preparation areas too. |
| Transferable residues | Similar to surface wipes, using a surrogate for the transfer from the surface to the skin. |
| Duplicate diet | Use to assess ingestion exposures from food. Exact duplicate of amount and items eaten by participant and analyzed for pesticides, metals, etc. Includes drinking water samples as part of diet or other beverages consumed. |
| Handled food | Finger foods like cheese or luncheon meets that have been prepared and processed identically to foods children might eat to evaluate how much pollution may be removed from surfaces and ingested with the food. |
| **Human Activity Data** | |
| Time-activity diaries | Recall diaries to account for all times and activities in a day. Information includes location and activities. |
| Activity loggers | Device used to assess the nature of a person's activities. Portable nephelometers have been used to keep up with people's activities by showing when they were near PM sources. Accelerometers to measure level of activity of children at play. GIS and inertial devices to try to measure locations as a function of time of day. |
| Questionnaires | Query participants about things like daily activities for themselves or their children; housing characteristics; participant characteristics, including occupation, diet, smoking habits, hobbies, etc.; and recent use of pesticides or other consumer products. |
| Videotaping | Use videos to measure frequency and duration of mouthing activities in children. |
| Household inventories | Inventory consumer products in house. Use items to ask about usage frequency and history. |
| Researcher observations | Information about open doors and windows (air exchange), heating and cooking sources, pets, and other activities that may lead to potential exposures may be observed. |
| **Personal or Biological Samples** | |
| Urine | Urinary excretion of pollutants and their contaminants give important information about the nature of prior exposures and their magnitude. |
| Personal air monitors | Individual wears samplers on his/her person while going about normal activities to measure pollutants in breathing zone of individual. |
| Hand wipes | Hand wipes remove contaminants from skin surface. Analyze for pesticides, metals, organic chemicals, and use values to estimate dermal exposure and hand-to-mouth ingestion of pollutants. |
| Dermal surrogates | Participant may wear cotton garments or socks as a collector. Clothing is analyzed for pesticides, metals, organic chemicals, etc. Measured contaminant quantities are used to estimate potential for dermal exposure. |
| Saliva samples | Test for antibodies to infectious agents, suggesting prior exposure and infection by microbial agent. |
| Blood | Some epidemiological studies that NERL scientists have collaborated on have collected blood samples. |

## Appendix B

# The Process for Development of This Document: Description of the Expert Panel Workshop (November 28 and 29, 2006), the External Peer Review by the HSRB (October 21-24, 2007), and Public Comment

## Expert Panel Workshop

An Expert Panel Workshop was convened in Durham, NC, on November 28 and 29, 2006. An ad hoc panel of experts was assembled to discuss issues associated with the preparation of this document prior to beginning its first draft. The workshop was coordinated by ERG, Inc., who was also responsible for compiling information from the workshop in a final workshop report, available on the Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES) Web site at www.epa.gov/nerl/sots.

The charge to the Expert Panel Workshop members was as follows.

> The panel is asked to consider these issues prior to the workshop in preparation for discussion during this workshop meeting:
>
> 1. Provide recommendations on the content and organization of the document.
>    a. Identify the major scientific and ethical areas/issues in the design and implementation of observational human exposure measurement studies that should be considered for inclusion in the document.
>    b. Identify specific elements in each of these major areas that should be considered for inclusion in the document.
>    c. Provide recommendations on the type and level of information that should be considered for inclusion in the document when describing state-of-the-science approaches, methods, techniques, or standards.
>    d. Provide recommendations on the criteria that should be considered when evaluating and identifying the state-of-the-science for the approaches, methods, techniques, or standards.
> 2. Provide recommendations and listings of sources of information for developing the document including case studies where available.
> 3. Identify at least ten specific elements of the design and implementation of these studies that the panel considers to have the most uncertainty with regard to the "state-of-the-science," discuss these elements, and provide recommendations on state-of-the-science approaches for them.

The following individuals were members of the Expert Panel.

