PROTECTING HUMAN SUBJECTS

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

Number 4 Fall 2000

Inside this issue

Contacting us

This newsletter can be found at the Protecting Human Subjects Program web site:
www.science.doe.gov/ober/humsubj/

Human Subjects Newsletter
Oak Ridge National Laboratory
1060 Commerce Park, MS 6480
Oak Ridge, TN 37830
E-mail: catongm@ornl.gov
Fax: (865) 574-9888

Editorial: Challenging the human subjects community

Serious concerns not being addressed in the current dialogue

By Dr. Susan Rose, Human Subjects Program Manager

A new forum

This is the first editorial that the DOE *Protecting Human Subjects* newsletter has printed. I would like to dedicate space in future newsletters to provide a forum for those of you in the human subjects community to issue "challenges" related to serious concerns not being addressed in the current national dialogue.

Dr. Susan Rose

This newsletter has been used to highlight issues of concern to the human subjects community, to identify individuals and programs that have merit, to describe DOE publications, and to report on DOE meetings.

We will continue to do this. But as part of an ongoing interest and continuing contributions to improve the human subjects process nationally, we would like to invite you to participate by writing an article for this newsletter.

You can write something that "challenges" the rest of the human subjects community. You can provide resources or tell a story or highlight "good works" that can be a model for action.

I would like this space to encourage the development of collaborations, to use synergy creatively, and to provide assistance to meeting organizers and writers of guidelines and program materials.

The challenges:

- *Unaffiliated members initiative:* educating/recruiting ideas.
- *After the Institutional Review Board (IRB) says 'Yes':* staying in touch with the research.
- *Nontraditional, nonclinical International Human Subjects issues.*
- *Altruism:* does it still have a place in subject volunteering?

The overlooked, unaffiliated IRB member ("community member") is an essential component of the human subject process. From the many site reviews we have done at DOE, we have seen a range of talents, caring, and knowledge among community members.

Perhaps it is time to partner with groups like the American Association of Retired Persons or other national membership or

>

volunteer groups to identify new sources of "community members," to educate them on the latest in science and bioethics, and to refresh our rosters across the nation. Retired folks are great contributors.

As a further challenge, perhaps each IRB should try to have one member who comes from the same cohort as the majority of subjects used at the site or by that institution.

For example, at DOE we are encouraging appointment of a worker or union member on each IRB where workplace studies predominate.

After the IRB says "Yes!"
The IRB is the one term or group that is identifiable to the media, congress, patients, etc., and as such, is portrayed in various ways: heroic, villainous, rectifier of misdeeds, promoter of good, etc.

The challenge for many sites arises from atypical studies, and guidance is sparce.

The reality of the process is that boards are limited or enhanced by talent, resources, research portfolio, the institutional philosophy, etc.

A big challenge is to create and utilize new and regular interactions between researchers and the IRB, including ways to stay in touch with the process after the IRB says yes. After IRB approval is obtained, the researcher is expected to conduct research in a responsible manner, but this appears not always to be the case.

A challenge ahead is to engage IRBs in the research process in a creative way that makes sense for the research and the institution—observing consents, spot checking of files or records, principal investigator updates on research, recruitment observing, etc.

Shouldn't useful methods be developed for IRBs to stay in touch . . . and really share in the process?

Creativity and site consideration make each project and IRB different. But what really matters is what occurs during the time *after* IRB approval is granted. Because IRBs are presumed to be "responsible" for the research, whether true or not, shouldn't useful methods be developed for IRBs to stay in touch during the 365 days of approval, and really share in the process?

Regulatory removal of IRB work load burdens that don't actually protect subjects is of course an equal challenge to be met.

International human subjects issues: not what you think
We have all read about the ethical issues surrounding international HIV trials and large-scale pharmaceutical and clinical trials. However, the challenge for many sites arises from atypical studies, and guidance is sparse.

These studies often raise interesting or problematic dilemmas, including:

- U.S. research labs doing sophisticated specimen analyses not available elsewhere,
- genetic research or health research with samples or subjects from abroad,
- unique or accidental exposure effects studies using techniques and follow-up not known in the country of origin, and
- collaboration issues.

The studies raise important questions:

- Who is responsible for obtaining the understanding of the donors and protecting the circumstances of the donation?
- How do we ensure the quality of the science in these one-of-a-kind studies? Or should we?
- If a U.S. investigator partners with a surgeon in another country to get aliquots of a surgical specimen, what ethical leverage does he or his IRB have?
- What guidance do current rules provide regarding IRBs, consent, and ethical equivalence?

These questions and dilemmas are challenges for many of us.

Must we guard against altruism? Be suspicious of it? Deter its expression?

Altruism—what is its place?
Altruism is often what motivates volunteers to participate in human subjects research. Must we guard against it? Be suspicious of it? Deter its expression? Are all the controls, presuppositions, and publicity on wrongdoing affecting volunteers' willingness? How can we best honor the altruistic contributions of volunteers without letting our presuppositions get in the way?

These challenges seem to be worth some discussion, some oral histories, or some research. What do you think?Δ

ORCA: A new VA guardian

New levels of federal protection for both humans and animals

Editor's note: This is the first of two articles in this newsletter highlighting federal offices that are partners in the effort to protect human subjects. We will devote space in future issues to feature other agencies.

