PROTECTING HUMAN SUBJECTS

U.S. DEPARTMENT OF ENERGY • OFFICE OF BIOLOGICAL AND ENVIRONMENTAL RESEARCH

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Contents

Protecting Human Subjects Workshop: Highlights

More than 50 Department of Energy (DOE) Headquarters, field offices, and national laboratory personnel attended the Protecting Human Subjects Workshop held in Alexandria, Virginia, February 8-9, 1993. Staff from other Federal agencies involved in human subjects protection, such as the National Institutes of Health (NIH), Department of State, Department of Education, and Department of Defense, also attended and participated.

Dr. Susan Rose, who directs the human subjects research program for the Office of Energy Research, organized and chaired the workshop. A variety of speakers from the DOE community, other Government agencies, and private or academic institutions participated in the panel sessions. Dr. Robert Levine, Professor in the Department of Internal Medicine at Yale University, Chairman of the Human Investigation Committee, and Editor of the journal *IRB*, delivered the keynote presentation.

Dr. Susan Rose of DOE headquarters welcomed Dr. Jerry Williams, newly appointed Medical Director at Los Alamos National Laboratory.

In his opening speech, Dr. Robert Simon, Principal Deputy Director of the Office of Energy Research, emphasized DOE's commitment to protect human subjects and urged the group to increase their awareness of and sensitivity to bioethical issues. Dr. Rose added that she hoped the workshop would broaden understanding of ethical concepts and address the range of implementation issues facing the Department.

The meeting was divided into six panel sessions which covered

1. implementation of human subjects regulations at DOE,
2. bioethics,
3. occupational medicine and epidemiology,
4. volunteers in research,
5. a mock institutional review board (IRB), and

6. challenges for the future.

Keynote Speech

Dr. Levine delivered the keynote presentation on the ethics of research involving human subjects. He described several incidents of abuse inside and outside of the United States. These exposés raised awareness that not only was unethical conduct a part of Nazi war experiments, but it occurred in other countries including the United States. He described the historical precedents, such as the Nuremberg Code and the Declaration of Helsinki, that led to the U.S. Belmont Report, the National Commission for the Protection of Human Subjects, and the U.S. Federal Common Rule (10 CFR Part 745). He also spoke about recent developments in research and technology, including investigational drugs and devices, which pose new questions. In the still-evolving international collaborative research area, Levine pointed out that the Council for International Organizations of Medical Sciences, along with the World Health Organization, issued in 1993 the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" that addresses performing research in other countries.

Dr. Robert Levine, Professor at Yale University's Department of Internal Medicine, delivered the keynote presentation.

Implementation of Human Subjects Regulations at DOE

Implementation of human subjects regulations was addressed from three perspectives: Headquarters, field office, and laboratory. Dr. Rose emphasized that although a fairly rigorous system for managing human subjects research is now in place at DOE, the system is still evolving. Issues still unresolved include developing procedures for international research and audits, tracking work-for-others projects, and increasing automation.

Mr. Joseph Aaron of the San Francisco Field Office described the system he set up to assure compliance in each of the five DOE laboratories under his field office's purview. Each laboratory presented a slightly different challenge.

Dr. Ronald Walters, Manager of the Life Sciences Center at Pacific Northwest Laboratory, described the system for evaluating human subjects research projects at Los Alamos National Laboratory (LANL), which involved agreements with field offices and Headquarters and intra-laboratory outreach. Dr. Walters was formerly Program Director of Biological and Environmental Research at LANL. He described the process and challenges associated with formalizing project assurances, institutionalizing the IRB, and developing appropriate documentation and communication vehicles. He said that frequently encountered deficiencies in submissions to the IRB included incomplete or uninformative consent forms and lack of clarity about experimental procedures. For LANL, competence obtained through the single project assurance process resulted in the laboratory's receiving the first DOE multiple project assurance.

Bioethics

This panel addressed past abuses of human participants in research and the history of bioethics, in addition to discussion of legal and ethical considerations for conducting research.

