PROTECTING HUMAN SUBJECTS

U.S. DEPARTMENT OF ENERGY,
OFFICE OF BIOLOGICAL AND ENVIRONMENTAL RESEARCH — ISSUE NO. 16

Inside

Consent issues..... 5
OHRP response..... 6
SACHRP 7
News notes... 7
Oral history 9
Sandia in Russia..... 10
Hinder research?... .. 12
Ethical duty?..... 13
Not without risk..... 14
Genetic twists..... 16
HS resource book ... 17
Helsinki..... 18
News notes 19
Vulerability..... 20
Genetic bill passed... 22
Meetings..... 23

Improving the effectiveness of IRBs

This edition of *Protecting Human Subjects* focuses on issues raised in talks at the Human Research Protection Programs (HRPP) Conference in Boston, especially those about improving the effectiveness of institutional review boards (IRBs). We have included updated highlights of some of those talks because they raised concerns and suggested ideas that we think deserve further discussion.

In some ways this is a continuation of discussions begun in the last edition, which considered recommendations by the U.S. Department of Health and Human Services (HHS) Secretary's Advisory Committee on Human Research Protections (SACHRP). The committee discussed the protection of decisionally impaired subjects, what minimal risk is, and when it is reasonable to waive or alter consent requirements.

Adding to that conversation, this issue begins with the front page account of ethicist **Art Caplan's** suggestion that IRBs focus their reviews on informed consent and let other issues, including conflicts of interest, be handled elsewhere. Other discussions, including those by **Joanne Lynn, Mary Marshall Clark,** and **Simon Whitney,** raise questions about whether current regulations work for all types of research.

To receive e-versions of *Protecting Human Subjects*

To receive e-mail notification about future online issues of *Protecting Human Subjects*, please send your name, organization, telephone number, and e-mail address to humansubjects@science.doe.gov.

IRBs & research changes

Caplan says IRBs should focus on informed consent, relinquish oversight of conflicts of interest

The world of IRBs is changing in ways that the current model is not equipped to handle, according to bioethicist **Art Caplan**, a keynote speaker at the last HRPP meeting.

Art Caplan

Caplan, director of the Center for Bioethics at the University of Pennsylvania, outlined the way research is changing and how it will affect IRBs, and listed ways in which they can prepare for a world that will require a very different model.

Among other things, he recommended that IRBs should focus primarily on improving consent processes, relinquishing some other responsibilities, including oversight

(Continued on next page)

Is it coercive to offer incentives to subjects?

Alan Wertheimer

The promise of financial or other incentives to participate in research does not ordinarily compromise the voluntariness of a subject's decision, according to philosopher **Alan Wertheimer**.

In addition, Wertheimer, a philosopher in the National Institutes of Health Department of Bioethics, said it could be a violation of a prospective subject's autonomy if she were not allowed to take risks in exchange

(Continued on page 4)

Caplan: Private sponsorship with very large amounts of money is more common and has brought with it substantial conflicts of interest.

Caplan: *IRBs and research changes*

(Continued from page 1)

of conflicts of interest and adverse events. He said the research protections community should gather more data about what it does and how well it is working because they will need it when responding to critics who say that IRBs are either too protective or not protective enough. He also said the community has failed to use what data are available to improve the system.

IRBs, he said, were created in a world where the goal was to minimize risk in research conducted at just one institution, using subjects from just one region. IRB members in that world knew the investigators because they were their colleagues, and local review allowed them to keep an eye on the study. In addition, medical research focused on developing "blockbuster" drugs that would make a lot of money by being a "one-size-fits-all" pill for everyone with a given condition.

World of local oversight is disappearing

Caplan said the world of local research, local oversight, and blockbuster drugs has almost disappeared.

Research now is multi-institutional and not infrequently international, which means that IRBs are having to collaborate with each other and that local governance and local values are being set aside. Private sponsorship with very large amounts of money is more common and has brought with it substantial conflicts of interest.

Personalized medicine

Personalized medicine will soon end the era of blockbuster drugs, he said. Genetic and biologic information will be used to develop drugs to fit each person's body, or those of the same genotype. IRBs will have to rethink their roles because research itself will be very different. "IRBs will be faced with new issues that are specific to personalized medicine, including the question of whether the burdens of research fall fairly by race and ethnicity," Caplan said.

IRBs may have to give up trying to police issues of conflicts of interest, he said, because the complexity of relationships, the availability of private money, multi-institutional research, and changing research goals will make such policing impracticable for them.

In the meantime, several immediate issues must be addressed, he said. One of these is to find a meaningful way to respond to those who claim that the human subjects protection system is broken, either because there is too much protection or too little protection.

Dysfunctional system?

Those who say there is too much being done by IRBs argue that the regulatory system is dysfunctional, spending too much time on activities with marginal utility, and thereby unnecessarily inhibiting research. "Too much minutia, legalese, too much attention paid to minor proposals," he said.

The other side argues that there is more protection for animals than for humans. "We know what research animals are used in, the pain involved. The data is reported. There are unannounced spot checks. No warning; they just come, unannounced."

The way to respond to these criticisms and the way to improve the system is to gather and analyze data about what is being done now.

"If someone asks, do you think vulnerable populations such as the mentally ill are overutilized? Nobody can

(Continued on next page)

Related Web sites

Public Responsibility in Medicine and Research (PRIM&R) conferences
http://www.primr.org/Conferences.aspx?id=56

University of Pennsylvania bioethics
http://www.bioethics.upenn.edu/

Center for Practical Bioethics
http://www.practicalbioethics.org/

IRB: Ethics and Human Research
http://www.thehastingscenter.org/publications/irb/irb.asp

IRB Forum
http://www.irbforum.org/forum/

Caplan: "I don't see much debriefing or follow-up to see whether what the IRB approved is what the subjects experienced."

answer that. There is no public database. "Who is on IRBs? What kind of proposals gets to them? We don't know."

Ignoring data

Making things worse, he added, is that we ignore data that are available.

We know, for example, "about cultural gaps, and about vulnerability, about problems communicating risk information, informed consent, problems with competency.

"We know some factors make subjects vulnerable: literacy challenges, poor education, reading ability, age, language proficiency problems, fear. Fear about entering hospitals can make some unable to listen or understand during the process of informed consent. Poverty plays a role in power relationships. Disease itself is coercive. Decisions to enroll in phase one studies often are made when people feel they have no choice and so do not adequately consider risks."

Knowing this, the research community does too little to address the issues. Data are available indicating that some techniques empower people, improving comprehension. "But how many have devoted budgets to video informed consent presentations to help people understand? How many IRBs are insisting on an informed consent quiz to demonstrate comprehension? I don't see much debriefing or follow-up to see whether what the IRB approved is what the subjects experienced."

The forms might look good, he said, and the "lawyers are happy. We feel satisfied we did the best we could to make sure people know what's going on. But then, if there are issues about their ability to process information, we act as if it's beyond our ability to do anything about them."

IRBs may be doing a good job, Caplan said, but data showing that are not available, which makes IRBs vulnerable to people who argue that they create more problems than they solve. The solution is to gather more data about what does work, which would result in strategies that expedite reviews by being more efficient.

Recommendation: divide functions

One of those strategies might be to divide functions. The focus for IRBs should be on informed consent, he said, shedding themselves of other responsibilities that can be handled better by others. The Department of Health and Human Services can handle oversight of adverse effects. Sponsors should watch for conflicts of interest. "IRBs should not have to police for conflicts of interest; they are often the last ones to know about conflicts, especially in the world of giant studies."

Caplan said "It's a new, new world," he said. "The world of knowing the subject, knowing the investigator is long since gone. Big, collaborative research with a huge presence of private money has changed everything."Δ

Related Web sites

Bioethics discussion archive
http://www.irbforum.org/forum/read/5/2389/2389

Harvard Program on Ethical Issues in International Health Research
http://www.hsph.harvard.edu/bioethics/

Ethica: International research ethics
http://www.hf.uib.no/i/Filosofisk/ethica/research.html

World Health Organization—Ethics & Research
http://www.who.int/ethics/topics/en/

Resources for international research ethics
http://www.hf.uib.no/i/Filosofisk/ethica/research.html

Hastings Center Report
http://www.bioethicsforum.org/Genetic-Information-Nondiscrimination-Act-genetic-discrimination.asp

Bioethics News
http://www.bioethics.net/news.php/

Center for Bioethics and Human Dignity
http://www.cbhd.org/

Bioethics blog
http://blog.bioethics.net/

"It's false to complain about undue inducement in situations where only study participation gives people who are HIV positive access to antiviral drugs . . ."

