PROTECTING HUMAN SUBJECTS

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

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Contents

Feature Article: Protected to Death?

Robert Levine, M.D., Yale University School of Medicine, was the keynote speaker at the Fall 1995 Interagency Human Subjects Conference. During his speech, he applied the term therapeutic orphans to children who are "protected to death" by Federal regulations. He reminded the audience that through the 1950s, the collective benefit of research using human subjects was rarely questioned. A number of shocking studies exposed in the 1960s, however, led to a tightening of the protections for human subjects in the years that followed. Limits were placed on who could participate in research, and special protections were enacted for vulnerable populations, such as children and women biologically capable of becoming pregnant. Thus, therapeutic orphans, women of child-bearing age, and others were often denied the option of research participation.

In the 1980s, publicity surrounding medical developments and research into cures for fatal diseases such as cancer and AIDS roused affected patients who began to demand inclusion in research projects. AIDS activists inspired others to consider their own status vis-à-vis research projects. Some previously exempt groups no longer wished to be considered vulnerable and, therefore, ineligible to participate. They saw expanded access to clinical trials, for example, as a benefit, not a burden.

Attitudes toward research—including research with children and adolescents—changed, but the regulations have been slow to follow. Current practice imposes a hierarchy when choosing research subjects: adults first, then teenagers, young children, and finally, infants. This practice does not work well in all cases. For example, Dr. Levine noted that physicians treating children with AIDS cannot necessarily rely on research findings from adults with AIDS. The AIDS virus in children challenges the "adults first" standard established in the current regulations.

Research involving adolescent subjects is complicated by the privacy issue. Waiver of parental permission can be a crucial factor in subject participation. Many teenagers would rather have nothing to do with research than have their parents learn about their behavior. Because current regulations are not sufficiently specific enough on the privacy issue, the scientific community, government, health care workers, and others seek a remedy to the situation.

Dr. Levine was pleased to announce that the Society for Adolescent Medicine, through its Journal of Adolescent Health, would be presenting new Guidelines on adolescent privacy versus parental consent and the inclusion of "mature minors" in research. He urged everyone to study the Guidelines and offer comments.

Adolescents: Perspective on Research

Should research involving 16-year-olds be subject to the same rules as research involving 8-year-olds? For many legal purposes, both of these age groups are considered children and thereby classified as "vulnerable populations" requiring special protections under current Federal regulations (45 CFR Part 46, Subpart D). The regulations do not, however, recognize the physical and psychological differences between adolescents and children. Nor do they address in detail the privacy issues in adolescent health research or waivers of parental consent.

Increasingly, researchers and Institutional Review Boards (IRBs) are facing varied interpretations of the human subjects protections when applied to adolescents and are seeking ways to remove unnecessary barriers to adolescent participation in health studies. Moreover, segments of society previously excluded from research due to their "vulnerable" status no longer wish to miss out on potential research benefits.

To address these concerns, the Society for Adolescent Medicine released Guidelines for Adolescent Health Research, which interpret and clarify current Federal regulations, in the November 1995 Journal of Adolescent Health. The product of a 15-month national consensus project sponsored by the Society, the Guidelines draw on the experience and wisdom of a diverse group of experts.

Evolution of Protections for Minors, 1944–1976

The new Guidelines evolved from a series of attempts dating back some 50 years to establish formal protections for human subjects—especially those considered "vulnerable." Framed in 1949, the Nuremberg Code stated that the "voluntary consent of the human subject is absolutely essential." If literally interpreted, no child could ever be used in research. The Code, however, was not intended to address research using children.

The 1964 Declaration of Helsinki gave some guidance to researchers on the ethical treatment of legally incompetent research subjects, including minors. The Declaration required that the consent of the minor be obtained, whenever possible, along with the consent of the child's legal guardian.

In 1971, the National Institutes of Health (NIH) published The Institutional Guide to the Department of Health, Education and Welfare (HEW) Policy on Protection of Human Subjects. The policy allowed an "authorized representative" to give consent for another person. That term, however, was not defined. The circumstances for appropriate use of this policy also were left unspecified.

Two years later, in response to increasing criticism, NIH published draft regulations for protecting adults and children, passing them on to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) when it was created in 1974. Charged with drafting recommendations for research involving adults, children, and other vulnerable populations, the Commission then submitted a report on research involving children to HEW (now Health and Human Services [HHS]) in 1977.