By John Mather, M.D.

The new Veteran's Administration (VA) Office of Research Compliance and Assurance (ORCA) was established because there had been some persistent problems with failure to abide by the "Common Rule" at a VA Medical Center (VAMC) in West Los Angeles.

John Mather, M.D., ORCA Chief Officer

That center was shut down in March 1999, prompting a re-evaluation by the VA of its protections for human and animal subjects.

ORCA formally came on line towards the end of 1999 and ever since has been growing in scope and influence. It has taken on activities that will more evidently ensure for the VA the protection of human subjects and the welfare of animals involved in research.

It is also addressing vulnerabilities for scientific misconduct and the education of researchers. All of this is important because VA patients who enroll in research programs have the right to expect that their welfare will be the highest VA priority.

ORCA was established as an independent and objective oversight office assigned to assure the VA that research is conducted with the appropriate respect and welfare for human subjects and animals.

It is the primary Veterans Health Administration (VHA) component for enhancing ethical conduct in research by ensuring conformance with regulations and policies. The office investigates all allegations of research improprieties and scientific misconduct.

Education and training
ORCA is distinguished by its emphasis on continuing quality improvement, especially in promoting education and training in research conduct for everyone involved with the VHA.

This includes investigators, members of local VAMCs and academic affiliate Institutional Review Boards charged with approving research protocols. The task also extends to ensuring that the consent process, when enrolling human subjects, is conducted ethically.

Note:

Joining Dr. Mather at ORCA as his associate director is Dr. Joan Porter, who for nearly 20 years has been a friend and mentor to DOE's Human Subjects Protection Program.

ORCA hopes to forge a different and balanced role, which has been described as the **ACE** approach. The acronym refers to the intention to create a culture of Assurance/assessment, Counselor/cop and Educator/enforcer.

Integrity
The ORCA staff has a deep commitment to encourage and enhance the work of ethical researchers. Ethics-trained investigators can then act as appropriate "watch dogs," ensuring the integrity of the VA research enterprise.

ORCA administers this program of "assurances and compliance" specifically intending to prevent problems that can result when research programs are shut down because of violations of the "Common Rule" regulation.

Patients have the right to expect that their welfare will be the priority.

The office will have a headquarters component providing oversight of several regional offices. These regional offices will be the main operational arms for ORCA, developing working relationships with about 30 VAMCs and their networks.

Regional task
The regional offices, in collaboration with other key offices, will have several tasks. They will, for example:

- Complete annual mini-assessment program reviews.
- Accompany site visits for accreditation of human studies and animal welfare.
- Investigate allegations of research improprieties and scientific misconduct.

➢

• Promote and conduct training and education.

Managing VA contracts
ORCA will also manage the Multiple Project Assurances (MPAs) contracts signed by VAMCs. The contracts commit centers to abide by regulations governing research with human subjects.

These contracts are similar to agreements issued by the Public Health Service through its Office of Human Research Protection (formerly OPRR). ORCA has established close ties to this office as well as the comparable centers in The Food and Drug Administration.

Better coordination and cooperation is expected to result from the various contacts at these and other agencies involved in animal welfare.

The main activity planned for the near future will be to enhance training and education activities.

VHA policy advice
Over time, as ORCA builds its staff and collects information related to VA research, the office will be in an increasingly strong position to advise VHA on new policies related to research and the protection of animals and humans.

ORCA will be working with several VHA offices, including the Office of Research and Development and the Center for Ethics, as issues emerge and need resolution.

As noted by Dr. Thomas L. Garthwaite, Under Secretary for Health, "This office is a cornerstone of our efforts to continuously improve our high ethical standards in research, and it will provide independent and routine assurance that VA research is conducted legally, safely and with integrity."Δ

ORCA Web site and address

For information about the Veterans Health Administration's Office of Research Compliance and Assurance, contact:

ORCA
810 Vermont Ave. NW
Washington, D.C. 20420
(202) 565-9080

or see the ORCA Web site at: www.va.gov/ORCA/

Notes

Updates and notices

■ LAWRENCE LIVERMORE IRB SEMINAR

The November 7 meeting of the Lawrence Livermore National Laboratory Institutional Review Board (IRB) will include a seminar at which various IRB issues will be discussed by Cynthia Kenny of IRB Specialists, Inc.

She will focus on Food and Drug Administration (FDA) regulations, especially those governing investigational medical devices and drug studies. It will cover differences between FDA and National Institutes of Health (NIH) regulations, conflicts of interest, and roles and responsibilities of sponsors and investigators. Kenny will also discuss device studies, including the exempt and non-significant risk/significant risk determinations, and drug studies, focusing on metabolism research involving the ingestion or injection of radio-labeled compounds.

Participating in the seminar will be the IRB's board members and staff, principal investigators, contracts officers, finance personnel, and anybody else who is interested.
(*From Bree Klotter, IRB administrator*)

■ GOT A GOOD TUTORIAL?