Wertheimer: *Is it coercive to offer incentives to subjects?*

(Continued from page 1)

for money. "Offers do not coerce," he said. "Payment is an offer, not a threat, and payment for research is not coercive. It would be coercive if a doctor threatens to abandon a patient if he doesn't agree to participate in research, but that is a different matter."

Various incentives are offered to prospective subjects, he said, including money, free medical examinations, access to experimental treatment, and access to standard treatment a person might not otherwise be able to afford.

An unquestioned precept

"It is an unquestioned precept of research that subjects shouldn't be coerced, that they must be capable of choosing freely, that they must do so voluntarily, without duress, without being subjected to threats or the promise of too great a reward," he said. "But does the offer of incentives compromise the validity of their consent in any way that should trouble us?"

Payment constitutes undue influence, Wertheimer argued, "only if it distorts the participant's judgment or reasoning."

Two forms of coercion are usually cited in this context, he said. One is the "threat" view. The second is the "no reasonable alternative" view. Threatening is not the same thing as providing options: "Threats reduce the options and thereby reduce autonomy and voluntariness. An option is merely giving someone another item on the menu, and that is not coercive.

No reasonable alternative

It is a mistake, he said, to think that a person is coerced to do something whenever she has "no reasonable alternative." Consider this: A doctor tells a patient that unless she agrees to surgery she will die within a year. The patient agrees. Does the patient have a reasonable alternative? No. Has the patient been coerced? No. Can the patient give voluntary consent? Yes. Illness does not coerce."

The danger many people see in offering inducements, Wertheimer said, is that it gets them to do things they would not otherwise do. "As a general matter, inducements are morally unproblematic. If I offer $100 to mow my small lawn, that would be getting someone to do something they wouldn't otherwise do. But it is not coercive.

"People take on risk because we pay them to do so. Is participation in research morally different?"

"There is undue inducement only when it distorts the target's decision-making such that they do not appropriately consider the risks of participation."

Irrational decisions

There is reason to worry about inducements that distort decision-making, "but not because they are inducements. The reason to worry is when undue inducements result in irrational decisions.

"It's false to complain about undue inducement in situations where only study participation gives people who are HIV positive access to antiviral drugs that can forestall otherwise certain death," he said. "It's false because there's nothing irrational about participating for that reason."

One way of thinking about this, he added, is to remember that people do many risky jobs for money: coal mining, being a soldier, firefighting, and others. "People take on risk because we pay them to do so. Is participation in research morally different? There may be reasons to worry more about incentives in research than in ordinary employment, but I don't think this is obviously so.

"Just as we would not be respecting a structural steel worker's autonomy if we did not allow him to take risks in exchange for money, we would not be respecting a prospective subject's autonomy if we did not allow her to take risks in exchange for money," he said.Δ

The initial fear was that if IRB approval and consent procedures were required, "a demonstrated method of improving health care would be in jeopardy and could endanger the lives of patients."

Informed consent requirements for quality improvement initiatives should make sense


Joanne Lynn

*(Editor's note: **Joanne Lynn** gave her presentation at the HRPP meeting before the Office for Human Research Protections (OHRP) issued its response to criticism of the OHRP ruling she discusses. That response is on page 6.)*

Quality improvement in health care can be hindered by unnecessary requirements that IRBs must review and approve all forms of data collection related to patient care, Joanne Lynn told HRPP during a panel discussion about whether current rules work for all types of research.

Controversy

Lynn, a physician who focuses on chronic illness and end of life issues, referred to a controversy about whether Michigan hospitals erred by not seeking IRB review before they used a checklist and other measures to prevent hospital-acquired infections.

In that case, Michigan hospitals began using a system recommended by researchers at Johns Hopkins University to reduce catheter-associated infections in intensive care units. The hospitals tracked the results, finding that infections were reduced from 7.7 to 1.4 infections per 1000 days. An anonymous complaint to OHRP asserted that the process should have been designated human subjects research and hence should have been reviewed by an IRB to determine whether patient consent was appropriate.

OHRP eventually ruled that implementing the checklist did not require IRB approval but that an earlier stage of data collection did.

The initial fear, Lynn said, was that if that were to be required, a demonstrated method of improving health care would be in jeopardy and could endanger the lives of patients.

Patients' lives may be risked

Lynn said data-driven quality improvements works, but that if clinicians have to take the time, money, and other resources necessary to seek approval from hundreds of IRBs, the improvements may not be implemented, or may risk the lives of patients during the additional time it takes to get IRB approval and to implement informed consent procedures.

"There are times when quality improvement research should be reviewed," she said. "If it's getting beyond established science, beyond what is well proven, beyond standard practice, then review is needed."

Too often, she noted, the results of quality improvement research end with the cessation of that project's funding. The results are not sustained by being widely implemented.

Inhibiting research?

One of the exceptions is the Michigan case, in which recommendations from the Johns Hopkins research were implemented by the hospitals. Soon afterward, however, it appeared that the hospitals would have to suspend implementation until the IRB completed a review of its plan. The case is an example of why many people in the research community are concerned that IRBs and human subjects regulations often serve to inhibit rather than encourage research.

Quality improvement research is different, Lynn said, from other kinds of research in that it is an integral part of a physician's responsibilities to continually improve patient care.

(Continued on next page)

Issue No. 16

Michigan hospitals controversy

OHRP on quality improvement oversight

The Office for Human Research Protections (OHRP)—part of the U.S. Department of Health and Human Services (HHS)—has concluded that Michigan hospitals can continue implementing a checklist to reduce the rate of catheter-related infections in intensive care units (ICU) without falling under regulations governing human subjects research.

"We do not want to stand in the way of quality improvement activities that pose minimal risks to subjects," said **Ivor Pritchard,** acting director of OHRP. "HHS regulations provide great flexibility and should not have inhibited this activity. The regulations are designed to protect human subjects."

"We do not want to stand in the way of quality improvement activities that pose minimal risks to subjects."

Following the publication of an op-ed entitled "A Lifesaving Checklist" in the December 30, 2007, edition of *The New York Times*, some readers contacted OHRP, expressing concern that hospitals in Michigan and elsewhere were prohibited from implementing a program intervention consisting of a checklist and other measures to prevent certain hospital-acquired infections. OHRP said it has taken no such action.

On the contrary, if any hospital or intensive care unit decides to implement the use of checklists or other measures only for the reason that they believe those measures will improve the quality of care provided, they may do so without consideration of the requirements of the HHS regulations for the protection of human research subjects (45 CFR part 46).

A Johns Hopkins study had demonstrated that a comprehensive five-step program can dramatically reduce the incidence of catheter-borne infections in ICUs. The Michigan hospitals were implementing this program. HHS strongly encourages hospitals nationwide to adopt the program, which it says can save thousands of lives and millions of dollars each year.

The research was described in an article published in the December 28, 2006, edition of the *New England Journal of Medicine* (Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725-32). **(http://content.nejm.org/cgi/content/full/355/26/2725)**

OHRP noted that the Johns Hopkins project has evolved to the point where the intervention, including the checklist, is now being used at certain Michigan hospitals solely for clinical purposes, not medical research or experimentation. Consequently, the regulations that govern human subjects research no longer apply and so IRB approval is not necessary.Δ

Lynn: Consent requirements should make sense

(Continued from page 5)

"The nature of quality improvement doesn't fit within the usual processes of an IRB, in which you state a protocol and stick with it. In quality improvement, the procedures change as we constantly learn new things, and it doesn't necessarily work in one place in the same way it does in another."

There are times when quality improvement research should be reviewed, she said. "If it's getting beyond established science, beyond what is well proven, beyond standard practice, then review is needed.

"Also, if you create randomized groups to see the effect or if you are delaying feedback of data to obtain statistically significant findings, then it should be reviewed.