Dr. Frances Menlove, a psychologist who works in applied ethics at LANL, defined confidentiality from a bioethical standpoint as the "boundaries surrounding shared secrets." She stressed that the information

explosion has created a discrepancy between reality and people's expectations of confidentiality. She noted that confidentiality and informed consent issues pose universal problems for occupational wellness studies at the laboratories.

Recently, LANL struggled with these issues in a proposed program designed to evaluate its wellness center. Program participants were to be asked moderately intrusive questions; more importantly, they would be selected from a larger study that combined personal data about individuals from several databases. This study design, said Dr. Menlove, poses difficult considerations for the IRB review—e.g., how can confidentiality be maintained? when does combining databases yield information sufficient to identify individuals even without their names? when are questionnaire respondents required to give informed consent? when are other participants required to provide informed consent?

Dr. Frederick Bonkovsky, Acting Chief of the Bioethics Program at NIH, focused on the new challenges in bioethics brought about by modern technological changes and directives, including living wills and designated powers of attorney. One of the new challenges for bioethics, he said, was to ensure protection for impaired subjects. He presented a case study about a cognitively impaired woman who was incapable of making decisions. As her health deteriorated, she agreed, through a power of attorney, to allow her brother to act on her behalf if she became incapacitated. When she was diagnosed with Alzheimer's disease, her brother wanted to enroll her in a research program. Various questions arose: What are the risks and benefits of participation? What is the role of family members in making decisions?

Bonkovsky said the bioethicist, the IRB, and the principal investigator face tough questions. For example, what is impairment? Who are the moral actors? How does society view the matter (e.g., what is the law?)? Bonkovsky noted that principal investigators are responsible for "character ethics." Yet, he said, they are becoming much more involved in the business side of project implementation—for example, pursuit of grants and funding—than they used to be. In conclusion, he urged bioethicists and IRBs to make investigators "more virtuous and less vigorous."

Dr. Michael Goldsmith, Law Professor at Brigham Young University, looked at the roots of informed consent and the requirements spelled out in the Nuremberg Code. He reviewed several abuse cases—for example, Tuskegee and Willowbrook—in relation to legal concepts of negligence and battery. Noting the rising incidence of legal liability suits, he urged researchers to take seriously their duty to fully disclose information and adhere to informed consent requirements. Behavior that passes the legal test, he cautioned, does not necessarily pass the ethical test.

Occupational Medicine and Epidemiology

In this session, panel members discussed key differences between human subjects research, including epidemiology, and occupational medicine. "Research" activities aim to test a hypothesis and develop or contribute to generalizable knowledge. "Practices," such as occupational medicine, are designed solely to enhance the well-being of an individual through diagnosis, preventive treatment, or therapy. While these definitions seem clear, the panel presented studies and programs that showed that the lines between research and practice are often blurred.

Dr. George Gebus, Director of the Office of Occupational Medicine, discussed his office's responsibility for recognizing, treating, and preventing work-related illness. Ms. Kathleen Noonan, Deputy Department Head of Lawrence Livermore National Laboratory's (LLNL's) Health Services Department, reviewed four case studies.

The first study used a new low-level urine bioassay to determine heavy metal exposure for a worker population "at risk" and an unexposed "control" population. Here, only the control population required human subjects research protections. The second study, which pooled and analyzed data about LLNL's security inspector population, was considered human subjects research. The third study recruited clinical patients undergoing treatment for carpal tunnel syndrome (CTS) to evaluate a predictive tool for CTS. The research records were subject to a workers' compensation subpoena. This study thus showed how difficult it is to separate research records from clinical records. The last case study showed how clinical practice can lead to a research activity. When a physician clinically observed what appeared to be an excess of melanomas in employees, it was considered practice. When the physician conducted a study of workplace factors contributing to melanomas, it was considered research.

Dr. Cliff Strader, Epidemiologist for the Office of Epidemiology and Health Surveillance, reviewed a DOE health surveillance program that provides ongoing monitoring of the health status of workers and identifies health hazards. He observed that this activity does not qualify as human subjects research until problems are identified, when it then gives rise to an epidemiological investigation. The Department's Comprehensive Epidemiological Data Resource (CEDR) systematically organizes and documents data from DOE worker studies and disseminates them to independent researchers. However, certain omissions, such as lack of names and Social Security numbers, prevent the data from being linked to individuals.