The DOE Protecting Human Subjects Program is looking for the best tutorials in both the areas of Research Integrity and Human Subjects Research Ethics. There are also plans to develop a DOE Tutorial for Human Subjects Protections. Submit tutorial information to Terry Reser, Sandia National Laboratory, treser@sandia.gov

Policy advice for Congress

Trans-bioethics committee crosses the institutional boundaries

Editor's note: One of the goals of this newsletter is to provide information about governmental offices and programs involved in the effort to protect human subjects. This article focuses on some aspects of the work done by the Office of Science Policy (OSP) at the National Institutes of Health (NIH).

When Congress announces that it is going to look into research involving human subjects, or any of a variety of other ethical issues, it begins looking in various directions for information.

Julie Kaneshiro

Among the first places Congress calls is the Office of Science Policy, which houses an amalgam of resources, including:

- Trans-NIH Bioethics Committee (T-NBC),
- Office of Science Policy and Planning,
- Division of Evaluation,
- Office of Science Education
- Office of Biotechnology Activities (this office encompasses the Recombinant DNA Advisory Committee, the Secretary's Advisory Committee on Genetic Testing, and the Secretary's Advisory Committee on Xenotransplantation).

NIH's bioethics contact

The T-NBC, which is NIH's central bioethics contact, has for some time now been specifically focused on issues related to protecting human subjects.

Julie Kaneshiro, T-NBC's executive secretary, has been responsible for helping the group identify bioethical issues and create ways for various agencies, including DOE, to communicate with each other.

"NIH is decentralized," Kaneshiro explains. "All of the institutes have their own policy offices, legislative offices, ethics groups, and so forth. This means there is no discrete home for bioethics issues. T-NBC now provides policy direction."

So finding the specific office most appropriate to deal with the nuances of ethical dilemmas on which Congress or anyone else is focussing can be a challenge.

Think tank

T-NBC's mandate is to act both as a centralized think tank, bringing in expertise from across the maze of NIH offices, and as a clearinghouse for questions that cross the boundaries of specific institutes.

It is a very direct effort to focus NIH's bioethics brainpower and experience, bringing into the process representatives from each of the 24 NIH institutes and centers, as well as many of the offices within NIH's Office of the Director.

T-NBC is a powerful tool that has been used by the President's National Bioethics Advisory Commission (NBAC) as an entree into the NIH, which has used it for

- a report on research involving human biological materials,
- a report on research involving people with mental disorders,
- a report in progress on ethical and policy issues in international research and on issues related to oversight of human research in the United States.

(Note: NBAC's completed reports are available at http://bioethics.gov/pubs.html)

T-NBC's mandate is to act both as a centralized think tank and as a clearinghouse for questions that cross the boundaries of specific institutions.

Focus: research ethics, privacy

"T-NBC was created," Kaneshiro explained, "to focus on research ethics—primarily human research. Because of the decentralized nature of bioethics at NIH, there needs to be a way to share information across the institutes. It is a way to coordinate NIH responses to broad research policy and ethical issues.

"For example, when privacy protection began surfacing as a public concern, we started developing ideas that could help protect privacy of health and research information.

"T-NBC developed an NIH white paper on recommended principles for protecting the confidentiality of individually identifiable research information. We're

➢

using those principles now to help the Department of Health and Human Services (DHHS) develop its Congressionally mandated health privacy regulations."

DHHS is drafting regulations because Congress in 1996 passed a law ordering that if a comprehensive health privacy bill had not been enacted by August 1999, DHHS should take on the task itself.

Because Congress did not meet the deadline, DHHS is proceeding. It is trying to sort out one of the most complex and far-reaching issues in the area of protecting human subjects.

T-NBC undertook as a focus of its work assisting DHHS in developing the regulations.

When DHHS asked for public comment on its first proposal, it got more than 50,000 responses. It is now developing the final rule, responding to those comments.

When the privacy rule is completed, it may address, among many other things, how researchers can get access to individual records for epidemiological, clinical, and other studies. It may also speak to the way researchers who provide health care to research subjects will be required to protect research information.

Health records

Among the limitations on access is a proposed IRB-like structure for disclosure of medical records without patient consent. If the final rule contains this structure, Kaneshiro explained, researchers and institutions will have to think about how this new structure will dovetail with existing IRB rules.

One of the differences is that this proposed IRB-like structure would apply not just to researchers subject to the Common rule; it would also apply to those not now bound by the protections of the Common Rule.

"Is it any tissue? Any blood? Or does it have to be more specific?"

Because the privacy rule is so far-reaching, the DHHS working group has deliberately involved a range of departments and ideas.

It is necessary to gather as much information as possible about various policy options from as many sources as possible, she said, because many people were unhappy with the proposed regulation.

Human biological materials

"People don't realized how easily accessible their records are now. We're closing the door, not opening it," Kaneshiro said.

T-NBC was created during the time when issues such as cloning and privacy of medical records were first coming seriously to the public's attention.

It quickly developed a system of communication and consultation that created the ability to move fast when asked to provide information about ethical positions and policy recommendations.

For example, when Congress wanted to know more about research involving human biological materials, T-NBC called together a working group that considered a wide range of potential problems and solutions.

It looked into what constitutes an identifiable sample of biological material. Is it any tissue? Any blood? Or does it have to be more specific? What, precisely, is a human subject? Is it limited to a living person? What if the researcher has had no direct contact with the individual donor?

The T-NBC working group thoroughly examined the NBAC draft report on research involving biologic materials and provided an official NIH response.