"Review would also be appropriate if you have key staff in the project who define themselves as researchers, people not intrinsic to the delivery of care. And if external funding is used, rather than the project being a part of internal funding for ongoing care, then it should be reviewed," she said.Δ

SACHRP panel: Exempt QI activities from IRB oversight

Five panelists agree that QI procedures and QI-related research should not require review

Panelists at a meeting of the U.S. Department of Health and Human Services (HHS) Secretary's Advisory Committee on Human Research Protections (SACHRP) agreed that most quality improvement (QI) activities should be exempt from Common Rule and IRB oversight.

The panel discussion, "Quality Assurance, Quality Improvement and Health Services Activities," addressed the recent controversy about Michigan hospitals implementing QI procedures without submitting the plan for IRB approval.

The controversy centered on whether QI procedures and QI-related research should be considered human subjects research and thus subject to IRB review.

The *New York Times* opinion article that helped precipitate the panel review was written by a reporter for *The New Yorker*. It can be found by going to **http://www.nytimes.com/pages/opinion/index.html**, then searching for "A Lifesaving Checklist," which was published December 30, 2007.Δ

News notes

Study finds lack of reporting of monetary compensation in research articles

A study published in the ***Journal of Empirical Research on Human Research Ethics*** (vol. 2, no. 4, Dec., 2007) found that few research articles mention having paid money to research subjects.

Authors **Robert Klitzman, Ilene Albala, Joseph Siragusa, Kristen Nelson**, and **Paul Appelbaum** said studies that included substance users were significantly more likely than others to mention payment. Only 13.5% of articles surveyed mentioned financial payment in any way; only 11.1% listed amounts.

Information can be found at:
http://caliber.ucpress.net/toc/jer/2/4

Study says research Web sites often mention incentives but not risks

A study in the **Hastings Center (http://www.thehastingscenter.org/)** publication ***IRB: Ethics & Human Research*** (January–February 2008) found that a variety of clinical trial Web sites that described incentives to participate failed to mention risks or details about what was required of participants.

Access to data from the study is at **http://www.thehastingscenter.org/publications/irb/irb.asp**

It said that three-quarters of the sites for diabetes and certain depression studies list incentives available for research subjects but do not fully disclose risks. For-profit entities were more likely not to provide balanced information.

A second study reported in ***IRB: Ethics & Human Research*** (January–February 2008) found that a clinical trials information handbook used during the informed consent process improved individuals' knowledge about the process, and decreased perceived risk from trial participation.

Participants who read the handbook scored 80% higher than those who did not read it. They recruited subjects from the outpatient waiting areas at both facilities.

The information handbook, written at a seventh-grade educational level, was developed by the authors for use in the study they conducted at the New Mexico Veterans' Affairs Health Care System and the University of New Mexico Hospital.

News notes

Pacific Northwest National Laboratory earns AAHRPP accreditation

Pacific Northwest National Laboratory (PNNL) is the first of DOE's labs to earn accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).


Sherry Davis

For PNNL, accreditation is "a visible way of demonstrating that we value research protections for human subjects and that we are worthy of our clients' confidence and collaboration in research," says Sherry Davis, manager of PNNL's Human Research Protection Program and IRB. "It was important to our laboratory to take our place among institutions that have earned this prestigious distinction."

The decision to seek accreditation came at the urging of DOE and the PNNL Laboratory Director and was supported at all levels by management, researchers, and IRB members and staff.

"We are very serious about promoting quality improvement for all activities conducted at our laboratory," Davis said. "While we recognize that our Human Research Protection Program will always be a work in progress, accreditation is a significant milestone and an affirmation of our efforts."

PNNL is one of 107 national and international organizations that have received accreditation since AAHRPP was established five years ago. Others include the Florida Department of Health, the University of Michigan, and the New York University School of Medicine. Information regarding AAHRPP's accreditation is at **http://www.aahrpp.org/www.aspx?PageID=234.**Δ

The New Yorker article, "Guinea-Pigging," examines the ethics of HS research

The New Yorker magazine in its January 7, 2008, issue published a lengthy discussion of the ethics of using human subjects in research. It focused on people who participate in studies primarily as a way of earning money.

The article, "Guinea-Pigging," by **Carl Elliot**, concludes that there is something "inherently disconcerting about the idea of turning drug testing into a job."

"Because such studies require a fair amount of time in a research unit, the subjects are usually people who need money and have a lot of time to spare: the unemployed, college students, contract workers, ex-cons, or young people living on the margins who have decided that testing drugs is better than punching a clock with the wage slaves. In some cities, like Philadelphia and Austin, the drug-testing economy has produced a community of semi-professional research subjects, who enroll in one study after another. Some of them do nothing else. For them, 'guinea-pigging,' as they call it, has become a job. Many of them say that they know people who have been travelling around the country doing studies for fifteen years or longer."

Elliot says there is uncertainty about harms that might be caused by testing because "no one institution is keeping track of how many deaths and injuries befall healthy subjects in clinical trials.

"Nobody appears to be tracking how many clinical investigators are incompetent, or have lost their licenses, or have questionable disciplinary records. Nobody is monitoring the effect that so many trials have on the health of professional guinea pigs. In fact, nobody is even entirely certain whether the trials generate reliable data.

"A professional guinea pig who does a dozen drug-safety trials a year is not exactly representative of the population that will be taking the drugs once they have been approved."Δ

"It's the standard protocol of IRBs to have researchers destroy the tapes of interviews. People have spent hours explaining their experience and at the end of the process, you erase the history. That's a problem."

Oral historian: IRB scrutiny often unnecesssary

There are better ways to examine risks and benefits than the legalistic definition of ethics often employed by IRBs. Ethics should be evolving and consensual throughout the interview process

Mary Marshall Clark

Oral historians should not ordinarily be subject to IRB scrutiny because the entire process of recording people's accounts inherently protects them from harm, **Mary Marshall Clark** said.

Consent-driven process

Clark, who is director of the Columbia University Oral History Research Office, said oral historians do not test people. Instead, "we engage in conversations with them. Our process is consent-driven from the beginning."

People are invited by issuing a letter of invitation explaining why a historian wants to interview them, she said. "We give them the right to review the recordings or transcripts before the interview is deposited in a public archive. They have the right to edit it or to withdraw their participation. They also have the right to self-publish. Columbia doesn't own the transcripts to the exclusion of people owning the transcripts themselves."

Participation always voluntary

Participation is always voluntary, she said. "And we encourage people to be active participants. They can withdraw at any time."

Clark, who was involved in interviewing 700 people who experienced the World Trade Center attacks in 2001, said that IRBs sometimes are oriented to a "legalistic definition of ethics" and that there are better ways to examine risks and benefits.

"In oral history, ethics is evolving and consensual throughout the interview process. We don't see people as victims, but as agents of history who are able to tell us what they experienced and their reaction to it. They have rights as agents of history to explore this," she said.

A pernicious view

"If you were to see the person as a victim, this would lead to the pernicious view that nonmedical researchers are seeking to take advantage of subjects and are guilty until proven innocent."

Some members of the Columbia University faculty have this view of IRBs, she said, in that they believe they must prove their innocence. "It's the standard protocol of IRBs to have researchers destroy the tapes of interviews. People have spent hours explaining their experience and at the end of the process, should you erase the history?

"In oral history, we don't see people as victims, but as agents of history. They tell us what they experienced and their reaction to it. They have rights as agents of history to explore this."

Victimizing, not protecting

"That's a problem. That's victimizing the individual you sought to protect. They have a right to their own narrative, a right to choose whether it will be in an archive, and a right to publish it."

Clark said a "climate of fear" exists between many nonmedical researchers and the IRB community that "is not conducive to dialogue. Neither is it conducive to compliance."

There are areas of congruence between the two groups, with both having much to share, she said, but only "if this climate of fear can be relaxed."Δ

Sandia delegation in Russia

Preparing for review of collaborative study involving Sandia and two Russian institutions

by Terry Reser, Administrator, Human Studies Board Sandia National Laboratories

Like most Human Studies Board DOE sites, Sandia National Laboratories (SNL) collaborates with research institutions across the United States, and while a given study may be quite complicated, the collaboration itself is usually straightforward. However, when the other institution is located in a foreign country, complications can creep in quickly.