In conclusion, the panel stressed that informed consent, data sharing, and confidentiality issues are not always simple to resolve.

Volunteers in Research

The DOE volunteer population, cross-cultural communication, and equitable choices in selecting research subjects were discussed in this section.

Dr. Walters presented findings of a small informal survey of the DOE human subjects volunteer population. The survey showed that DOE recruited volunteers from the following groups: 47% employees, 9% employees of contractors or subcontractors, 21% general public, 20% university students, 0.4% children, 0.6% mentally disadvantaged, 0% pregnant women, and 0.1% prisoners.

Dr. Nsenga Warfield-Coppock, a social scientist and consultant, provided insight into breaking through cross-cultural barriers to communicate with volunteers. She stressed that researchers must possess both competence in research methodology and cultural sensitivity. She offered specific ways to infuse cultural sensitivity into research design. She also talked about the need to broaden the DOE volunteer population base so that all people could benefit equally from the research results. (For more details, see "Communicating with Volunteer Populations: Breaking Through Cross-Cultural Barriers".)

Dr. Joan Porter, Senior Analyst of the Office of Protection from Research Risks at NIH, talked about how to make equitable choices in selecting research subjects. This is a major initiative and concern at NIH at present. She referred the audience to the Belmont Report and cautioned that those who are particularly "available" for research may be in a compromised position and therefore relatively easy to manipulate. She talked about two levels of justice: justice on an individual level and on a societal level. The application of the principle of justice is not an easy one.

Dr. Levine added a few pointers for selecting research subjects: for example, don't burden already burdened individuals, don't exclude those who could benefit directly or indirectly from research, and do involve the *least* vulnerable of the vulnerable.

Mock IRB

Members of the mock IRB and their respective roles, in italics, included—

- Dr. Robert Jones, Associated Director, Inhalation Toxicology Research Institute *(chair)*.
- Dr. Dale Minnner, Medical Director, Oak Ridge Institute for Science and Education *(ethicist)*.
- Dr. William Burr, former Medical Director, Oak Ridge Institute for Science and Education *(physician)*.
- Dr. Ronald Walters, Manager, Life Sciences Center at Pacific Northwest Laboratory *(scientist)*.
- Ms. Linda Erickson, Human Studies Board Administrator, Sandia National Laboratories *(community member)*.

Simulating an IRB discussion of a sample research protocol, the members of the mock IRB played their respective roles, and audience members raised challenging questions. Dr. Bart Gledhill, Deputy Associate Director of Biology and Biotechnology at LLNL, played the dual role of principal investigator and audience facilitator. He presented the details of a study that very roughly reflected an existing international project. The purpose of the study was to investigate the magnitude and nature of radiation exposure from the Chernobyl nuclear accident. To do so, research participants provided blood samples in exchange for a year's supply of vitamins, which were unobtainable in the former U.S.S.R.

Together, the mock IRB participants and audience scrutinized the research design and process. They identified several problems with the selection process. For example, many questioned whether offering vitamins was an unfair inducement to participate in the study. The audience found problems with the informed consent form, such as missing key elements and the apparent lack of a provision for translating English into Russian. The audience looked at other problems and considerations unique to international research. For example, more information should be provided on the former U.S.S.R. human subjects policies and on the coordination/management of blood samples.

Challenges for the Future

This panel addressed several questions. What areas of the human genome project require human subjects protections? What kinds of issues arise as collaboration with institutions in foreign countries increases? What are the challenges associated with an IRB?

Dr. Eric Juensgt, Acting Chief of Ethical, Legal, Social Implications Branch of the National Center for Human Genome Research, discussed a variety of ethical considerations faced in the human genome project.

Examples of problems are:

1. persons who discover they are carriers of disease genes risk loss of insurability and
2. when entire families are used as research subjects to track disease genes, informed consent, privacy, and confidentiality issues are more far reaching than they are in research involving individuals.