1977 Recommendations for Children, Including Adolescents

In its report, the Commission recommended a method for handling informed consent with children—parents were required to give "permission" for their child to participate in research and the child was required to give "assent" to participation. A child was deemed old enough to give assent at age 7.

The Commission also recommended a four-tiered system for categorizing proposed research:

- *No more than minimal risk*—Research may take place with or without individual benefit to the child, with one parent's permission and the child's assent.
- *Greater than minimal risk, some benefit to the child*—If the research benefits outweigh the risks, research may take place if one parent gives permission and if the child assents.
- *Minor increase over minimal risk, no benefit to child*—If the research benefits future children with the same condition and poses a small increase in risk (over minimal), the research may take place. Both parents must give permission, and the child must give assent.
- *Special research*—This category, requiring special review, is for research that does not fit into the first three categories but is so important and compelling that it should be considered.

1977 Recommendations for Adolescents

Because of the unique developmental needs of adolescents, the Commission also recommended that parental permission be waived for adolescents who want to participate in clinical trials in the following cases:

- When, in certain jurisdictions, the adolescent may already legally receive treatment without parental consent (for example, when minor adolescents may receive health care based on their own informed consent).
- When the subjects are mature minors and the procedures involve no more than minimal risk.
- When research involves "children whose parents are legally or functionally incompetent."

New Guidelines

In 1983, HHS adopted the Commission's four categories of research involving minors and most of the other recommendations as Federal regulations in 45 CFR Part 46, Subpart D. HHS did not, however, specifically adopt the Commission's provisions for waiving parental permission for adolescents. Part 46.408 (c) only mentions an exception from parental permission for minors who are abused or neglected. This lack of precision in the current regulations led to the release of the Guidelines for Adolescent Health Research.

The Guidelines address waivers of parental permission and consent by mature minors. Under certain conditions, state and Federal law and judicial decisions permit those adolescents termed "mature or emancipated minors" to make personal health care decisions on their own. In contrast, under some interpretations of current regulations, a 16-year-old legally able to consent to his/her own health care may not be allowed to consent to participate in research. The new Guidelines explicitly extend the "mature minor" recognition to certain research situations in health care settings, while maintaining protections for adolescents not considered mature minors.

Adolescents: New Guidelines for Research

In late 1995, the Society for Adolescent Medicine issued new Guidelines for Adolescent Health Research. The Guidelines interpret and clarify existing Federal protections for children involved as subjects in research (45 CFR Part 46, Subpart D).

The full text of the Guidelines appears in the Journal of Adolescent Health (November 1995, pp. 264–267). Below is a summary of Sections II and III, which deal specifically with principles of adolescent health research and consent for participation of adolescent minors in research.

Consent for Participation of Adolescent Minors in Research

Federal regulations allow parental permission for research to be waived when it is not "a reasonable requirement." Under the offical research categories below are recommended criteria for an adolescent's participation without parental permission.

- **A. Research not involving greater than minimal risk** Many types of adolescent research fit into this category. Examples cited in the Guidelines include anonymous surveys, confidential surveys that collect identifying information, behavioral prevention and intervention research, and routine physical or psychological examinations. Because the associated risk is nonexistent or very slight, the Guidelines state that most adolescents should be presumed capable of giving informed consent. Four conditions must be met for an IRB to approve research without parental permission. Investigators must have—
    - 1. Ensured the privacy of the adolescent.
    - 2. Obtained the consent of the adolescent.
    - 3. Encouraged the adolescent to seek the support of a parent or another adult before participating.
    - 4. Created procedures for the adolescent to seek confidential assistance after participating in a survey with questions on sensitive issues. (For instance, after completing a study of behavior relating to HIV/AIDS pre-vention, an adolescent may desire additional information.)
- **B. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects**

  Examples of this type of research are investigational studies of new drug treatments, FDA Phase II and III protocols, and certain randomized controlled trials. Whenever a possibility of more than minimal risk exists, researchers should encourage adolescents to involve their parent(s) in the consent process, if possible. If seeking parental involvement is not possible or if the potential subject declines parental involvement, the adolescent may provide consent. Four conditions must be met for the IRB to approve research without parental permission. Investigators must have—