I recently spent a week in St. Petersburg, Russia, to help Sandia's IRB prepare for an upcoming review of a collaborative study involving SNL and two Russian institutions. This article may be useful if you find yourself in a similar circumstance.

The Sandia delegation in St. Petersburg, Russia, at a local restaurant. Elaine Hinman-Sweeney (back left), Courtney Dornburg (front left), Conrad James (front right) and Terry Reser (back right). The photo was taken by their translator, Larissa Sheglova-McMahan. The food, Terry says, was reasonably priced and delicious.

Our project will evaluate ways to quickly gauge whether people are able to reliably perform a safety-sensitive job each time they show up for work. Actual testing will take place at the Russian Federal Nuclear Center (VNIIEF), in Sarov, Russia.

"IRB folk over there are pretty much like they are here. I knew we could work together."

VNIIEF does not have an IRB or local ethics committee (LEC), as they are known in Russia, and the principal investigator (PI) at VNIIEF is not familiar with human subject protection. However, the second institution, St. Petersburg State University (SPSU), does have an LEC, and even a Federal-Wide Assurance (FWA).

When a U.S., institution has an FWA, you can assume your counterparts at the other institution are up to speed on federal regulations and have completed a certain level of training. You also know what specific U.S. laws and DOE directives are applicable, and the level of oversight provided by federal agencies. Outside the US, you need to verify all the above.

Before I travelled to Russia, I had a truckload of concerns. Afterward, I still had several large containers full, but I discovered a fundamental truth—IRB folk over there are pretty much like they are here—and I knew we could work together to sort things out. Here's what else I learned.

FWAs

I expected to find a handful of FWAs in Russia, but it turned out there were 128 listed! Of those, 98 were full FWAs, and 30 were components. I'm still exploring all the nuances come into play when an FWA is granted to a foreign country.

Russian specialist

Since there are so many FWAs in Russia, it seemed likely that OHRP would have a Russian expert on staff, but I wasn't able to locate one. However, they did refer me to Olga Kubar at the Pasteur Institute in St. Petersburg, who was very knowledgeable and a great help.

Foreign laws

OHRP provides a "Compilation of National Policies" on its website, which is an excellent resource on local laws around the world. When I checked in 2007, there was an entry listed under the Russian Constitution, but the web site was in Russian

(Continued on next page)

so the info was as inaccessible as if it were locked inside the Kremlin. Thanks to Olga, the 2008 version includes a new 358-page overview of Russian human subject protection — in English!

Unexpected details
Some Russian cities don't appear on most maps, especially those from the Soviet era. I finally located Sarov 500 km SE of Moscow.

Russian oversight
Some studies (e.g., social/behavioral ones) need only Local EC review. Others also require approval from the National EC in Moscow. Verify which applies to your study, and also investigate whether any other local customs or expectations may come into play.

Training
Comprehensive IRB Training Initiative (CITI) is not available in Russia or in Russian. The CITI folks assure me it will be soon, but could not say when. Similarly, other training readily available here is not available there. However, **Tatiana Balachova**, at the University of Oklahoma, has developed some Russian language training with English translation. She conducted this training two years ago for the entire SPSU LEC and it looks quite good.

Language
This project included several face-to-face meetings as well as conference calls, hallway banter, and other informal conversations, both here and in Russia. SNL has exceptional translators on staff, including one who accompanied us to Russia. However, even with that advantage, translating technical conversations is very time-consuming, and conversing through translators takes some getting used to. If I travel to another country, I will make time to take one of those intense, short-term language courses, so I can do more than simply smile and nod politely when the interpreter is not around.

Culture
Similarities between cultures are seized on as touch-stones, but differences can be tricky. They can be a source of amusement, present awkward or tense moments, or be an opportunity to build rapport. A little homework here will serve you well.

Travel paperwork
In addition to your passport, you'll need a visa. The visa application must be accompanied by an invitation letter from an institution in Russia.

Vaccinations
Check on what shots are recommended and allow plenty of time to complete this process. I received inoculations for tetanus, diphtheria, typhoid, tuberculosis, and hepatitis A and B. Some are a multiple-shot sequence, which requires allowing wait time between vaccinations. Mine took six weeks.

Travel time
Flying to St. Petersburg will take at least 24 hours. If you can afford it, fly business class to avoid the cramped quarters in coach. And get plenty of rest before you go – you'll want all your wits about you when you arrive.

Local travel within Russia
Arrange your travel through the U.S. Embassy or alert the State Department of your itinerary. If you need help while there, these precautions will ensure it arrives quickly. Also, arrange for a 'meet and greet' service to pick you up at the airport and return you there.

Taxis—Cab drivers in St. Petersburg apparently belong to the same kamikaze brotherhood that seems to control such conveyances worldwide. Be sure to agree on a price BEFORE you start moving.

Personal safety—Visiting a place that used to be on the other side of the Iron Curtain may give you pause. It did me. However, on a person-to-person level, Russian folks are just like us. Our group walked almost everywhere and had one near miss with a pickpocket, but for the most part, I felt as safe in St. Petersburg as I do in any U.S. city.

Your turn
If you have an opportunity to visit St. Petersburg, I recommend most enthusiastically that you do. It's an enchanting place filled with warm-hearted and gracious people, exceptional architecture, stunning scenery, and fascinating folklore.Δ

Can accidents be reduced at nuclear waste sites?

The Sandia Labs team traveled to St. Petersburg for a joint Russian-American project investigating ways to reduce the number of accidents at Russian nuclear materials facilities.

An article in the *Sandia Lab News* (**http://www.sandia.gov/LabNews/080314.html#three**) said the Russians asked Sandia for help in developing a protocol for assessing human readiness for duty.

The Russian researchers are teaming up with several Sandia human factors and cognition experts to develop methods that can determine on any given day if workers are ready to perform critical operations.

Issue No. 16

"The patient is terrified. He's in pain. He feels unwell. And someone is trying to get him to listen to a 20-minute reading about the risks and benefits of aspirin. This guy is just praying he will live to see his daughter graduate."

Does complex consent hinder beneficial research?

Simon Whitney, physician, attorney, and ethicist, says consent requirements unnecessarily delayed blood thinner study

Simon Whitney

When British and U.S. researchers demonstrated that blood thinners such as aspirin could each year save the lives of 50,000 people in the United States, it was obvious that the findings had to be implemented immediately, Baylor University physician and ethicist **Simon Whitney** said.

Each day of delay after the results were reported would result in hundreds of deaths for people having heart attacks.

It was similarly obvious that getting the results sooner rather than later would also save lives. If it took six months longer than necessary to complete the study, 25,000 people would die.

"I believe it's not practicable to obtain a thorough informed consent from someone having a heart attack."

Which is why Whitney faults IRBs in the United States for requiring unnecessary safeguards that in this case delayed the heart study and likely caused 25,000 people to die who might have lived.

Even more might have died

If the research had been conducted solely in the U.S. rather than in both countries, it is likely that even more people would have died.

"The informed consent procedures in the United States are different than in the U.K.," he said. "The British consent process is very simple." When patients were brought into the hospital in the U.K. they were told about their condition and that the hospital was participating in a study testing whether blood thinners are effective in reducing deaths from heart attacks. They were told they would get one of two drugs or neither of them and were asked if they would participate.

In the United States, on the other hand, patients were read a consent form that is at least three pages long. They would be told about every possible result of taking aspirin.

The patient is terrified

"The patient is terrified. He's in pain. He feels unwell. And someone is trying to get him to listen to a 20-minute reading about the risks and benefits of aspirin. This guy is just praying he will live to see his daughter graduate. And we're telling him about the risks of aspirin?

"The U.K. folks think this is very funny. We say the lawyers say we have to."

Whitney, who is an attorney as well as a physician, said researchers and IRBs misunderstand the rules when they believe they are required to use a lengthy consent process in studies like this one.

"I am a lawyer, and although we've been doing it for years, we don't have to read the 20-minute form. We can waive consent if it's not practicable to obtain it, and I believe it's not practicable to obtain a thorough informed consent from someone having a heart attack.