Dr. Juensgt reviewed several ethical questions for which the Federal Common Rule on human subjects (10 CFR Part 745) provides no clear guidance. Who gives permission for children to participate in genetic family studies? What are the material risks associated with the research
(e.g., how do researchers proceed when they discover people are carriers of a disease)? What information about individuals should be disclosed to physicians, employers, and others?

Dr. Porter summarized NIH's involvement with international human subjects research projects and reviewed the provision of the Common Rule (10 CFR Part 745) that applies to foreign research. Specifically, researchers must not only look at a foreign country's code with respect to human subjects but must also assure that the other country's procedures are appropriate to accommodate principles in the U.S. Federal regulations. Dr. Porter identified several challenges associated with international research: the need to translate foreign languages, address cultural sensitivities, ensure informed consent, correct misunderstandings about the U.S. regulations, and address conflict-of- interest on IRBs, and others.

Ms. Linda Erickson, Human Studies Board Administrator at Sandia National Laboratories, described the eight-month process of establishing an IRB at Sandia, a weapons laboratory seeking to broaden its mission. Her efforts involved extensive research, outreach, organization, training, coordination, and approval by a variety of people in the Sandia organization. (For more details, see "Setting Up an Institutional Review Board: Spotlight on Sandia".)

Setting up an Institutional Review Board:
Spotlight on Sandia National Laboratories

Ms. Linda Erickson, Human Studies Board Administrator in the Occupational Medicine Center, recently established the first IRB at Sandia National Laboratories (SNL). Ms. Erickson came to this position after transferring from SNL's Yucca Mountain Project group, where she served as a project manager. Although she was new to the human subjects research area, her 15 years of experience at SNL gave her knowledge of its organizational structure and inner workings that was extremely helpful in getting the job done. Speaking at the DOE Human Subjects Workshop, Ms. Erickson stressed that the person in charge of setting up a new IRB needs to be knowledgeable about IRB requirements *and* familiar with the organization to be served. She amplified her remarks at the meeting during a recent interview.

When did Sandia realize an IRB was needed?

"Until very recently, we did not realize that some of SNL's physical safeguards research, which aims to control access to weapons or facilities, actually meets the criteria for human subjects research. Because this research is defense-funded, it does not fit into the typical biomedical (clinical) research area, so our investigators didn't realize that it constitutes human subjects research in the eyes of the Federal Government. However, the passage of the Common Rule (10 CFR Part 745) for human subjects protection in the summer of 1991 helped sensitize Federal agencies to the requirements for human subjects research, and SNL investigators were startled to be told that their research funds were on hold until they obtained an IRB approval. A '*what* approval?' was a fairly common reaction."

How did the IRB project get started?

"We felt we had to get an IRB established quickly because our researchers' funds were on indefinite 'hold'. Also, these days, SNL emphasizes its Strategic Plan, a major goal of which is to attain organizational excellence through integrity and accountability in research. SNL is committed to becoming a model of excellence in environmental safety and health. Because the Federal guidelines of the Common Rule (10 CFR Part 745) require this type of accountability and integrity, both needs helped gain SNL management's support for creation of SNL's IRB."

What steps were involved?

"To set up SNL's IRB, we first defined establishment of the IRB as a project with corporate-wide impact. Then, we defined the activities needed to establish a new IRB and organized them into the categories of requirements, procedures, paperwork and records, membership, briefings and training, and approvals."

"I spent the largest block of my time in trying to understand the Federal requirements from the Code of Federal Regulations (CFR) and DOE Orders. I surveyed stakeholders' needs and interests, especially at Sandia's California site, because our corporate-wide IRB has to comply with state and local requirements at *all* SNL geographic locations. I then created operational procedures that would comply with all requirements and also meet local needs. To avoid 'reinventing the wheel,' I looked at how other organizations, such as LANL and LLNL, run their IRBs. I also sat in on some local IRB meetings at the University of New Mexico and at Lovelace Scientific Resources, and both were extremely helpful in providing insight into the process and practices of IRBs. Paperwork, of course, is needed to meet Federal requirements, but I also had to look at SNL's corporate needs and requirements. In developing a pool of potential IRB members, we solicited assistance from SNL's Public Affairs Office in identifying community members and from SNL's Vice Presidents to identify a cross-representation of SNL technical and support staff, including individuals from Sandia's California site. We recognized a need for informational briefings on the IRB process. In addition, we identified a need to train IRB members in the IRB process and requirements. And finally, we had to obtain approvals from SNL's Legal Department, Policy Board, and President, and ultimately, from DOE Headquarters."