**Timothy Buckley** (Chair)
Division of Environmental Health Sciences
School of Public Health
Ohio State University
Columbus, OH

**Sophie Balk**
Attending Pediatrician
Children's Hospital at Montefiore
Professor of Clinical Pediatrics
Albert Einstein College of Medicine
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**David Carpenter**
Director, Institute of Health and Environment
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**Giselle Corbie-Smith**
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**Michael Lebowitz**
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**Jerry Menikoff**
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Kansas City, KS

**Rebecca Parkin**
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Professor of Environmental and Occupational Health
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George Washington University Medical Center
Washington, DC

## Review by the EPA Human Studies Review Board and Public Comment

The process for developing this document included the following steps after the Expert Panel Workshop.

- A draft document was written by NERL researchers.
- The draft document was distributed to internal EPA staff for review and comment (see Acknowledgements for the list of reviewers).
- The draft document was revised to address internal reviewer comments; an external review draft document was prepared.
- The availability of the external review draft document for public comment was announced in a *Federal Register* notice.
- An EPA docket was opened, and the external review draft document was available for public comment for 45 days.
- The external review draft document also was provided to EPA's Human Studies Review Board (HSRB) for review and comment (see http://www.epa.gov/osa/hsrb/ for information on the HSRB).
- The review by HSRB was announced in a *Federal Register* notice.
- HSRB met October 21-24, 2007, and discussed the document during the meeting.
- HSRB provided EPA with comments on the document in their final report of the October meeting.

The charge to the HSRB for the SEAOES document review was that shown just below.

**Draft Document on *Scientific and Ethical Approaches for Observational Exposure Studies***
**Charge to the Human Studies Review Board**
**(October 4, 2007)**

Observational human exposure studies are performed to collect information about individuals and the environment around them in order to better understand people's exposures. 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. It is important to understand why and how people are exposed to chemicals in the environment for EPA to fulfill its mission to protect human health.

EPA scientists and their managers take the protection of human subjects who participate in their observational studies very seriously. The steps needed to ensure protection of the human subjects are often complex, and the specific actions will vary depending on the objectives of the study, details about the participants, and the communities in which the studies are performed.

This document is intended as a resource and reference for scientists in EPA's Office of Research and Development (ORD) National Exposure Research Laboratory (NERL) as they develop and implement observational human exposure studies. The authors recognize that this document may also prove to be useful to others involved in exposure science research, but the document is not meant to represent an official Agency "guidance document" and should not be used that way. This document does not provide solutions to the scientific and ethical issues that will undoubtedly arise as such studies are undertaken: no document could provide all of the answers in advance or develop a comprehensive checklist for all such studies. Rather, this document attempts to identify the types of issues that will need to be considered and addressed as NERL researchers plan and implement observational human exposure studies. The researchers will need to work with others – the study team, IRB members, EPA Human Subjects Research Review Official (HSRRO), the participants and their community, and other stakeholders – to identify and address all of the relevant issues for their particular study in order to ensure that the specific elements of the study will safeguard and protect the human research subjects.

Charge to the Human Studies Review Board

The draft document on *Scientific and Ethical Approaches for Observational Exposure Studies* consists of the following seven sections:

1. Introduction
2. Elements to be Considered in Study Conceptualization and Planning
3. Ensuring Protection of Vulnerable Groups
4. Privacy, Confidentiality, and Other Concerns Related to Observational Human Exposure Measurement Studies
5. Creating an Appropriate Relationship Between Participant and Investigator
6. Building and Maintaining Appropriate Community and Stakeholder Relationships
7. Designing and Implementing Strategies for Effective Communication

The Human Studies Review Board is asked to address the following questions for each section of the draft document:

1. One of the goals of the document is identify the major scientific and ethical areas and issues that researchers should address in the design and implementation of observational human exposure measurement studies, with the emphasis on the areas requiring ethical considerations. Does each section identify the major areas and issues where ethical considerations should be addressed?
2. The document is intended to serve as a reference and resource of information that researchers can use in the design and implementation of observational exposure studies. For each section, are there additional sources of information that should be considered for inclusion?
3. Is the information presented accurately and clearly in each section?

## Appendix C

# Recommended Content of a Human Subjects Protocol

The Council for International Organizations of Medical Sciences (CIOMS, 2002) has developed a comprehensive list of items that they recommend for inclusion in a human subjects research protocol. Many of the items that they identify are also useful for observational human exposure studies.