"Almost everything this office does," Kaneshiro said, "in some way involves educating people about how to conduct themselves in an ethical manner that both protects human subjects and allows good research. The T-NBC is just one of many strategies NIH has developed to further that intention."Δ

NIH Bioethics Web sites

National Bioethics Advisory Commission. This site provides access to reports the Commission has issued.
http://www.bioethics.gov

NIH primer on research provisions of the proposed health privacy regulation.
http://www.nih.gov/news/privacy_primer.htm

NIH Office of Science Policy.
http://www.nih.gov/icd/od/

Vulnerability: The worker as study subject

New DOE handbook of issues, guidelines, sources, and recommendations for researchers

A compendium of guidelines and issues related to research using workers as study subjects has been published by DOE's Human Subjects Protection Program.

Explaining in the preface to the guide the purpose of the project, program manager Dr. Susan Rose says it describes ethical concerns in studies using workers and makes recommendations to ensure that workers are protected legally, scientifically, and ethically.

Essential data
"Studies to assess the health effects that may be related to occupational environments and workplace exposures provide data essential to reducing or preventing illnesses, injury, or disease among current and future workers," she said.

"We have concerns, however, that unless their rights and welfare are fully protected, collecting these data may expose participating study subjects—the workers—to significant personal, professional, and economic risks. There is also the concern that, in some cases, worker studies are not recognized as research."

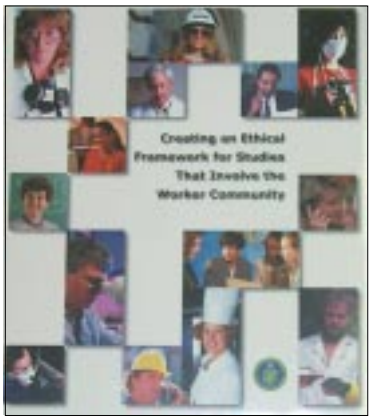
No formal framework
Rose says these concerns imply a need for approaches, safeguards, and scientific and ethical reviews specific to workers studies. But she says there is currently "no formal ethical framework that addresses the unique vulnerability that participating workers face."

In the absence of an established and functional ethical framework, she adds, "and despite the good intentions of the researcher, the employer, and other stakeholders, worker-subjects may be denied adequate protection of their personal autonomy, economic status, or social position."

Models/Codes of conduct
Included in the guide are professional codes of conduct from several organizations. Also included are the requirements for submitting worker health and research study protocols to IRBs.

Examples are provided of model documents approved by IRBs and used in worker studies.

Contributors to the guide include workers, employers, researchers, DOE facility contractors, IRB members, occupational physicians, union, and other governmental agencies.Δ



The handbook, *Creating an Ethical Framework for Studies that Involve the Worker Community*, has been published by DOE's Human Subjects Protection Program. For a free copy, write:

DOE Human Subjects Protection Program Manager
Office of Biological and Environmental Research, SC-72
Office of Science
U.S. Department of Energy
19901 Germantown Road
Germantown, MD 20874-1290

Some contents of the new guide book

- The need to protect workers as human research subjects
- Foundation of an ethical framework
- The challenge of genetic information in worker studies
- Privacy, confidentiality, and protection of personal information
- Stakeholders: their interests, concerns, and responsibilities
- Planning and conducting ethical worker studies
- Historical background
- The National Institute for Occupational Safety and Health approach to workplace studies
- Update of DOE policies
- Professional codes of conduct
- Bibliography and resources
- Informed consent forms and information pamphlets

One mother's perspective: Pattie Tobler

Informed consent as the responsibility of patient & researcher

For the six years her son battled leukemia, Pattie Tobler learned first hand the difference between "consent" and "informed consent."

Pattie is a fifth-grade teacher at St. Christopher Middle School in Richmond, Va. The experience with her son brought her to the attention of the Human Subjects Protection Program, which asked her to assist in reviewing several California research sites.

She was a subject-advocate reviewer for DOE's series of California reviews in the summer of 2000, providing what Program manager Susan Rose said was a "unique and very compelling viewpoint."

Pattie Tobler played an important role in recent DOE human subjects site reviews in California. The experience and understanding she gained from her son's six-year illness and his participation as a subject in research studies has made her an effective advocate for patient-subjects.

Art critic, author

Jay Tobler, who was 33 when he died in February, was a highly regarded New York art critic and writer. He was the author of The American Art Book and an expert in folk and conceptual art.

From the moment he was diagnosed, Jay and his family took very seriously the importance of gathering detailed information about treatments, about the focus of studies at various research centers, about protocols, and about researchers themselves.

Pattie Tobler, seated, with her children, from left, Mary, Jay, and Anna.

The research in which Jay participated was not connected with DOE-sponsored studies, but the issues are nevertheless the same.

They used the internet, contacted friends, acquaintances, read reports of results, considered alternatives, and asked questions, and then asked more questions, and then more questions.

A measure of peace

Their effort—Jay's, his family's, his physicians'—bought him time and opportunities. It also gave them a measure of the peace that comes from knowing they had sought every resource, looked at every reasonable possibility, and at many less than reasonable possibilities.

"Much of this was possible," Pattie said, "because we had the understanding and some of the resources necessary to make sure we understood everything that was going on, to get where we needed to be, and to ask the right questions."