    - 1. Ensured the privacy of the adolescent.
    - 2. Obtained the informed consent of the adolescent.
    - 3. Ensured that clinical staff assist the adolescent in finding an adult advocate who understands the adolescent's personal situation and is committed to his/her well-being.
    - 4. Obtained confirmation from a trained professional (not involved in the research) that the adolescent has the capacity to give informed consent to the research.
- **C. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition**

Examples of this type of research include FDA Phase I drug trials, collection of body fluid or tissue specimens by invasive means, and studies involving the administration of radioactive tracers. In this category, the Guidelines concur with Federal requirements calling for adolescent assent and parental permission. IRBs may approve this type of research if the—

- 1. Risk is a minor increase over minimal risk.
- 2. Procedure involves an experience reasonably equivalent to experiences that are part of the adolescent's actual (or expected) situation.
- 3. Research is likely to provide some benefit to others.
- 4. Adolescent gives assent and a parent or guardian gives permission.

- **D. Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of minor adolescents**

  Research may be conducted when there is more than a minor increase in risk over minimal risk and no prospect of direct benefit to the adolescent only if the situation is extraordinary. This type of research requires a special review process conducted by the Secretary f the Department of Health and Human Services and a panel of experts. The Guidelines support the procedure in the current Federal regulations.

Special Considerations for Research Conducted in Health Care Settings

In many states, adolescents have the right to make personal health care decisions without parental permission. If adolescents are allowed to give consent for health care, the Guidelines recommend that they also be permitted to give informed consent for research—provided the guidance on waiving parental permission summarized in Parts A through D above is honored.

IRBs on the Edge:
Continued Vigilance Critical to the Protection of Human Subjects

Faced with ever increasing workloads and budget cutbacks, can Institutional Review Boards (IRBs) continue to ensure the protection of human subjects while controlling the regulatory burdens placed on their institutions?

Two professional gatherings held in October 1995 focused on the pressures facing IRBs and ways to manage the situation. "IRBs on the Edge—Managing and Mastering Current and Future Issues" was sponsored by ARENA, Applied Research Ethics National Association. PRIM&R, Public Responsibility in Medicine and Research, hosted "IRBs: Encountering Special Problems of the Decade." Following the ARENA meeting, one participant, Christine Byrne, Human Subjects Point of Contact at Lawrence Berkeley National Laboratory (LBNL), stated that some IRB staffs have experienced a 20–30 percent increase in the workload while administrative budgets have been cut or frozen. Salaries for lead IRB administrators are falling while institutional accountability is on the rise.

What Is Working?

A recent report by the General Accounting Office (GAO) confirms the concerns raised at the professional meetings. Although the GAO report held some good news—namely that the "conspicuous activity of local institutional review boards and human subject protection efforts by Federal agencies have heightened the research community's awareness of ethical conduct standards, increased compliance with Federal regulations, and served as deterrents to abuse of subjects' rights and welfare"—it also warned about increasing pressures.

"Given the many pressures that can weaken the effectiveness of the protection system, continued vigilance is critical to ensuring that subjects are protected from harm," noted Sarah Jaggars, GAO's Director of Health Financing and Public Health Issues for the Health, Education and Human Services Division in testimony before the Senate Committee on Governmental Affairs on March 12, 1996.

IRBs: The Challenges

IRBs face ever more challenging situations that could erode their ability to remain vigilant. As described in the GAO report, some of these are—

- **Increasing number of projects:** The number of projects submitted for IRB review is growing. Because IRB members are volunteer professionals, they generally meet only once a month. The large number of projects scheduled for review at each meeting means the IRB can devote only a few minutes to each project. Usually, one or more selected members will review specific projects before the meeting and present a summary to the convening IRB. The others must depend on the judgment of these initial reviewers. Time does not usually permit a thorough review of each project by the entire IRB.
- **Increasing administrative workloads:** The number of projects is increasing, but administrative staff is not. The paperwork necessary for compliance with Federal regulations is substantial. Add to that the scheduling of continuing reviews, corresponding with investigators, and reporting to the public (such as submitting data for DOE's Human Subjects Research Database), and the workload becomes overwhelming.
- **Competing professional demands:** The competing demands on IRBs can cause conflict. The IRBs must answer to their institutions, the investigators, the Federal Government, the public, and their peers. Each of these parties has its own priorities. The independent IRB must delicately balance rival goals so that the safety of human subjects is always ensured.
- **Increasing complexity of research:** Research, like technology, is constantly adding new knowledge. Areas of specialization for professionals, however, are becoming more narrow. As a result, IRB members may have to review research for which they lack in-depth knowledge or experience. In addition, new scientific pursuits (such as gene therapy protocols) raise as yet unresolved ethical issues.