## Items Relevant to Observational Human Exposure Studies

(1) The title of the study
(2) A summary of the proposed research in lay or nontechnical language
(3) A clear statement of the justification for the study
(4) The investigators' views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them
(5) A summary of previous studies on the research problem, including unpublished studies known to the investigators, and information on previously published research on the topic
(6) A statement that the principles of the Belmont Report and requirements specified in 40 CFR 26 will be implemented
(7) An account of previous submissions of the protocol for ethical review and their outcomes
(8) A brief description of the sites where the research is to be conducted, including information about the adequacy of facilities for the safe and appropriate conduct of the research, and *relevant* demographic and epidemiological information about the population to be studied
(9) The names and addresses of the funding organization, research partners, and collaborators
(10) The names, addresses, institutional affiliations, qualifications, and experience of the principal investigator and other investigators
(11) The objectives of the study, its hypotheses or research questions, its assumptions, and its variables
(12) A detailed description of the design of the study
(13) The number of research subjects needed to achieve the study objective, and how this was determined statistically
(14) The criteria for inclusion or exclusion of potential subjects and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or other reasons
(15) The justification for involving as research subjects any persons with limited capacity to consent or members of vulnerable social groups and a description of special measures to minimize risks and discomfort to such subjects
(16) The process of recruitment (e.g., advertisements) and the steps to be taken to protect privacy and confidentiality during recruitment
(17) A description and explanation of any and all interventions
(18) The measurements to be performed in the study, including environmental and biological sample collection, and other data and information that will be collected
(19) If applicable, clinical and other tests involving the study participants that are to be carried out
(20) The rules or criteria according to which subjects may be removed from the study or the study may be terminated
(21) The methods of recording and reporting adverse events or reactions, and provisions for dealing with complications
(22) The potential benefits of the research to subjects and to others
(23) The expected benefits of the research to the population, including new knowledge that the study might generate

(24) The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent
(25) When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative.
(26) An account of any economic or other compensation or incentives to prospective subjects to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the subjects, such as payment for medical services
(27) The plans and procedures and the persons responsible for communicating to subjects information arising from the study (on harm or benefit, for example) or from other research on the same topic that could affect subjects' willingness to continue in the study
(28) The plans to inform subjects about the results of the study
(29) The provisions for protecting the confidentiality of personal data and respecting the privacy of subjects, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject
(30) Information about how the code, if any, for the subjects' identity is established; where it will be kept; and when, how, and by whom it can be broken in the event of an emergency
(31) Any foreseen further uses of personal data or biological materials
(32) A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study if necessary
(33) A list of the references cited in the protocol
(34) The source and amount of funding of the research, including the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the investigators, the research subjects, and, when relevant, the community
(35) The arrangements for dealing with financial or other conflicts of interest that might affect the judgment of investigators or other research personnel, including informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the ethical review committee; and the transmission by that committee to the research subjects of the parts of the information that it decides should be passed on to them
(36) The time schedule for completion of the study
(37) Particularly in the case of an industrial sponsor, a contract stipulating who possesses the right to publish the results of the study and a mandatory obligation to prepare with and submit to the principal investigators the draft of the text reporting the results
(38) The circumstances in which it might be considered inappropriate to publish findings, such as when the findings of any study may present risks to or stigmatize the interests of a community or population or of a racially or ethnically defined group of people
(39) A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor to take appropriate action against such unacceptable procedures

**Source:** CIOMS (The Council for International Organizations of Medical Sciences) (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. World Health Organization. Geneva, Switzerland.

## Appendix D

# Recommendations for Enhancing Public Trust

Although the *Report and Recommendations on Public Trust in Clinical Research for the NIH Director from the Director's Council of Public Representatives (COPR)* was developed in the context of NIH-supported clinical research, many of the recommendations are applicable to observational human exposure studies. A summary of recommendations from the report is provided below.

### Building Trust Through Community Partnerships

*Recommendation 1*: Incorporate into the NIH mission and philosophy that it values the involvement of the community in research and create language that expresses this value.

*Recommendation 2*: Encourage change in the culture of the scientific community to ensure that medical research is viewed in the context of a long-term commitment to the community, not a one-time research study.

*Recommendation 3*: Investigate ways to provide mechanisms that allow for follow-up health care when a clinical trial or treatment ends.

### Building Relationships with Patients (Participants) (True partnerships with patients may not be possible, but bidirectional relationships must be enhanced.)