"Our approach in the past has been to say that if it's possible we have to do it. That's on the theory that more consent is more ethical than less consent."

The problem is that when infusion of the blood thinner is delayed by the 20 minutes necessary to obtain consent, people will die.

In the United States, researchers recruited only 400 patients for the study. In the U.K., 6000 patients were recruited. Whitney attributes the difference to obstacles resulting from informed consent requirements.

(Continued on next page)

The delay caused by the inability of U.S. researchers to recruit more patients slowed the trial by six months. "25,000 people died because publication of the results was delayed six months by our informed consent process. The legal requirements don't make sense. They were real people who died," he said.

Whitney said that OHRP's new acting director, Ivor Pritchard, is committed to changing the sometimes difficult climate that exists between his office and researchers. He said Pritchard is encouraging investigators to call OHRP if informed consent requirements appear to be impeding improvements in health care. "I hope this means OHRP is understanding the problem. If we all work together, consent can be a tool that helps. But it should be set aside when it is not needed and when that can improve research and help people."Δ

When regulations conflict with our moral sense

Is there an ethical duty to participate in research?

Regulations governing informed consent can sometimes provide very bad guidance—guidance that conflicts with our moral sense of what should happen, according to **Simon Whitney**, a Baylor College of Medicine physician and ethicist.

"Our moral sense says we have a duty as well as a desire to help each other, and that in some instances we have a duty to participate in research."

One result of blindly following regulations is that some needed research is not being done because investigators believe that IRBs are too unyielding about issues such as informed consent, he said.

Can less informed consent in research studies be more ethical?

For example, when neonatologists deliver severely premature infants, they are not sure whether it is better to clamp the umbilical cord immediately or a moment later, allowing more blood to flow into the baby.

"There is a real chance that depriving the infant of blood can lead to problems related to anemia that could lead to death. But permitting additional blood to flow can lead to congestive heart failure, respiratory distress, and death," he said.

Neonatologists argue this back and forth. They don't know the answer because there are no good data. It is possible to do the research to get the data, but investigators are not doing it because they believe the IRB would require them to get informed consent from the woman during labor—not a time conducive to making good choices. It is not practicable to get consent from the women prior to beginning labor because it is not usually known who will deliver prematurely and who will not.

The solution, Whitney suggested, is to waive consent requirements. This would be possible if IRBs would develop a new ethical view, "one that recognizes the morality of our everyday lives. We don't live by rules and regulations; we live as interconnected people. We desire to help. We have duties to others. It is assumed that you will stop and help people in trouble. It is the debt of caring that tugs in our heart when we try to understand why the regulations stand in the way of important research.

The woman who has given birth at 28 weeks is in a situation now where she does not know whether her baby is better or worse off, depending upon whether the clamping is done sooner rather than later. If she were in a randomized research study, she would be in a similar situation but would have the advantage of knowing that the research could help future babies.

It seems counterintuitive, Whitney said, to think about a study with less informed consent as being more ethical, but "ethics isn't informed consent. Consent can make a study more ethical, less ethical, or make no difference."

Arguing for a duty to participate in research, he said that the ethical thing to do in this situation and many others is to waive consent requirements.

"If you want to know what's ethical, the best place to look is in your heart, not in the regulations," he said.Δ

Issue No. 16

"Even though we're not talking about brain biopsies and liver transplants, bio-psycho-social interventions nevertheless introduce risks of different sorts."

Social-behavioral research is not without risk

Some IRB review may be too burdensome for certain low-risk studies, but establishing a category of no-risk research would be a mistake

David Strauss

While there is merit to the criticism that IRB review is sometimes too burdensome for certain low-risk studies, the risks of psycho-social-behavioral research are not inconsequential.

Psychiatrist **David Strauss,** director of the office of human subjects research in the department of psychiatry at Columbia University, said critics of the review process overstate the case when they argue that social and behavioral research has little or no risk.

"The view from the field is that IRBs misapply notions of vulnerability, overestimate risk of nonbiomedical research, and conduct reviews that are unnecessarily burdensome for nonbiomedical, low-risk research." he said.

"The view from the field is that IRBs misapply notions of vulnerability, overestimate risk of nonbiomedical research and conduct reviews that are unnecessarily burdensome."

"The oversight community should take these complaints seriously. There is a lot of merit to much of them." It is possible, he said, to be more flexible about oversight, but it would be a mistake to make radical changes.

Minimal risk is not no risk

"For example, I don't think it's true that we need a category of no-risk research. I don't think minimal risk research is the same thing as research that lacks any risk of harm.

"We have to be careful. Even though we're not talking about brain biopsies and liver transplants, bio-psycho-social interventions nevertheless introduce risks of different sorts."

Strauss spoke during the HRPP panel discussion on "The impact of an expanded view of vulnerable populations on social, behavioral, and educational research."

IRBs, he said, tend to think about vulnerability and equate it with heightened susceptibility to risk, in that some people, and occasionally some populations, are vulnerable to exploitation.

For example, if a group of patients are being studied who have been diagnosed as HIV positive, "an inadvertent breach of confidentiality" can be harmful and "therefore additional safeguards should be considered."

Another concept of vulnerability applies to those who are susceptible to exploitation or coercion because they are unable to properly protect themselves through the consent process.

"I am the IRB chair at a psychiatric hospital. Every patient who walks in our door is vulnerable. It would never occur to us to think about it in any way other than 'person-in-situation,'" he said. "Vulnerability requires us to consider population-specific and sometimes individual-based safeguards."

Schizophrenia and decision making

In practice, properly applying safeguards can be difficult. For some at-risk populations, vulnerability is specific to the individual, not the group.

"Recent studies have shown that the majority of people with schizophrenia can make decisions for themselves," Strauss said. "That means the burden is

(Continued on next page)

"Nobody gathers data about socioeconomic status. The investigators say their subjects' motive is usually altruism. But, if that's the case, then altruism seems to be epidemic among poor people."

on the investigator to determine who specifically is vulnerable."

No formal guidance from OHRP
The process is made more difficult because OHRP has never issued formal guidance on a definition of minimal risk.

"We need more guidance. Especially in social behavior research, the consequences of miscategorization can be significant. "Minimal risk research sets the threshold that allows for expedited review, which is less of a big deal, but it is also the threshold for waiver of consent. Certain research is not practicable without a waiver. So the distinction between what is low enough for waiver and that which is not is critically important."

"We need to tell investigators that if you're conducting 17 hours of structured interviews with a subject, why not make it 17½ and collect data about the subject's experience."

One way to meaningfully assess vulnerability, he said, is to consider harms and discomforts in relationship to the environment from which subjects are recruited.

For example, in a study of end-of-life decision-making by patients with Lou Gehrig's Disease, it matters whether they are going to be interviewed at the time they were diagnosed or after they have been in a support group. "Patients are likely to experience risk in a quite different way if they just that morning learned they have a terminal illness," he said.

Tailor to specific circumstances
The person conducting the interview makes a difference as well. The same interview done by an experienced clinician or a college student interviewer can have different risks. IRBs have to tailor risk assessment and minimization to the specific circumstances of the study, which can be difficult, considering the availability of resources, including expertise, to many IRBs.

There are opportunities for IRBs to be more flexible in assessing risk and vulnerability in social and behavioral studies, he said. For example, subcommittees of experts can review ethically and procedurally complex research, and then make recommendations to the full IRB.

Continuing review
Continuing review of studies and assessment of studies in process could also be useful. "We need to tell investigators that if you're conducting 17 hours of structured interviews with a subject, why not make it 17½ and collect data about the subject's experience," Strauss said.

"Ask how well did the consent process prepare you for what you experienced in the research. IRBs regularly wring their hands, generating worst-case scenarios about what might happen. It would be good to find out what actually happened."

Subject's experience
If more information were obtained about the way subjects experienced research, it could help IRBs in deciding when there is minimal risk. With that information, IRBs would be in a better position to make decisions about actual minimal risk rather than suppositions of minimal risk.

IRBs have been limited in how well they assess vulnerability to exploitation among those who are unable to properly protect themselves through the consent process. Regulations are in place defining protections for children, prisoners, and pregnant women, but not for the mentally disabled or the economically and educationally disadvantaged, he said.