Coping Strategies

How can DOE IRBs and their administrators cope with heavier workloads while maintaining an effective system for reviewing research and ensuring the protection of human research subjects? Last year's professional meetings provided a good opportunity for IRBs to discuss ways to cope with the demands.

Networking

Networking opportunities for IRB members and IRB administrators exist via two well-respected organizations—PRIM&R and ARENA. PRIM&R addresses research concerns (including IRB workloads) by sponsoring conferences, publishing educational materials, providing training, and serving as an information clearinghouse. PRIM&R's conferences have become "trusted and valued outlets for easing work pressure through expanded access to knowledge of regulatory requirements, information on administrative procedures, and most importantly, the support and assistance that only a well oiled and expansive network can provide."

Recognizing the importance of networking, the PRIM&R Board of Directors organized its sister membership organization, ARENA, 10 years ago. ARENA disseminates current information on research ethics issues and promotes networking among professionals through its quarterly newsletter and membership rectory. Local

ARENA contacts serve as conduits for information about regional networking opportunities. One way to promote networking is for Federal agencies and research facilities to provide funds for travel expenses.

Education

To ensure the quality and comprehensiveness of IRB reviews, IRB members must keep abreast of the latest research findings in their fields as well as changes in human subjects protection policies and procedures, especially as new technologies emerge. At DOE, for example, the Protection of Human Subjects Program provides educational outreach to the laboratories and institutions funded by DOE. Some of the resources available to IRBs and researchers through this program include the—

- *Human Subjects Research Handbook*
- Informational brochure on human subjects research.
- Protecting Human Subjects home page on the World Wide Web.
- *Protecting Human Subjects* poster.
- *Protecting Human Subjects* bulletin.

Another educational tool is the performance review. DOE has organized the performance review site visits with the goal of developing educational recommendations for areas or processes in need of improvement. The DOE Protecting Human Subjects Handbook says that "at both the opening and the closing of the site visit, the review team should emphasize the educational value of the process and the desire for performance improvement." IRBs should look at the site visit as an opportunity to develop better ways to work.

The Office for Protection from Research Risks (OPRR) at the Department of Health and Human Services has a series of instructional videos available to IRBs, researchers, and institutional officials. The three videos cover the history and background of the effort to protect human research subjects (including the Belmont report) and examine an IRB "in action." Information on the videos and other OPRR educational resources can be found on the World Wide Web at http://www.nih.gov:80/grants/oprr/resource.htm.

Technology

Technology, particularly the computer, promises to ease the workload of IRBs. The volume of research data that IRBs collect and track is an obstacle for the time-pressed IRB. Databases for information storage and retrieval save time and reduce the need for cumbersome paper files. Helen McGough, with the Human Subjects Division at the University of Washington, noted that "We use our database system to generate continuing review notifications, track proposals, and generate IRB meeting agendas." Because much of the IRB's work is reading and reviewing documents, a well-organized information management system is key to reducing administrative burdens.

Some IRBs have purchased custom-designed and supported databases, while others report using commercially prepared databases.

Because of the complexity of the data being collected and the widely varying administrative needs of each IRB, the time and expense of developing, running, and maintaining a database can be prohibitive, with the bulk of the costs in start-up for computer programming. Ms. Byrne, LBNL, said that designing a custom database of this nature could take a good programmer up to 6 months, including quality assurance testing. She added that the "average cost for such systems seemed to be running in the $40,000 to $50,000 range." Nevertheless, this could be a worthwhile investment for an IRB, depending on the number of projects and the workload.

One company, for example, that has created software for IRBs is Insight Solutions, Inc., of Palo Alto, California. The firm's IRB!info® software helps "manage and report critical IRB information." Designed specifically for IRBs, this database tracks continuing review dates, produces reports, and creates form letters. Such products may prove to be a more economical way to lighten the workload than a custom-programmed system.