Protocols not translated

Where there is a language problem, the consent form should be written in the language used by the subject.

"It's important that treatment information be made very clear, be made accessible to the target group. If a protocol is targeting an ethnic group, the information has to be explained in a way that's clear for that group. If it's for children, if it's for the elderly, make sure they understand it.

"In most studies, people are given a consent form to read, and then they're allowed to ask questions. But they often don't know what questions to ask. It's the researcher's responsibility to help them with that."

Many people participating in studies, she said, are involved because it's their last chance. "They're so hopeful, so desperate, they're willing to overlook shortcomings in the study. Even when they read that the treatment might cause terrible side effects, they're willing to risk it.

"When people are that desperate," she said, "they may have no real idea what's going to happen to them during the study. Consent forms have to be clear, not only as to the benefits, but that there may not be much benefit at all, at least not to you—though it may help somebody else in the future."

Jay quickly became very realistic about the possibilities offered by

>

studies in which he became involved. He had received a bone marrow transplant from his sister, Anna, which everyone thought would be successful. But two years later the cancer re-appeared in an unusual and unexpectedly aggressive phase.

Everything was experimental
"From then on," Patty said, "he knew that everything was experimental. Some patients go into research protocols thinking they're going to be cured, and of course you hope that. But Jay was very realistic. He knew that everything he did after the first transplant was risky.

"Sometimes doctors are so anxious to do the latest research that they don't tell patients everything. But we became a very informed family after all those years. Our whole family pitched in and did research on the disease.

We learned early on that you have to take charge of your own health.

Best-case scenario
"But we're the best-case scenario. We learned early on that you have to take charge of your own health and participation in research.

"You can't wait for others to tell you things; you have to get out there and look. When one place wasn't willing to do anything, we looked elsewhere until we found someone who was willing.

We were always seeking two, three opinions about everything. We talked to other people. We went on line to get in touch with others with the same disease, or who had experienced the same treatment. We'd ask, Where did you have the procedure done? How did it go? How are you now? Did they help you understand the protocol?

Jay's younger sister, Anna, was the bone marrow donor for his first transplant. She later donated stem cells for another transplant.

After Jay's unexpected relapse, his sister provided a second transplant of her stem cells, but he relapsed again. Several tries with donor leukocyte infusion were attempted along with a combination of various treatments and drugs. Patty, and Jay's youngest sister, Mary, regularly donated platelets in efforts to hold off the disease's progression.

Third transplant
Jay was involved in a study at Houston's M.D. Anderson Center that provided a hopeful new drug that seemed to help others, but didn't help Jay. A third full transplant was performed using an unrelated donor, but that, along with massive doses of chemotherapy, also failed.

During the six years of his battle, Patty said, Jay turned down some studies as too invasive, or, given his lack of an immune system, presented too great a risk of infection. But he kept looking.

"The people at Johns Hopkins were especially good to work with," she said. "They were very clear about their protocols and they helped us find treatments at other research centers. They were the ones who told us about the work being done at M.D. Anderson, which didn't cure him, but did give him an extra 10 or 11 months of life."

Jay and Anna both were constantly seeking new treatments and trying to understand their possibilities, risks, and complexities.

"Anna, as a donor, also had consent forms to sign. So she learned quickly how to ask the right questions and how to recognize whether a consent procedure was adequate. She refused to sign some of them."

If people feel that they're being given all the information they need, then they won't feel like they're just the object of experiments.

Working together
Throughout, it was the working together of the entire family that was key to being informed and to feeling the comfort of believing that every resource had been explored.

"Jay gained strength from his sisters' willingness to donate and to help him search for other possibilities," Pattie said. "I think that helped, and I think that the other thing that helped him was knowing that he was actively involved in making decisions.

"That's why the consent process is so important. If people feel that they truly understand, that they're being given all the information they need, then they will feel that they have some control over how their lives proceed. They won't feel like they're just the object of experiments."Δ

Former worker: "A noble effort, but still a very long way to go"

John Campbell, retired miner and test site worker, is an advocate for former workers

John Campbell, a retired uranium miner and Nevada Test Site worker, is a voice for a group of former workers who until recently felt unacknowledged and unappreciated by their government.

Campbell, who lives in Las Vegas, has been involved for the past several years with Dr. Susan Rose and the DOE Human Subjects Protection Program's working group, acting as both a source of information, an advocate for former workers, and a member of DOE human subjects review teams. As a result, he has been invited to speak at several large human subjects meetings.

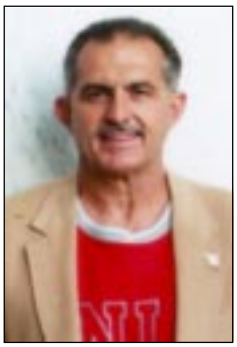
"In the past they felt like nobody would ever help them."

"Most of the people I talk to," Campbell said, "say that in the past they felt like nobody would ever help them, even though they'd spent most of their lives doing dangerous work for their country."

He says he is encouraged by the government's development of protection mechanisms. But he is at the same time increasingly frustrated by what many workers see as reluctance to provide health care and to adequately compensate for harm.

"I know one family where both the husband and the wife and their two sons all worked at the test site. The husband got cancer, which by the time they found it was already very advanced.