"This is because nobody gathers data about socioeconomic status. The investigators say their subjects' motive is usually altruism. But, if that's the case, then altruism seems to be epidemic among poor people."Δ

Issue No. 16

"If I give a sample for a cancer study, I might be willing for it to be used for a variety of studies related to cancer research. But there might be other kinds of studies I wouldn't give consent for."

Ethics of genetic studies have novel twists

Research becomes ethically tricky because appropriate use must consider risk to family groups and to ethnic or tribal groups


Wylie Burke

While much is anticipated for the results of genetic studies, several thorny ethical difficulties have still to be resolved—issues common to other kinds of research as well, but with novel twists, **Wylie Burke** said during her HRPP keynote address.

Burke, chair of the Department of Medical History and Ethics at the University of Washington, said genetic investigators are trying to figure out the factors that contribute to disease, including the way these factors interact with the environment.

To do this, the "urgent current issue is that we need large databases." Because the task is so complicated, she said, "it will be more productive if information can be shared among all the people doing this research."

Data sharing, banking

There are tensions in the process of data sharing and banking, including the integrity of the informed consent process and issues related to group harm and group protection.

"There are tensions in the process of data sharing and banking, including the integrity of the informed consent process and issues related to group harm and group protection."

When the National Institutes of Health (NIH) late last year implemented a policy for genome-wide association studies, it said researchers were expected to submit information about their results to a public-access data bank. But after listening to concerns from investigators and others about privacy and the dangers of public access to large amounts of genomic and clinical information, NIH decided to control access to the material.

It also concluded that when researchers submit data, it must undergo IRB review and there must be a determination of appropriate use of the data. Appropriate use will be determined largely by the kind of informed consent used to obtain authorization for banking of the data.

Risk to ethnic, tribal groups

This process becomes ethically tricky, Burke said, because, among other things, appropriate use must consider risk to family groups and to other populations, such as ethnic or tribal groups.

For example, results were recently published of a study using samples from a repository. The authors reported that they found genetic variants with presumed association for brain development that was highly present in Europeans and Asians, but not in Africans.

"The paper was written without acknowledgement of the social ramifications of such a finding. The response was quick and hot. Other researchers did their own studies and showed there is no association for brain size or cognitive development," she said.

"Maybe that's science correcting itself," she added, "but publication of the study's interpretation seemed to be scientific endorsement of racist views."

The point, she said, is that there should be concern about how the people whose data are in the repository would have felt had they known their data were being used for this kind of research.

What are the boundaries?

"So what are the boundaries for how we should be able to use genetic data? If I give a sample for a cancer study, I might be willing for it to be used for

(Continued on next page)

a variety of studies related to cancer research, but there might be other kinds of studies I wouldn't give consent for."

Similarly, the Havasupai tribe filed a lawsuit again investigators who shared samples collected for diabetes research. The samples were later used for studies unrelated to diabetes, including inbreeding and migration patterns. This was offensive to the tribe, she said, and examples like this have led to a lack of trust that can hinder research efforts.

Use of genetic data by the criminal justice system is also generating some uneasiness, Burke said. Technology now permits identification of suspects through close family members, which has serious implications for the civil liberties of the family.

Protecting repositories

Samples are now being taken when a suspect is arrested, not just when convicted. "So, how do we protect the inviolability of data repositories where DNA was appropriately collected for health research and then law enforcement wants to use it?"

Also, if data are going to be submitted to repositories for future use, "we can't do informed consent in the way it's been done before. We have to think about it in a different way. The purpose of consent is to let the individual decide whether to be involved in a study. But what if we don't know what study will use the data in the future. We will have to rethink informed consent to resolve this kind of issue."Δ

Related Web sites

Ethical, legal, social issues in genetics
http://www.humgen.umontreal.ca/int/geneinfo.cfm?lang=1&period=2&year=2008

Issues in the Human Genome Project
http://www.kumc.edu/gec/prof/geneelsi.html

American Society of Human Genetics
http://poynter.indiana.edu/lforms/poynter-trebibindex.html

HumGen International
http://www.humgen.umontreal.ca/int/index_lang.cfm?lang=1

Public Health Genomics
http://www.cdc.gov/genomics/default.htm

National Information Resource on Ethics and Human Genetics
http://bioethics.georgetown.edu/nirehg/

HS Resource Book is on line

Comprehensive source for everything from recruitment of subjects to FDA regulations, cooperative research, and international issues

DOE's new *Human Subjects Protection Resource Book* is available on line at **http://humansubjects.energy.gov/doe-resources/humsubj-resource-book.htm**.

For information or assistance in downloading, contact Denise Viator, Oak Ridge Institute for Science and Education, at Denise.Viator@orise,orau.gov.

The 27 chapters and 5 appendixes include the following topics:

- Roles and responsibilities for HS protection.
- Ethical guidance
- The regulatory mandate
- Education in HS protection
- IRB registration and assurances of compliance
- Regulatory compliance and oversight
- IRB membership, roles, and authority
- Types of IRB review
- Subject recruitment and informed consent
- Privacy and confidentiality
- After initial review
- Cooperative and multi-institution research
- FDA-regulated research
- Social and behavioral research
- Specimens, data, documents, and records
- Ethical, regulatory issues in internation studies
- Workers as research subjects
- Vulnerable subjects
- Conflicts of interest
- Accreditation of HS protection programs
- Guidance for genetic research
- Embryo and fetal tissue research
- Human cloning

Other DOE resources for human subjects protection are at **http://humansubjects.energy.gov/**.Δ

Issue No. 16

Suggested revisions to the Helsinki Declaration related to the right of research subjects to be informed about the outcome of studies and to obtain medical care after a study has ended.

Planned Helsinki changes raise questions

Is the historic declaration still useful, relevant?

The World Medical Association (WMA) has released a draft version of the revised Declaration of Helsinki, asking for responses before a final version is considered by the WMA later this year.

Originally adopted in 1964 in Helsinki, Finland, as a set of ethical principles regarding human experimentation, it is not legally binding but is often cited as a worldwide guide to protecting research subjects. This will be its sixth revision.

Some argue that because the declaration has no legal status it is routinely ignored. For example, **Stuart Rennie**, a research professor of bioethics at the University of North Carolina, states in his Global Bioethics Blog that some in the bioethics community view it as both irrelevant and misguided (**http://globalbioethics.blogspot.com/2007_12_01_archive.html**).

He says the declaration is sometimes regarded as an "oft-cited document containing lofty moral aspirations but zero legal bite, a brief laundry list of problem areas in human subjects research rather than a resource for real-world solutions . . . . The Declaration joins the bewildering number of international guidance documents that bioethics workers/policy geeks pay far more attention to than researchers ever will or should."

Placebos are among controversial changes

Some of the more controversial changes included in the proposed revision relate to the use of placebos. Authors **Harald Schmidt** and **Annette Schulz-Baldes**, writing in the *Hastings Center Bioethics Forum*, say the changes do not adequately address "Questions about the limits of placebo use in research and about the best local, as opposed to the best globally available standard of care, when this is absent locally . . ."

Other controversial revisions relate to the right of research subjects to be informed about the outcome of studies and to obtain medical care after a study has ended, especially care related to benefits that result from the study. This would include "access to prophylactic, diagnostic, therapeutic, or palliative treatments identified by the study." Schmidt and Schulz-Baldes say the draft declaration "seems to both emphasize and deemphasize post-trial access to care."

Other changes relate to getting equitable access to research for populations previously underrepresented in research, especially children and pregnant women. Also included are provisions that cover consent, treatment of patients who suffer as a consequence of research interventions, risks and benefits to communities, and requiring family as well as individual consent.

While some argue that the declaration provides guidance, Rennie says it has become largely viewed as being too aligned with powerful interest groups, "especially regulatory bodies in the United States and their associates in the pharmaceutical industry." For years, the FDA and pharmaceutical interest groups lobbied hard to change the sections in the Declaration pertaining to placebo controlled trials, and successfully pressed for the use of placebo-controlled trials for less serious illnesses. But the controversial requirement of testing new clinical interventions against the 'best available therapies' remained intact.