*Recommendation 4*: Educate and reorient the current research community to the importance of treating the public as a partner in the research process.

*Recommendation 5*: Set the expectation across the entire research community, NIH funded research and beyond, that study results and outcomes should be shared with the research participants and the larger community promptly and consistently. This will ensure translational research.

### Building Partnerships with Community Providers

*Recommendation 6*: Take action to interest community providers in clinical research and maintain their involvement.

*Recommendation 7*: Provide incentives (not just financial) for primary health care providers and community specialists to play a role in clinical trials.

### Building Trust in Scientists

*Recommendation 8*: Engage researchers, educators, and academic institutions in incorporating the public's perspective consistently at every level of training and in both the conduct of clinical research and the publication of findings from that research.

*Recommendation 9*: Focus on educational strategies to help patients and communities better understand clinical research. This will help scientists because educating the public will empower and prepare individuals to be informed partners in the clinical research process. An informed and trusting public will enhance research participation.

### Building Trust in the NIH and Scientific Research

*Recommendation 10*: Continue to develop and fund efforts to build a national identity for the NIH based on what NIH does best—research and education—as a basis for enhancing public trust in clinical research.

*Recommendation 11*: Review the role and impact of Institutional Review Boards and other patient protections in the clinical research process because the public views these protections as less effective than they should be.

*Recommendation 12*: Document and publish "best practices" from efforts to reengineer the clinical research enterprise as soon as the NIH begins to see results, so that progress in improving public trust in medical research grows rapidly and steadily.

**Source:** NIH (National Institutes of Health) (2005). *Report and Recommendations on Public Trust in Clinical Research for the NIH Director from the Director's Council of Public Representatives (COPR)*. National Institutes of Health, Director's Council of Public Representatives, January 14, 2005. Available: http://copr.nih.gov/reports/public_trust.asp [accessed 12 June 2007].

## Appendix E

# List of Acronyms and Abbreviations

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AHS | Agricultural Health Study |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BEI | biological exposure index |
| CAB | community advisory board |
| CBPR | community-based participatory research |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Sciences |
| COPR | National Institutes of Health Director's Council of Public Representatives |
| CPSC | Consumer Product Safety Commission |
| CTEPP | Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants |
| DEARS | Detroit Exposure and Aerosol Research Study |
| DHEW | U.S. Department of Health, Education, and Welfare |
| DMOC | data monitoring and oversight committee |
| DNA | deoxyribonucleic acid |
| DSMB | data safety monitoring board |
| DSMP | data and safety monitoring plan |
| EHCRB | environmental health and community review board |
| EPA | U.S. Environmental Protection Agency |
| ERG | Eastern Research Group |
| FCN | Federal Communicators Network |
| FDA | Food and Drug Administration |
| HHS | U.S. Department of Health and Human Services |
| HSRB | Human Studies Review Board |
| HSRRO | Human Subjects Research Review Official |
| HUD | U.S. Department of Housing and Urban Development |
| ICR | information collection request |
| IOM | Institute of Medicine |
| IRB | institutional review board |
| NAS | National Academy of Sciences |
| NBAC | National Bioethics Advisory Commission |
| NCI | National Cancer Institute |
| NCS | National Children's Study |
| NEI | National Eye Institute |
| NEJAC | National Environmental Justice Advisory Council |
| NERL | National Exposure Research Laboratory |

| | |
|---|---|
| NGO | Nongovernmental organization |
| NHANES | National Health and Nutrition Examination Survey |
| NHAPS | National Human Activity Pattern Study |
| NHEXAS | The National Human Exposure Assessment Survey |
| NHLBI | National Heart, Lung, and Blood Institute |
| NHRPAC | National Human Research Protections Advisory Committee |
| NIH | National Institutes of Health |
| NRC | National Research Council |
| OHRP | Office for Human Research Protections |
| OMB | Office of Management and Budget |
| OSMB | observational study monitoring board |
| PM | particulate matter |
| Q&As | questions and answers |
| QAPP | quality assurance project plan |
| RfD | reference dose |
| SEAOES | Scientific and Ethical Approaches for Observational Exposure Studies |
| TEAL | Tribal Efforts Against Lead |
| TEAM | Total Exposure Assessment Methodology |
| TLV | threshold limit value |
| VOC | volatile organic compound |
| WHO | World Health Organization |

## Appendix F

# Glossary

**Agent.** A chemical, mineralogical, biological, or physical entity that may cause deleterious effects in an organism after the organism is exposed to it [EPA/600/Z-92/001, May 1992].