Web sites have also become a popular way for IRBs to share information regarding policy, IRB memberships, meeting dates, deadlines, and events. For example, the University of Connecticut Health Center has created an Internet questionnaire that principal investigators fill in and E-mail back to the Health Center's IRB.

As gatekeepers to approving research, IRBs face many pressures, and it seems unlikely that current challenges will diminish. The tasks assigned to IRBs are vital to protecting human subjects. Continuing to network with other professionals and using technology for administrative support are practical coping strategies for IRBs.

NASA'S New Human Subjects Policy

DOE laboratories and cooperating institutions that use employees in research projects should find the updated human subjects policy of the National Aeronautics and Space Administration (NASA) a valuable resource. Released August 8, 1995, the NASA Management Instruction (NMI) is a model for any organization conducting traditional and non-traditional biomedical research (instrument, device, or product testing) using employees or enlisted personnel.

Speaking at the Fall 1995 Interagency Human Subjects Conference, Dr. Earl W. Ferguson, Director of Aerospace Medicine and Occupational Health, NASA, explained that human subjects research at NASA is complicated by the fact that space-based, aeronautical flight, and ground-based studies are an integral part of employees' jobs. Participation or non-participation may affect their careers. The new NASA human subjects policy is the result of collaboration among personnel from NASA-Johnson Space Center, NASA-Ames Research Center, and a special NASA Bioethics Policy Task Force. Created in response to a 1994 Presidential directive, the Task Force (composed of five external experts) reviewed NASA policies on human subjects research and recommended modifications and additional protective measures.

The resulting NMI, said Dr. Ferguson, fulfills the requirements of the Common Rule and incorporates the preliminary recommendations of the President's Advisory Committee on Human Radiation Experiments (ACHRE) released earlier in 1995. Notably, the revised NASA human subjects research policy—

- Presents a broad definition of research involving human subjects.
- Includes an exact definition of minimal risk for research involving a human subject whose job in space flight/exploration by its nature already carries significant risk.
- Gives subjects the right to request an IRB meeting to evaluate a human research experiment that may affect the health or well-being of any human subject. This privilege given to NASA research subjects is unique and makes it easier for them to express concerns without having to officially withdraw from or decline participation in research projects, or communicate directly with principal investigators.
- Establishes procedures for withdrawing from research projects and sets criteria for replacing a crew member who withdraws from research on a given space mission.
- Strengthens Institutional Review Board (IRB) authority, responsibilities, and functions. For example, (1) the IRB must define for each approved experiment the extent to which the consent process and/or the

conduct of the research will be monitored, and (2) the IRB and researchers must consider the collective risk of human subjects involved in multiple protocols. When appropriate, informed consent must include a description of any collective impact of participation in multiple protocols.
- Sets guidelines for diversifying IRB membership.
- Requires all cooperating institutions and partners, whether domestic or international, to comply with the revised NMI. "In the case of foreign institutions, assurances must include that their research proposal has been approved by an IRB, meeting at least the standards of the Declaration of Helsinki."

In addition to making recommendations to strengthen the NMI, the NASA Bioethics Task Force assisted Johnson Space Center and Ames Research Center in determining how the new policies could be implemented. As a result, both locations have revised their manuals on using human subjects in research. In its final report submitted February 14, 1996, the Task Force addressed agency-wide issues such as refining the assurance process, including international partners as members of the Johnson Space Center IRB, ensuring privacy in electronic databases, increasing educational efforts, and addressing diversity in subject selection.

Ethical Issues and Repositories

Medical repositories—among them tissue banks—are invaluable to the research community. These specimen "warehouses" allow researchers to preserve, extract, and link data derived from the stored samples, ultimately finding new ways to detect and treat disease. This resource is not, however, risk free.

Introducing a panel discussion on repositories at the October 1995 interagency conference, Dr. Joan P. Porter, Senior Policy Analyst, Office for Protection from Research Risks, National Institutes of Health (NIH), raised ethical concerns about current and future use of and access to repository specimens and related data.

Each of the four panelists addressed these concerns from a different perspective:

- The patient's/donor's expectations.
- The human subject's perspective.
- Ownership and profits.
- The IRB's perspective.