"They spent all their savings trying to fight that illness and



John Campbell

they ended up completely broke. Didn't even have enough money to bury him. The Mormon church had to pay for it. And the widow was left with nothing."

Campbell said DOE's Human Subjects Program facilitated a connection between a tissue registry and the family. The registry's autopsy demonstrated that the cancer was work related. This means the worker's wife will probably receive $100,000 as compensation.

" It won't go far with all the bills they've still got, but it's a help," Campbell said.

Others also need medical help, he said, but can't get it. "They're getting to be 50 or 60 years old, and some bad medical things are starting to show up. The worker screening studies help to identify problems early. But after something is identified, they just refer you to a doctor and from there on you've got to take care of it yourself.

"Medical care needs to be provided. Even if they're not going to compensate workers for damages any time soon, they should get the medical care now and talk about compensation later."

Campbell strongly argued for strict requirements of informed consent. He said workers who are asked to be research subjects should be given all the information possible and then be allowed to make their own choices about joining in and receiving results.

"About half the people I talk to say that if they'd known in the beginning about all the workplace dangers, they wouldn't have gone into this work. But the other half say they would do the same as they did, that knowing wouldn't have changed their minds."

Workers who are asked to be research subjects should be given all the information possible and then be allowed to make their own choices.

He is concerned that as scientists are able to identify genetic susceptibilities, some people will be forbidden to work at some potentially dangerous jobs.

"I don't think that should happen. They shouldn't be able to stop you from working because of something that might happen. The person should be given the choice."

>

He believes the issue is similar to that of smoking cigarettes. "They tell you there's a chance you will get sick if you smoke. Then it should be up to you to decide."

They should get the medical care now and talk about compensation later.

Campbell says the best way to protect both workers and workers who are research subjects is by caring about what happens to them.

"That's the only really effective protection," he said. "Researchers, the government, employers—they just have to ask, are we creating a situation that might be dangerous? And, how can we protect them? If they're really serious about that, we'll be ok."

The best way to protect workers who are research subjects is by caring about what happens to them.

But unfortunately, he added, "all the safety rules we've got now are written in blood. Some people had to give their life or their health before any of these rules were written.

"The DOE worker screening programs are a big step. All the things they're doing to encourage protection is a great help. It's a noble effort. But I think there's still a very long way to go."Δ

McInerney is seeking IRB at Rocky Flats

John McInerney is beginning to understand some of the interesting difficulties of starting an IRB.

He and others at the Rocky Flats Environmental Technology Site have been trying to organize and get approval for a new board.

John McInerney

An IRB had existed previously at Rocky Flats, but it was established specifically to work on a beryllium-monitoring program for former workers. When that program left Rocky Flats, a new IRB had to be established to serve continuing projects at the site.

McInerney is also medical director at Rocky Flats, heading a project that conducts medical surveillance of beryllium exposure in current workers. He needed an IRB to approve his and other work.

"It took us eight months to get enough people interested in doing it," he said. "We started with five members and got the current worker program approved by them."

Then two of the five members left the site, leaving McInerney, the IRB president, and a union worker.

"Now we're searching for replacements. This time we're trying to get seven people on the committee. If one or two leave, it won't have such an impact.

"But we're still waiting for approval. Until then, we're in the odd predicament of having sort of an IRB that maybe has enough members and maybe will be approved, but nothing official can be done until we get that approval.

"I'm determined to do it, and do it soon, and do it right. It's needed to protect workers, and I'm committed to doing that."Δ

Notes

Updates and notices

NBAC REPORTS DUE IN DECEMBER

Two much-anticipated reports from the National Bioethics Advisory Committee (NBAC) are due to be released in December. They are "Adequacy of Federal Protections for Human Subjects in Research" and "Ethical and Policy Issues in the Oversight of Human Research in the United States."

For information: http://bioethics.gov/oversight.pdf

For a description of the report: http://bioethics.gov/oversight.pdf

For the letter and memo sent to President Clinton regarding NBAC's preliminary findings: http://bioethics.gov/news.html

Explaining the RDRCs & DSMB

A brief overview of two little-understood links in the long chain of human subjects protection

Editor's note: Two important elements in the chain of protecting human subjects are the Data Safety Monitoring Boards (DSMBs) and the Radioactive Drug Research Committee (RDRC). Both are relatively new and the workings of both are little understood. The following is a brief look at the purpose and operation of each. The information here was distilled from the Web sites, which are listed at the bottom of these pages.

Data Safety Monitoring Board: Guarding safety in conduct of trials

The National Institutes of Health (NIH) declared, in a June 1998 policy, that each NIH Institute and Center (IC) "should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials."

For multisite clinical trials involving interventions that entail potential risk to participants, the policy calls for establishment of a Data Safety Monitoring Board (DSMB).

The main principles of the policy are that:

- all clinical trials (phases I–III) require monitoring of safety and data, and
- monitoring should be commensurate with risks.

Monitoring may be conducted by the principal investigator in a small phase I study, but will require an independent DSMB for a large phase III clinical trial.

In the latter type studies, DSMBs play a key role in protecting the safety of participants and assuring the integrity of the data.

Protection of subjects requires that the board become familiar with the protocol, proposing appropriate analyses, and reviewing the developing outcome and safety data.