How long did the entire process take?

"Eight months. This was the projected time to establish the Board—ours is now called the Sandia Human Studies Board—and to get our first review package approved by DOE Headquarters. Part of the reason the project took so long was because corporate bodies that had to be addressed (e.g., the Sandia Policy Board) meet only once a month, and we were working around summer vacations, too."

What were the most significant challenges?

"One of the challenges was to set up an IRB that would meet the various needs of corporate groups at different locations. Another was to understand the IRB process in a DOE context, which differs from the clinical orientation of the NIH-regulated community. (SNL will be operating under Single Project Assurances from DOE Headquarters, not NIH.)"

"However, the greatest challenges were and will continue to be overcoming the mindset that we don't do human (translate,'medical') research and dealing with the variety of types of projects our Board will encounter. Because our investigators are typically engineers or scientists and are not from the traditional biomedical arena, human

subjects research is a new concept to them. We will have lots of 'gray' areas to grapple with, but that's what makes it all so interesting!"

Features of An Institutional Review Board

What is the function of an IRB?

IRBs are designed to—

- Protect the rights and welfare of human subjects.
- Minimize the risks to subjects and ensure that risks are outweighed by potential benefits.
- Ensure equitable selection of human subjects.
- Ensure adequate and appropriate methods for obtaining informed consent.
- Ensure that informed consent is appropriately documented.
- Monitor the data collected to ensure the safety of subjects.
- Protect the privacy of subjects and the confidentiality of data.

IRBs must review human subjects research at intervals appropriate to the degree of risk—not less than once a year.

What is the makeup of an IRB?

IRBs must have at least five members who represent diversity with respect to race, gender, profession, ethnicity, and other factors. Specifically—

- No IRB should consist of all men or all women.
- Each IRB should include at least one member with scientific expertise.
- Each IRB should include one member whose concerns are primarily nonscientific.
- Each IRB should include one member who is not affiliated with the institution.
- If vulnerable subjects (e.g., pregnant women, children, prisoners, mentally or physically disabled people) are involved, IRBs should consider including one or more individuals knowledgeable about and experienced in working with these groups.

In addition, it is also recommended that—

- Each IRB include one member who has an ethical or religious orientation.
- Chairmen of IRBs have a medical degree.

Communicating with Volunteer Populations: Breaking Through the Cross-Cultural Barriers

At the Human Subjects Workshop in early February, social scientist Dr. Nsenga Warfield-Coppock addressed major themes related to cross-cultural communication and suggested approaches to promote cultural understanding between researchers and human subjects. Dr. Warfield-Coppock urged researchers to break with the tradition of "scientific colonialism," which leads investigators to claim rights to information about human subjects but avoid sharing information appropriately with them. To the greatest extent possible, a free exchange of information between researchers and human subjects is desirable.

The research setting provides many opportunities for cross-cultural communication and information exchange. For example, researchers must explain research design, risks and benefits, and the informed consent process; elicit and respond to questions and concerns; and deal with problems that arise. If researchers understand cultural differences and recognize the barriers to cross-cultural communication, they are much better equipped to present information to their subjects clearly and effectively. In doing so, researchers perform a vital role: they can help *all* subjects make informed decisions throughout their participation in research.

Seeing Through Communication Errors

Dr. Warfield-Coppock characterized culture as a dynamic, evolving force that shapes life events and experiences. She said that it is no wonder communication errors occur between people of different cultures. Humans interpret life events and experiences based on cultural tradition, and cultures differ widely in their traditions, values, and beliefs.