The Patient's Expectations

Karen Rothenberg, J.D., MPH
Special Assistant to the Director
Office of Research on Women's Health
National Institutes of Health

Professor Rothenberg urged the research community to consider the expectations of patients who give blood or tissue samples. They may not expect their samples to be used for any kind of research and may not even realize the samples will be stored in a repository. Even a patient who is aware of the potential research use may assume his or her sample will be limited to one specific type of research and strongly object to its use for other purposes.

A patient's right to privacy is crucial, both on a personal level and on the level of the patient's "social" group(s). Patients may strenuously object if they learn that blood taken for cancer research, for example, was diverted to an assessment of alcoholism levels in their particular ethnic group. Individuals and groups can be stigmatized when what they assume to be private information becomes public knowledge. They may also lose or be denied health insurance.

Similar breach-of-privacy risks apply to persons who participate in genetic studies. Repository specimens are a rich resource for genetic testing, but who should have access to the findings? By the end of 1995, only eight states had passed legislation that addresses health insurance and discrimination based on genetic information: Wisconsin, California, Colorado, Ohio, New Hampshire, Minnesota, Oregon, and Georgia. Such protection is necessary so that people who wish to volunteer for research studies will not be discouraged from doing so.

Professor Rothenberg challenged the human subjects community to determine how the use of stored samples can help science find answers to important medical questions without jeopardizing the right to privacy of the individuals who provide the samples.

The Human Subject's Perspective

Deborah Collyar
Advocacy Core based in San Francisco

Breast cancer survivor Deborah Collyar approached the topic from a perspective rarely heard in official forums—that of a human subject. Noting that her grassroots experience leading a volunteer group of cancer patient advocates has taught her that the public is generally unaware of tissue banks, she said that most patients believe their tissue and blood samples are used purely for diagnosis. They may sign a generic consent form when admitted to a hospital, but rarely do they read the research clause or even know it exists.

Although good in theory, informed consent for research projects is flawed in practice. For example, consent forms for clinical trials are cumbersome—anywhere from 15 to 40 pages—and overwhelming in their technical detail. Less text and more graphics would help "contextualize" for the subject the risks and the potential personal benefits of participating in the study.

To ensure confidentiality, some people argue that all personal identifiers be stripped from the specimens and data. However, some human subjects may wish to be informed of research outcomes. When considering tissue bank safeguards, officials should ensure that samples provided only for diagnostic use be treated differently from those with consent for both research and diagnostics. They should also address privacy and discrimination issues related to genetic testing.

The accessibility of personal information via computers is a major privacy issue. Those who really want access to personal information (including insurance companies, government agencies, and entrepreneurs for example) can find a way to get it. Consequently, people who are worried about losing their jobs or their insurance as a result of genetic susceptibility may not agree to be human subjects in clinical trials, and new solutions to medical problems will be delayed.

The following safeguards can help to protect human subjects who contribute specimens to repositories:

- Store research records separately from medical records.
- Protect material containing nucleated cells (tissue, blood, urine, breast milk, etc.) at each step along the research path—source, intermediary, and final laboratory.
- Seek "reconsent" from the subject if the research protocol involves heritable research using repository data.

The scientific community must protect human subjects without hindering their freedom to choose what is right for their individual needs—even experimental treatments and access to new therapies. The subject must (1) have the right to choose whether to participate in the research and whether to know the results; and (2) know how the specimens or data are, and will be, used so that he/she is protected from misuse. When identifiers or coding permit, donors should have access to research results with the appropriate counseling and education.

Ownership and Profits

Patricia Kvochak, J.D.
Office of the General Counsel
National Institutes of Health

"Who owns the blood or tissue once it is removed from an individual's body?" queried Patricia Kvochak. Do ownership rights change depending on whether the specimens are used for diagnostic (medical) purposes or for research? The only ruling to date on an individual's property interest (ownership) in removed cells is the Moore case. The California Supreme Court ruled that the plaintiff did not retain ownership of his cells once they were removed. However, the Court also ruled that the physician had a duty to disclose research or economic interests unrelated to the patient's health that may have affected the physician's professional judgment and that could have influenced the patient's decision to participate.