Reviewing data

These boards ensure the integrity of the study by reviewing data on various factors such as participant enrollment, site visits, study procedures, data quality, and other measures of adherence to the protocol as well as adverse effects and unanticipated problems.

DSMB monitoring is above and beyond that performed by IRBs.

Based on these reviews, a DSMB will make recommendations concerning appropriate protocol and operational changes. DSMBs (and the investigators) also monitor toxicity factors.

To successfully fulfill their role, DSMBs should be composed of experts in relevant disciplines (e.g., clinical trial experts, biostatisticians, bioethicists, and clinicians familiar with the disease and treatment under study).

DSMB functions for clinical trials are above and beyond the role traditionally played by a local Institutional Review Board (IRB). This makes DSMBs particularly important for multicenter trials.

IRBs at research institutions must still review and approve studies that involve human subjects to ensure that subjects are protected.

Once a study is approved, ongoing communication between the DSMB and the IRB is essential for the continual assessment of the protection of human subjects in a study. (The flow of information is from the DSMB to the study investigator, who then must forward it to the IRB.)

If DSMB reports provided to the IRB indicate unexpected harm to study participants, the IRB has the authority to suspend or terminate the research at its site. Thus, while DSMBs issue reports on their monitoring activities and can make recommendations based on those findings, IRBs have the final say at that site.Δ

Web sites

- NIH policy for data and safety monitoring (June 10, 1998)
  http://grants.nih.gov/grants/guide/notice-files/not98-084.html
- Guidance on reporting adverse events to IRBs for NIH-supported multicenter clinical trials (June 11, 1999)
  http://grants.nih.gov/grants/guide/notice-files/not99-107.html
- Continuing review of DSMB-monitored clinical trials (May 22, 2000)
  http://ohrp.osophs.dhhs.gov/humansubjects/guidance/dsmb.htm

Radioactive Drug Research Committees: Providing additional reviews for research

Scientific research involving human subjects normally requires regulatory approval.

When that research will involve the administration of radioactive drugs, the investigators will be subject to additional reviews, possibly by a Radioactive Drug Research Committee (RDRC).

These committees are formed, under the auspices of the Food and Drug Administration (FDA), to determine if the proposed administration of "certain" radioactive drugs [i.e., drugs not licensed by the FDA or covered by an investigational new drug (IND)] will be safe and effective in studies designed solely to obtain basic information on that drug (e.g., metabolism of the drug, effects on human physiology, biochemistry).

An RDRC's work is reviewed each year by the FDA .

Research with radioactive drugs intended for therapeutic, diagnostic, or similar purposes or to study their safety and effectiveness (i.e., clinical trials) requires submission to the FDA of an IND application.

RDRC review is in addition to any radiation safety review required by state or federal law for the site where the research is conducted.

Each RDRC must be approved by the FDA's Center for Drug Evaluation and Research.

FDA regulations in 21 *Code of Federal Regulations* (*CFR*) Part 361 specify that RDRCs "shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty or with a committee established by a State authority to provide advice on radiation health matters."

At least five members
Further, the committee is required to consist of at least five people. Of these five, the RDRC is to include at least

- one physician recognized as a specialist in nuclear medicine,
- one person qualified to formulate radioactive drugs, and
- one person with special competence in radiation safety and dosimetry.

FDA requires that the remainder of the committee be made up of people qualified in various disciplines related to the field of nuclear medicine (e.g., radiology, clinical pathology, radiation physics, health physics).

Nevertheless, the Director of the Center for Drug Evaluation and Research can modify these requirements in a situation where alternative factors basically provide the same composition and association.

Evaluating a study
Several factors must be considered by an RDRC when evaluating a potential study to determine if it will be "safe and effective."

Among other things, the RDRC is required to ensure that the investigators meet the pharmacological and radiation dose limits and guidelines specified by Part 361.

The committee must also see that the study meets requirements concerning:

- the qualifications of the investigator(s),
- licensure for handling radioactive materials,
- selection and consent of research subjects,
- quality of radioactive drugs used,
- research protocol design,
- reporting of adverse reactions, and
- approval by an appropriate Institutional Review Committee.

Finally, an RDRC's work is reviewed each year by the FDA in a report the committee must submit. These reports include a summary of each individual study they reviewed during the previous year and are a vital part of FDA's continual review of RDRCs.Δ

Web sites

Code of Federal Regulations (Part 361.1)—Radioactive drugs for certain research uses (21CFR361.1).
http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr361_00.html

Forms:
Radioactive Drug Research Committee (RDRC) report/research use of drug membership summary
http://forms.psc.gov/forms/FDA/Ps2914.pdf

Radioactive Drug Research Committee (RDRC) report on research use of radioactive drug study summary
http://forms.psc.gov/forms/FDA/Ps2915.pdf

Web sites

for human subjects protection and related resources

Association of American Medical Colleges—Research Compliance Resources
The site's focus is research with human subjects.
http://www.aamc.org/research/dbr/compliance/startcom.htm

National Association of IRB Managers
http://www.naim.org

Professional Testing Association (This vendor works with ARENA/PRIM&R.)
http://www.ptcny.com

CDC, Protecting Human Research Subjects, IRB Guidebook (NIH, OPRR)
http://www.cdc.gov/od/ads/irbguide.htm