Taking a new approach, the FDA recently decided to abandon the Declaration as ethical standard to be used when evaluating data from clinical trials conducted abroad, and use the less-demanding Good Clinical Practices (GCP) guidelines instead. It appears that when the wording of the Declaration conflicts with the interests of powerful agencies, the words can either be altered or ignored.

Rennie argues that while the Declaration may not have the power traditionally assigned to it, it may play a more modest educational role. By introducing students and researchers to areas of enduring debate in international health research, it may act as a useful springboard for ethical reflection.Δ

News notes

2008 International Compilation of Human Subject Protections

The 2008 edition of *The International Compilation of Human Subject Protections* is now available online. The document can be seen at

http://www.hhs.gov/ohrp/international/.

The 2008 version lists about 900 laws, regulations, and guidelines from 84 countries on human subject protections, including four new countries: Georgia, Kazakhstan, Kuwait, and Turkey. Many of the listings include the web address, allowing the reader to link directly to the law, regulation, or guideline of interest.

Also new this year is a separate listing of the standards that govern research involving embryos, stem cells, and cloning. The compilation highlights about 40 countries with such standards.

Prepared by the Office for Human Research Protections of the Department of Health and Human Services, the compilation is designed for use by IRBs, researchers, sponsors, and others involved in international human subjects research.

NIH publishes guide to planning genetic studies involving named populations

The National Institutes of Health (NIH) has published a guide to planning genetic studies involving members of named populations. The "Points to Consider" document is available at

http://bioethics.od.nih.gov/named_populations.html. *(See related story on page 16.)*

Among other things, it discusses issues related to conducting community consultation and provides specific advice about topics such as working with tribal communites and DNA banking studies.

Explaining the purpose of the document, NIH said "individuals and the communities to which they belong may fear that participating in genetic studies involving named populations may end up stereotyping that particular named population, potentially putting the entire community at risk of discrimination by insurers or other third parties.

"By being open with communities about the goals and process of their research before it is conducted, scientists can better design studies to yield meaningful data while working within distinct social and cultural contexts. By sharing results with a community after a study has been completed, research participants are more likely to know what to do to seek treatment or how to implement preventive measures to improve their health."

Science: Moving toward transparency in research studies

An article in the March 7, 2008, *Science* (1340–1342), argues that while new policies are promoting transparency of research studies through registries and results databases, the results of many studies may still be unavailable.

Deborah Zarin and Tony Tse say that "An almost steady flow of articles have focused on the dangers or lack of efficacy of widely used drugs, along with allegations of hidden information, misinterpreted data, regulatory missteps, and corporate malfeasance. Many of these accounts involve analyses of research on human volunteers that had never been publicly disseminated."

"Although advances in all areas of science depend on free exchange of data, clinical trials warrant particular scrutiny because of their use of human volunteers . . . Results may not be publicly disseminated for many reasons, ranging from lack of interest by authors or editors to publish results that seem uninteresting to outright attempts to hide 'inconvenient' results." Zarin and Tse argue that more rigid requirements for public reporting are needed.

Vulnerability should encompass a composite of individual characteristics: research setting, relationship of subject and investigator, temporal elements, and the research environment including procedures used.

When subjects' vulnerability is not clear

"Vulnerability" may be one of the most complex issues in the world of human subjects protection. The issues are many:

- Should vulnerability be assessed separately from risk?
- Should the focus be on kinds of vulnerability or on kinds of groups that may be vulnerable?
- Is vulnerability a trait inherent in subject populations, or is it a state of being?
- If it is the latter, are most of us vulnerable at one time or another?
- Can assigning vulnerability to a group unjustly exclude some from studies?


Andrée Ivanoff

Andre Ivanoff, of Columbia University, said that investigators have several responsibilities in addition to protecting subjects. They also should include subjects who will be affected by the findings, study "neglected" or "protected" populations, and educate IRBs about the issues.

"If the net is cast too wide, the designation can violate justice principles, sometimes by unjustly excluding people or groups from important studies."

Population-based vulnerability
Problems using population-based vulnerability as a criterion were discussed in an article published recently by **Robert Levine**, which Ivanoff said pointed to several problems. (Levine, R.J., 2006."Empirical research to evaluate ethics committees' burdensome and perhaps unproductive policies and practices: A proposal." *Journal of Empirical Research on Human Research Ethics*, 1:3, 1–4)**.**

"For example, too many categories are considered vulnerable, she said, which could make the designation too nebulous to be of use." And if the focus is on vulnerable populations, investigators and review boards may fail to consider the research environment as a factor that creates vulnerability.

In addition, if vulnerability is defined by population, it stereotypes the population without allowing for in-group variability—so that all members are equally vulnerable when in fact some may be more vulnerable and some less vulnerable.

Several categories of vulnerability designation can be considered, Ivanoff said. These can include person vulnerability, setting vulnerability (such as a prison), or vulnerability that results from procedures used by investigators.

It can also include time-based vulnerability. The last of these can include situations when someone has just experienced a crisis, such as having been raped or having just survived the World Trade Center attack. In that case, the person is not inherently vulnerable; the vulnerability occurs during a specific period of time.

Relationship vulnerability
Another form of vulnerability results from the relationship between the investigator and the subject. "Can an instructor in a classroom conduct an investigation with her own students? An employer with employees?

So is vulnerability a trait inherent in subject populations or is it a state? Are most of us vulnerable at one time or another. The student that I recruit on campus can be vulnerable by virtue of my being an instructor. But when that student is off campus, recruited by someone who is not an instructor, he would no longer be vulnerable."

Dale Hammerschmidt, director of education in Human Subjects Protection at the University of Minnesota, has recommended that vulnerability should encompass a composite of individual characteristics, Ivanoff said. He includes the setting in which research is conducted or subjects

(Continued on next page)

Three recent studies concluded that several population groups normally categorized as vulnerable might not be as vulnerable as many think. These include people with histories of sexual abuse, people who abuse alcohol or other substances, and prisoners.

are recruited, the relationship of the subject to the researcher, temporal elements, and the research environment, including procedures used in the protocol.

Difficulties can result from assigning decisional impairment to entire groups, such as those with mental disorders. "We know that under the right conditions a person with a mental disorder can give consent. Not always, but sometimes.

"Danger also exists," Ivanoff said, "in expanding the purview of vulnerable populations, expanding the definition of vulnerability too far." It is possible to violate the justice principle of the Belmont Report by systematically excluding people in the name of protection.

"Assigning vulnerability when it is not needed means that useful research may not get done."

An example of this is when suicidal subjects are excluded from studies of depression, including studies of drugs that might treat depression. When generalized conclusions are drawn from such studies, the results might be suspect since the generalizations were drawn from a sample that does not include those most at risk.

Minimal risk

A further problem occurs because IRBs categorize any research with vulnerable populations as above minimal risk. So, when research is considered minimal risk it often does not have to be reviewed by the full board, but if it uses a vulnerable population, the same research does have to go before the full board, and this lengthens the time of review.

This can be especially troublesome because many IRBs do not fully understand social and behavioral research, sometimes tending to classify populations as vulnerable when that may not be the case.

Ivanoff noted that three recent studies concluded that several population groups normally categorized as vulnerable might not be as vulnerable as many think. "These groups do not experience higher levels of distress when exposed to what we think would be distressing stimuli than do people not considered vulnerable." The groups included people with histories of sexual abuse, people who abuse alcohol or other substances, and prisoners.

The practical problem that results from assigning vulnerability when it is not needed is that useful research does not get done, Ivanoff said.

"In the real world of social service agencies, people try to use interventions they think would probably work, but they have no data to work with from studies using these populations as subjects."

What investigators can do

Some of these difficulties might be eased, she said, if investigators do several things. One is to do an individual assessment of the research environment. It is not sufficient to design a protocol and then take that out into the field and try to make it work in an extreme environment. "Investigators must begin by including the context of the research as an integral part of the design."

Second, investigators need to educate IRBs concerning risks posed to their populations.

Third, they must educate biomedical panels about behavioral and social science research. Not all institutions have both kinds of panels. The risks, liabilities, and promise of behavioral and social science research are not always well understood by IRBs.