Although hospital or repository ownership of the specimens may be the only practical choice, ownership does not give the researchers an automatic right to do anything they wish with the specimens. Informed consent and human subject protections still apply—specimens should be used for the purpose(s) intended and not contrary to the wishes of the subject. In addition, a subject who withdraws should not experience any further risk as a result of earlier participation. Commercialization of tissue or blood products raises other ethical dilemmas. In Moore, the Court ruled that the potential cell line and any products derived from it were not the plaintiff's property because they were distinct from the cell samples taken directly from his body. Generally, cells per se do not have value; it is the scientific additions and manipulations that make the cells patentable and perhaps commercially viable.

Ms. Kvochak closed with two provocative questions: Should the informed consent process, which critics say is already overwhelmingly detailed, include information on the future possibility of commercialization? Should human subjects share in future profits?

How Would the IRB See Things?

Ada Sue Selwitz
University of Kentucky

To illustrate the perspective of the Institutional Review Boards, Ada Sue Selwitz led a case study in which the conferees, taking the role of a mock IRB, assessed the adequacy of an informed consent document. At issue was

a continuing review of a National Cancer Institute mock protocol for establishing a repository in which tumor tissues and serum would be placed in long-term storage and accessible to NIH researchers. Although the tissues used in research would not include "identifiers," the tissue bank would maintain identifying links between the tissues and the subject's medical records. The IRB's task was to evaluate whether the previously approved consent form adequately informed the human research subject about privacy safeguards and the risks of genetic research.

The mock board members criticized the informed consent document for failing to inform the subject fully about the (1) use of tissues for genetic research, (2) protections for ensuring that information obtained would not be inappropriately disclosed, (3) potential risks associated with genetic research, and (4) provisions for treatment of tissue samples and data should the subject withdraw from the study. Another weakness noted was the requirement that the subject forfeit financial rights to any future commercial product(s).

Following the case study, Ms. Selwitz noted the Federal regulations that apply when IRBs review protocols involving tissue repositories, including the definitions of human subject and research, the exemption criterion involving existing data, the expedited review category involving existing data, and the criteria for waiving informed consent. IRBs must also consider the following questions during reviews:

- Does the project fall within IRB purview?
- How will the repository be used? Will samples be used for genetic research?
- Are adequate safeguards for maintaining confidentiality in place?
- Are the subjects adequately informed?
- Can the samples be retained with identifiers? If so, what are the provisions for providing access?

In summary, Dr. Porter commented that certain questions raised by the panelists are addressed in the Common Rule, in other regulations, or by prevailing ethical principles. Because judgments on complex ethical issues may vary, IRB review provides the necessary balance. **Full and open IRB discourse is an essential safeguard for human research subjects.**

Web Sites of Interest

National Institutes of Health (NIH)

NIH's Office for Protection from Research Risks hosts a Web site containing many items of interest to the human subjects professional. The home page, located at http://www.hhs.gov/ohrp/, provides access to the following resources—

1. A document library on the use of human subjects in research.
2. Information on other OPRR resources.
3. Frequently asked questions on human subjects.
4. Information on the National Bioethics Advisory Commission.

Go to http://www.nih.gov/grants/oprr/faxcall.htm for a listing of OPRR documents that can be faxed to your home or office. Call (301) 594-0464, and enter the document number of interest. It will be faxed to you shortly.

Food and Drug Administration (FDA)

FDA's Web site (http://www.fda.gov) contains many documents related to the protection of human subjects. Two, in particular, are good sources of information on informed consent. One is geared to IRBs and the other to clinical researchers. For the Guide to Informed Consent Document (focusing on the IRB), access http://www.fda.gov//oc/oha/aguide.html. For Informed Consent and the Clinical Investigator, choose http://www.fda.gov//oc/oha/informed.html.

Advisory Committee on Human Radiation Experiments (ACHRE)

ACHRE, created by President Clinton in 1994, investigated the use of human subjects in federally funded research involving radiation. Information about the Committee's activities is available to the public at http://www.gwu.edu/~nsarchiv/radiation/, including—

1. Information about the original ACHRE gopher.
2. Background on ACHRE, human radiation experiments, and government records.
3. Records of ACHRE Committee Meetings.
4. Names and functions of ACHRE staff.
5. The interim report of October 21, 1994.
6. Descriptions of the document collection and a bibliography.
7. The Final Report, also available at http://www.hss.energy.gov/healthsafety/ohre/roadmap/index.html.