University of Washington—Ethics in Medicine
http://eduserv.hscer.washington.edu/bioethics/topics/resrch.html

NIH—Protection of Human Research Subjects, Computer-Based Training for Researchers
http://ohsr.od.nih.gov/cbt/

University of Minnesota—Web-Based Instruction on Informed Consent
http://www.research.umn.edu/consent/orientation.html

FDA—Drug Applications, Information for Clinical Investigators
http://www.fda.gov/cder/about/smallbiz/clinical_investigator.htm

Fordham University, Center for Ethics Education
http://www.fordham.edu/gsas/psyc/cee/

University of California, Irvine—Research with Experimental Subjects (On-line Tutorial Services)
http://tutorials.rgs.uci.edu

University of Rochester—Research Subjects Review Board
http://www.urmc.rochester.edu/urmc/rsrb/RELDOCS.htm

FASEB, Science Policy and Public Affairs Alert
http://www.faseb.org/opar/news/sppa.html
The following site is a special issue of the Public Affairs Alert containing several resources related to protecting human subjects:
http://www.faseb.org/opar/news/sppa/sppa6x0.html

Harvard University School of Public Health, Ethical Issues in International Health
http://www.hsph.harvard.edu/bioethics/

DOE Human Subjects Research Database
The fiscal year 1999 database consists of 294 projects, of which 71% were conducted at DOE facilities and 29% at non-DOE facilities (such as hospitals and universities). There are 43 reporting research facilities; 12 are DOE laboratories, and 31 are non-DOE facilities.
http*://www.eml.doe.gov/hsrd/*

Office of Research Integrity
ORI is responsible for protecting the integrity of Public Health Services (PHS) extramural and intramural research programs. The site includes ORI forms, workshops, conferences, whistleblower issues, PHS administrative actions, legal decisions, appeals board information, and departmental appeals.
http*://ori.dhhs.gov/*

IRB Certification
This site provides information about the process of IRB certification.
http://www.primr.org/certification.html

Protecting Human Subjects

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 Subjects Research Program Manager
Dr. Susan L. Rose

This newsletter is prepared at Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

Managing Editor
Dr. Gloria Caton
catongm@ornl.gov

Editor, Designer
Tim Elledge
x3x@bio.ornl.gov

This newsletter is available at no cost to anyone interested or involved in human subjects research at DOE. Please send name and complete address (printed or typed) to the address below. Please indicate whether information is to (1) add new subscriber, (2) change name/address, or (3) remove name from mailing list. Enclose a business card, if possible.

Send suggestions and subscription information to —

Dr. Susan L. Rose
Office of Biological & Environmental Research, SC-72
U.S. Department of Energy
19901 Germantown Rd.
Germantown, MD 20874
Fax (301) 903-8521

Meetings

PRIM&R/ARENA
October 28–31, 2000
San Diego, California
IRB 101—Public Responsibility in Medicine and Research (PRIM&R) Training for Institutional Review Board (IRB) newcomers: October 28, Hyatt Islandia.
PRIM&R's 2000 IRB conference: October 29–30, Paradise Point Resort.
Applied Research Ethics National Association's (ARENA's) 2000 IRB meeting: October 31, Paradise Point Resort.
Contact: info@primr.org.
http://www.primr.org/conferences.html

VETERANS AFFAIRS/ORCA/IRB WORKSHOP
October 27, 2000 — San Diego, California
The Veterans Affairs Administration will conduct a special meeting in conjunction with the PRIM&R and ARENA conferences. It will focus on activities related to the Office of Research Compliance and Assurance (ORCA) and IRBs.
http://www.va.gov/orca/edu/

DOE HUMAN SUBJECTS GROUP
October 28, 2000 — San Diego, California
The group meeting will address upcoming regulations as well as DOE-related problems and events. The meeting will be held in conjunction with the PRIM&R and ARENA conferences.

RESEARCH CONFERENCE ON RESEARCH INTEGRITY
November 18–20, 2000 — Washington, D.C.
This conference will discuss "emerging challenges for the responsible conduct of research." The conference will provide a forum for sharing information and ideas to aid decision making about promoting research integrity and monitoring research misconduct. It is sponsored by the U.S. Office of Research Integrity. Cosponsors are the Association of American Medical Colleges, the American Association for the Advancement of Science, National Institutes of Health, and the National Science Foundation.
http://ori.dhhs.gov/html/news/page3.htm

A DECADE OF ELSI RESEARCH
January 16–18, 2001 — Washington, D.C.
Natcher Conference Center, National Institutes of Health
A conference to celebrate the first 10 years of research under the Human Genome Program's "Ethical, Legal, and Social Implications (ELSI)" component.
To register, contact:
Elizabeth J. Thomson
ELSI Program Director
National Human Genome Research Institute
National Institutes of Health
(301) 402-4997, (301) 402-1950 fax
et22s@nih.gov
http://www.nhgri.nih.gov/elsi/

UNITED STATES
DEPARTMENT OF ENERGY
Office of Science/SC-72
19901 Germantown Road
Germantown, MD 20874-1290

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

FIRST-CLASS MAIL
U.S. POSTAGE
PAID
MERRIFIELD, VA

PROTECTING HUMAN SUBJECTS

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