Finally, vulnerability refers to "a person in a situation. We must refine the ways we look at this."

Ivanoff's presentation was based on discussion and proceedings from the American Psychological Association-Columbia University Meeting "Defining Vulnerability in Minimal Risk Behavioral and Psychological Research" held November 9-10, 2007 at the Columbia University School of Social Work in New York. Publications from this meeting are forthcoming.Δ

Issue No. 16

Senate passes bill banning genetic discrimination

Law expected to ease concerns about enrolling subjects in genetic studies

The U.S. Senate unanimously passed the Genetic Information Nondiscrimination Act (GINA) in late April, ending a decade-long stalemate resulting from a hold placed on the legislation. President Bush has said he will sign the bill.

The bill is designed to prohibit health insurers, employers, and others from using information obtained by genetic tests to deny coverage, employment, or job assignments.

GINA's supporters say that people have been reluctant to enroll as subjects in genetic studies and are reluctant to seek genetic testing to learn about their risk for disease because the information obtained would be included in their medical records. Despite promises of confidentiality, studies show that people remain reluctant because they are suspicious about the likelihood that records can be kept from insurers and employers.

Fear of insurance cancellation

Many people who do get tested, including women concerned about inherited forms of breast cancer, pay for the testing themselves rather than allow health insurance to cover the cost. They fear that insurers would cancel their coverage if testing reveals anything that could in the future require expensive treatments.

A **Hastings Center** analysis of GINA (**http://www.bioethicsforum.org/Genetic-Information-Nondiscrimination-Act-genetic-discrimination.asp**) concludes that it will prevent overt discrimination but would not forbid so-called "disparate impact discrimination," that is, "unintentional discrimination." Hastings says this "may well create a loophole permitting employers and insurers to develop policies that have the de facto effect of discriminating on the basis of genetic status without running afoul of the law."

The medical community generally supports GINA because the development of personalized medicine, including pharmaceuticals, will require that treatment be matched to an individual's biology. Genetic tests will determine that biology.Δ

News notes

DOE directive approved for protecting research subjects

The third revision of the Policy (DOE P443.X) and Order (DOE O 443.1A) for the protection of human subjects in research was approved Dec. 20, 2007. The documents are available at **http://www.directives.doe.gov/pdfs/doe/doetext/neword/443/o4431a.html.**

The order establishes Department of Energy (DOE) procedures and responsibilities for implementing the policy and requirements set forth in what is known as the "Common Rule," 10 Code of Federal Regulations (CFR) Part 745, Protection of Human Subjects; and in DOE P 443.1A, Protection of Human Subjects, dated 12-20-07.

National Nuclear Security Administration

The one notable change in the order is recognition and accommodation of the authorities and responsibilities of the National Nuclear Security Administration (NNSA).

NNSA, established by Congress in 2000, is a semi-autonomous agency within DOE responsible for enhancing national security through the military application of nuclear science. Several of the DOE laboratories and sites fall under NNSA's jurisdiction.

The order notes separate (and in many cases parallel) responsibilities for the DOE and NNSA human subjects program managers. NNSA has named a program manager, John Ordaz, who will work closely with the DOE program manager.

NNSA sites should not notice any significant differences in day to day practice, however. As NNSA has indicated, its intent is to work within the existing DOE structure with regard to human subjects protection and to let many day-to-day responsibilities continue to be managed by the DOE program manager.

All DOE sites, including NNSA sites, will continue to be represented at the Human Subjects Working Group meetings and calls. The NNSA program manager will join these meetings and in conference calls and will work with the DOE program manager in addressing issues that arise with regard to any NNSA sites.Δ

Meetings

The 9th World Congress of Bioethics
Sept. 3–8, 2008
Rijeka and Opatija, Croatia
For information, see http://bioethics-international.org/drupal/?q=node/8

Informed Consent and More: Improving Human Research Protections
Sept. 16, 2008
Virginia Commonwealth University, Richmond, Virginia, U.S.A.
For information, see **http://www.hhs.gov/ohrp/education/conference.html**
Contact: Zena Bailey, 804-827-2156, zbailey@vcu.edu

American Society for Bioethics & Humanities 10th Annual Meeting
Oct. 23–26, 2008
Renaissance Cleveland Hotel, Cleveland, Ohio, U.S.A.
For information, see **http://www.asbh.org/meetings/annual/index.html**

The American Society of Human Genetics 58th Annual Meeting
Nov. 11–15, 2008
Pennsylvania Convention Center, Philadelphia, Pennsylvania, U.S.A.
For information, see **http://www.ashg.org/2008meeting/**

2008 Annual Human Research Protection Programs (HRPP) Conference
November 16–19, 2008
The Swan and Dolphin Hotels, Orlando, Florida, U.S.A.

Online version of classic research ethics books available for free

A free, searchable, online version of **Robert Levine's** classic book *Ethics and Regulation of Clinical Research*, second edition, has been made available by Yale University Press and Google Books. The book can be found at **books.google.com/.**

Other books are also available, including:

Timothy Murphy's book, *Case Studies in Biomedical Research Ethics* includes sections on oversight and study design, informed consent, selection of subjects, conflicts of interest, social effects of research, embryos/fetuses/children, genetic research, and use of animals.

Aurora Plomer's book, *The Law and Ethics of Medical Research: International Bioethics and Human Rights* discusses the revision of international ethical guidelines resulting from the growing globalization of medical research and the application of new biotechnologies in morally contested areas.

She examines controversies surrounding biomedical research in the 21st century from a human rights perspective, analysing the evolution and changes in form and content of international instruments regulating the conduct of biomedical research. The approach adopted is comparative and includes an evaluation of human rights and U.K. and U.S. law on embryonic stem cell research, the HIV/AIDS trials in the developing world, the Alder Hey Inquiry and the human radiation and nerve gas experiments on human subjects in the United States and the U.K.

This is the first book to analyse some of the major issues in biomedical research today from an international, comparative human rights perspective.

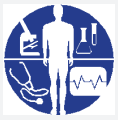
Protecting Human Subjects: E-version

To receive e-mail notification and the internet link to future online issues of *Protecting Human Subjects*, please send your name, organization, telephone number, and e-mail address to: humansubjects@science.doe.gov

U.S. DEPARTMENT OF ENERGY,
SC-23.2 / Germantown Building
1000 Independence Ave. SW
Washington, DC 20585-1290

Official business
Penalty for private use, $300

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



Protecting Human Subjects

This newsletter is designed to facilitate communication among those involved in emerging bioethical issues and regulatory changes important to both DOE and the human subjects community.

Elizabeth White, MPH, MBA,
DOE Human Subjects Protection Program Manager

Peter Kirchner, M.D., Scientific Advisor

This newsletter is prepared at Oak Ridge National Laboratory, managed by UT–Battelle, LLC, for the U.S. Department of Energy, contract DE-AC05-00OR22725.
Managing Editor, Gloria Caton, Ph.D., catongm@ornl.gov
Editor/Designer, Timothy Elledge, Ph.D., elledgetg@ornl.gov

Contacting the newsletter staff:
E-mail: catongm@ornl.gov
Fax: 865-574-9888

Mailing address for the newsletter staff:
Protecting Human Subjects
Oak Ridge National Laboratory
1060 Commerce Park
MS 6480, Room 139
Oak Ridge, TN 37830-6480
Attn: Gloria Caton

Suggestions and subscription information
The *Protecting Human Subjects* newsletter is available at no cost to anyone interested in or involved in human subjects research at DOE. Please mail or e-mail your name and complete address to the address below. Enclose a business card, if possible. If you have suggestions, use this same address.

Please indicate whether information is to
(1) add a new subscriber,
(2) change a name/address, or
(3) remove a name from the mailing list.

Human Subjects Protection Program
SC-23.2 / Germantown Building
U.S. Department of Energy
1000 Independence Ave., SW
Washington, DC 20585-1290

Phone: 301-903-3213
Fax: 301-903-0567
E-mail: human.subjects@science.doe.gov

Current and past issues of *Protecting Human Subjects* are available at:
http://humansubjects.energy.gov/doe-resources/newsletter/