She attributed miscommunication between people of different cultures to two well-documented phenomena. One is that people from different cultures who share a common experience analyze it differently. For example, two study populations respond to questionnaires filled with direct questions. The first group, which consists of Native Americans, typically responds in an indirect or symbolic fashion and may reinterpret the questions posed; the second group appreciates the direct style. If researchers recognize the diversity of communication style preferences across cultures, then they will do a better job designing questionnaires for the intended audience.

The second phenomenon is this: when observing behavior of people from one culture, observers from other cultures make interpretations according to their own backgrounds. If two researchers study women in poverty who are exposed to domestic crime, for instance, a white, affluent male researcher will no doubt observe the situation differently from a woman researcher who grew up in a violent environment. If researchers are aware of their own cultural biases, they can more clearly identify or communicate all the factors contributing to a problem.

Becoming Culturally Sensitive

What specific steps can help researchers become culturally sensitive? Dr. Warfield-Coppock agreed with the philosopher who said "to speak a language is to take on a culture," but acknowledged that learning a new language may not be practical. At a minimum, researchers must become familiar with the characteristics of other cultures, she said. That way they gain insight into which questions are appropriate to ask and how to

frame questions. For example, researchers who know that Native American cultures tend to honor language and take care not to waste words may adapt direct questions and offer lengthy interviews. Similarly, an awareness that Hispanics and members of other cultures highly value modesty and privacy may prompt researchers to reframe intrusive questions. Generalizations like these about cultural groups are helpful, but Dr. Warfield-Coppock emphasized that they are only generalizations. To avoid stereotyping, it is important to recognize that a wide spectrum of behaviors, attitudes, and experiences occurs in members of any culture.

Using Language as a Tool for Effective Communication

Language can be a tool to minimize and resolve communication errors. Researchers can enhance their listening skills, for example, and learn how to employ nonjudgmental questioning to elicit specifics and details. Researchers should also be aware that different cultures attribute different meanings to the same words; thus, language may have unintended implications for the listeners. Dr. Warfield-Coppock mentioned "minority" as a good example of a term that may inadvertently alienate members of an ethnic group. Imposed by outsiders, this term implies second-class status and tends to lump group members together. Furthermore, members of ethnic groups don't view themselves as minorities, Dr. Warfield-Coppock said. They tend to identify with the race, ethnicity, or other category to which they belong. Native Americans identify themselves by tribe; Asians, Hispanics, and Africans often identify with their places of origin.

Dr. Warfield-Coppock's overriding message was that researchers must possess both competence in research methodology and cultural sensitivity. Because both qualifications are rarely found in one person, Dr. Warfield-Coppock advised researchers to turn to research subjects and outside organizations to help develop cultural competence.

Infusing Culturally Sensitive Methods into Research Design

Some ways Dr. Warfield-Coppock suggested to promote cultural understanding include—

- Involving human subjects in a central way. For example, researchers might solicit input from human research participants about how to conduct a phase of research.
- Using community advisory groups to help formulate specific objectives. These advisory groups might include members of cultures participating in the research—people who can anticipate the community's concerns and voice its feelings.
- Ensuring that IRBs include community members who represent the research population.
- Ensuring that, as a general rule, translations into other languages are provided when English is not the subject's native language.
- Ensuring that translations yield true equivalence and reflect cultural sensitivity.

To ensure that informed consent requirements are clear, researchers might also—

- Get lay members of the IRB to suggest necessary modifications to the informed consent forms.
- Get members of the proposed ethnic population to review forms and indicate which aspects cause them discomfort or confusion.
- Use tests, audiovisual aids, or advisors to supplement informed consent forms.

Dr. Nsenga Warfield-Coppock contributed to this article. She is a Washington, DC-based consultant who specializes in cultural diversity training.

Coming Attractions

Activities

In August 1993, all field offices will be asked to give DOE headquarters an updated list of active and inactive human subjects projects.

Bulletin Articles

The next issues of *Protecting Human Subjects* will address the following topics:

- International Research.
- Distinctions Between Occupational Medicine and Human Subjects Research.
- Issues Related to Tracking Human Subjects.

Newsletter Information

This bulletin is designed to facilitate communication among those involved in human subjects research and to inform persons interested in human subjects research activities.

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