Public Responsibility in Medicine and Research (PRIM&R)

Applied Research Ethics National Association (ARENA)

PRIM&R and ARENA have recently set up Web sites. Each organization's home page contains information on conferences, publications, and other activities. The sites are sponsored by the Association of American Medical Colleges (AAMC).

PRIM&R's home page is found at http://www.primr.org/index.html.

ARENA's home page is found at http://www.primr.org/membership/overview.html.

September 26–27, 1996

NIH/OPRR/FDA Conference
Role of the IRB in Collaborative Research
Peoria, Illinois
Registration: Ms. Nancy Hibser
University of Illinois College of Medicine at Peoria
One Illinois Drive, P.O. Box 1649
Peoria, IL 61656-1649
(309) 671-8437
Fax: (309) 671-8513
Fee: $125

Description: This conference is designed to examine a broad range of contemporary scientific, ethical, regulatory, and legal issues relating to biomedical, social, behavioral, and anthropological research involving human subjects. Presentations will focus on the unique challenges presented to IRBs. Some of the topics to be covered include liability, informed consent, historical perspectives, issues in mental health management of IRBs, computerized management information systems for the IRB office, FDA regulations for clinical trials, guidelines on the inclusion of minorities and women, and research involving special populations.

For more information on this workshop or future NIH/FDA National Human Subjects Protection workshops, contact—

Ms. Darlene Marie Ross

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Rockville, MD 20892-7507
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November 10, 1996

Applied Research Ethics National Association (ARENA) Annual IRB Meeting
San Diego, California

November 11–12, 1996

Public Responsibility in Medicine and Research (PRIM&R) Annual IRB Conference
San Diego, California

For additional information on the ARENA meeting or PRIM&R conference, contact—

ARENA/PRIM&R
132 Boylston Street
Boston, MA 02116
(617) 423-4112
Fax: (617) 423-1185
E-mail: primr@delphi.com

November 22–24, 1996

The III World Congress of the International Association of Bioethics
San Francisco, California
For more information, contact—

Professor Alex Capron
The Law Center
University of Southern California
University Park

Los Angeles, CA 90033
E-mail: acapron@law.usc.edu

June 26-27, 1997

Federal Interagency Human Subjects Conference organized by DOE/HHS.
Draft Title: Genetics Research—Laboratory to Doctor's Office.

Details to follow in next issue of this bulletin.

Visit the 1995 Protecting Human Subjects Research Database on the Internet

This public database reports on 225 individual research projects using human subjects that are conducted at DOE facilities or funded by DOE at other institutions. Summary statistics are also provided. Since March 1994, DOE has collected and updated project information for this database on a yearly basis. To access the database, go directly to—

http://hsrd.orau.gov/.

The Protecting Human Subjects home page at http://orise.orau.gov/doehumansubjects/ also provides easy access to the educational materials and resources available through the DOE Protection of Human Subjects Program. Home page links will take you to—

- The DOE Human Subjects Research Database.
- The Protecting Human Subjects Within the U.S. Department of Energy brochure.
- Protecting Human Subjects newsletters (5 issues).
- Up-to-date news on human subjects research.
- Dates of upcoming meetings and conferences of interest.
- Ordering information for the—

1. Human Subjects Research Handbook.
2. Protecting Human Subjects poster.

Do you have your copy of the second edition of the DOE Human Subjects Research Handbook?

This 450-page manual is intended for researchers, laboratory personnel, institutional administrators, DOE officials, Institutional Review Board (IRB) members, and any others involved or interested in human subjects research.

As you might expect, the second edition updates essential information on protecting human subjects. But the newly revised manual also expands considerably on the first edition's offerings. It includes, for example, comprehensive descriptions of the roles and responsibilities of each participant in the preparation–review–

approval process for research projects involving human subjects. Samples of the forms and documents used in the process are supplied. The handbook also clarifies research project assurances, and it devotes seven chapters to topics of current significance to users, such as data protection, international research, and performance reviews. An expanded glossary and subject index make the second edition even more user friendly.

To obtain your copy of the revised Handbook, fax or mail your request to the DOE Human Research Subjects Program Manager.

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.

DOE Human Research Subjects Program

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