**Assent.** A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent [45 CFR 46.402(d)].

**Autonomy.** The capability and capacity to govern oneself.

**Beneficence.** The ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, *nonmaleficence* (do no harm).

**Child.** A person who has not attained the age of 18 years [40 CFR 26.202(a)]

**Collateral observations.** Potentially unsafe hazards, conditions, or situations unrelated to the research study that are observed by the research staff

**Common Rule.** The Common Rule is a short name for "The Federal Policy for the Protection of Human Subjects." It was adopted by more than a dozen Federal departments or agencies in 1991, with EPA adapting it in Title 40 CFR Part 26 Subpart A.

**Community-based participatory research (CBPR).** Collaborative research with a community in which the community is involved in all phases of the research. A fundamental concept is that the research aims to combine knowledge with action and to achieve social change to improve health outcomes and eliminate health disparities.

**Confidentiality.** The keeping safe or not redisclosing by one of the parties in a confidential relationship information that originally was disclosed in the confidential relationship

**Environmental justice.** The fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies

**Exposure.** Contact of a chemical, physical, or biological agent with the outer boundary of an organism (e.g., a person). Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact. (The definition is taken from Guidelines for Exposure Assessment [EPA/600/Z-92/001, May 1992]).

**Exposure concentration.** The exposure mass divided by the contact volume or the exposure mass divided by the mass of contact volume depending on the medium

**Exposure duration.** The length of time over which continuous or intermittent contacts occur between an agent and a target. For example, if an individual is in contact with an agent for 10 minutes per day for 300 days over a 1-year time period, the exposure duration is 1 year.

**Exposure event.** The occurrence of continuous contact between an agent and a target

**Exposure pathway.** The course an agent takes from the source to the target

**Exposure route.** The way an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption)

**Human subject.** 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 [40 CFR 26.102(f)]

**Informed consent.** A potential participant's autonomous authorization to participate in the research. The three pillars of valid informed consent are (1) information, (2) comprehension, and (3) voluntary participation.

**Institutional review board (IRB).** An IRB established in accord with and for the purposes expressed in EPA's Policy for Protection of Subjects in Human Research conducted and supported by EPA [40 CFR 26.102(g)]

**Justice.** The ethical obligation to treat each person in accordance with what is due to him or her. In the ethics of research involving human subjects, the principle refers primarily to *distributive justice*, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions among persons.

**Minimal risk.** The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [40 CFR 26.102(i)].

**Nonmaleficence.** The proscription of deliberate infliction of harm on persons

**Observational human exposure study.** Studies that involve collection of human exposure data (including environmental, biological, survey, activity, and various other forms of data) under real-world field conditions during normal participant day-to-day activities, with no additional exposures to the chemical being studied because of participation in the study. The studies involve interaction with study participants but do not involve intervention or manipulation of the factors being studied, and there is no attempt by the researcher to affect the outcome.

**Observational research.** Any human research that does not meet the definition of *research involving intentional exposure of a human subject* [40 CFR 26.302]

**Privacy.** Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others

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

**Research involving intentional exposure of a human subject.** 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 [40 CFR 26.202(b)]

**Respect for persons.** A fundamental ethical value that is the basis of much of modern bioethical thought and regulation. The concept incorporates at least two fundamental ethical considerations, namely (1) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and (2) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

**Source.** The origin of an agent for the purposes of an exposure assessment

**Stakeholder.** A person or group who has a valid interest in an activity, who can affect or is affected by the activity, and who stands to gain or lose depending on the decisions implemented

**Stressor.** Any entity, stimulus, or condition that can modulate normal functions of the organism or induce an adverse response (e.g., agent, lack of food, drought)

**Vulnerability.** A substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons.

**Vulnerable groups.** Populations extended additional human subjects protections, such as children, individuals with questionable capacity to consent, prisoners, fetuses and pregnant women, the terminally ill, students and employees, and comatose patients, etc.

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