PROTECTING HUMAN SUBJECTS

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Ethics & trust across boundaries

This issue of *Protecting Human Subjects* focuses on issues of ethics, trust, and the sometimes troublesome relationship between researchers and Institutional Review Boards (IRBs).

The University of Minnesota's Director of Research Subjects Protection, **Moira Keene**, said in her remarks at the opening of the last PRIM&R meeting that there "is a movement in our field to consider just regulatory compliance as our goal" but that many are resisting this direction because they believe it is important not to lose sight of the ethical underpinning of the work. The importance of not losing sight of the work's foundational purpose is discussed in several reports in this issue on such topics as whether a focus on checklists can be helpful or harmful in the review process and whether IRBs are "protecting people to death."

For those who believe protecting human subjects should be a cooperative venture between investigators, review boards, institutions, and others, the results of the survey by **Gerald Koocher** and his colleagues (see page 12) may seem disturbing. On the other hand, there is also reason for optimism, as in the report, below, from **Ann-Marie Bucaria Dake** at **Lawrence Livermore National Laboratory** about its very encouraging experience in acting as a surrogate IRB for the new University of California, Merced. We also have included in this issue updated highlights of some of the talks at the last PRIM&R meeting because they raised concerns that are on the agenda to be discussed at this year's meeting.

An IRB success story for LLNL

The agreement under which Lawrence Livermore Lab's IRB reviews research proposals for the new University of California, Merced, campus could have run into roadblocks. It didn't.

When the scientifically oriented IRB at Lawrence Livermore National Laboratory (LLNL) accepted the responsibility to review human subjects research for the new University of California campus at Merced (UCM), the result could have been a debacle for both.

Most of the UCM research reviewed by LLNL has been for social-behavioral studies, whereas all of LLNL's previous experience had been reviewing technical, scientific protocols.

Researchers are pleased

Not only did the possible debacle fail to occur, the result after two years has been that UCM researchers are pleased with the result and the LLNL board dramatically expanded its knowledge about the diversity of review processes.

From the very beginning of the arrangement, everyone knew the potential for difficulties. And the small glitches that were encountered could easily have escalated if it were not for the skillful way the two institutions proceeded with the process.

Ann-Marie Bucaria Dake

LLNL Senior IRB Administrator **Ann-Marie Bucaria Dake** said the board's first experience with a

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Ann-Marie Bucaria Dake *is the senior Institutional Review Board (IRB) administrator at Lawrence-Livermore National Laboratory in Livermore, Calif.*

UCM review was with a researcher who had assumed that most social-behavioral studies were exempt and that the LLNL board was asking for too much information.

"She was surprised by the documentation and explanation the IRB required" Dake said.

At that exact moment in the relationship, things could have proceeded for good or for ill.

"We told the investigator that we thought the board could do a good review and that we would work with her about any concerns she had," Dake said. "We also wanted to make sure we covered all the bases—that we protected people involved in the study, protected the investigators and the institution.

"It was a study involving a school district, geared to a minority group. Because of the nature of the study, it was possible that some people could have been identifiable.

Because it was the first study reviewed under the cooperative agreement, "it was very important that we got it right.

"Our focus was to be sure the people knew they could choose not to participate, could answer some of the questions, or none of them. The consent process was very important."

Got it right

Because it was the first study reviewed under the cooperative agreement, "it was very important that we got it right, that we did the best job possible in representing both LLNL and the university."

Get it right they apparently did. The researcher went away satisfied not only because she could proceed with the study, but also because she had completely satisfied the board's concerns.

"The last time I saw her," Dake said, "was at a meeting on the Merced campus. She came up to me, hugged me, and thanked me for the help. It was nice to get that response from the first UC Merced investighator who forged through the process with us. I was extremely proud of the work we had all done to reach a successful conclusion."

Helping rather than hindering

What made the difference between an impending debacle and a success? "I think she realized that our intentions were good and that we were trying to help, rather than hinder, her work."

That attitude apparently smoothed the way for the Merced researchers who followed. LLNL has since reviewed about 30 protocols, all of which have proceeded well.

She came up to me, hugged me, and thanked me for the help. It was nice to get that response from the first UC Merced investigator who forged through the process with us.

"There has been a time or two when a researcher believed the study should be exempt," she said, "but we've been able to work it out very easily. We explain what our concerns are and we get the issues resolved very quickly. Our office staff has been really good in the willingness to take time and put in extra effort to ensure that all goes well.

"More than anything, I think it's been the word-of-mouth among investigators at Merced that has given us such positive press and made this arrangement work so well."

Recruited community member

Dake said LLNL's board has been assisted by one of its members who is a social-behavioral scientist. "When we have issues we get stuck on, she's been able to help us out." In addition, the IRB recruited a community member from Merced to sit on the panel.

Otherwise, the board made no alterations in its composition, which is the typical mix of scientists⇛

Information about LLNL's human subjects protection program can be found at
http://www.llnl.gov/HumanSubjects/

Information about the University of California, Merced, research program can be found at
http://research.ucmerced.edu/

and nonscientists, including two community members.

The arrangement between LLNL and UCM has been in place for more than two years but will end in early 2007 when the university is expected to form its own IRB. It has already hired a director of research compliance and is assembling members. Dake has been asked to join the new Merced IRB.

The first protocol was reviewed in August of 2004, which was prior to the university's official opening in September 2005 at a site 88 miles southeast of LLNL.

To prepare for the new responsibilities, the IRB office revised its forms to include components for UC Merced applications.Δ

News notes

New OHRP guidance for investigators on obtaining or waiving consent

The Office for Human Research Protections (OHRP) has issued guidance covering two areas. The first is determining whether an institution is engaged in non-exempt research. The second provides information about obtaining or waiving informed consent requirements.

OHRP's announcement for the guidance, which became effective June 7, 2006, said it explains how to determine whether the HHS regulations at 45 CFR part 46 are applicable to the activities covered by the Food and Drug Administration's interim final rule, "Medical Devices; Exception From General Requirements for Informed Consent" (21 CFR 50.23(e)). Specifically, the document provides guidance on the following: (1) The determination of when institutions conducting activities covered by 21 CFR 50.23(e) would be engaged in non-exempt human subjects research; and (2) The requirements for obtaining or waiving informed consent under 45 CFR 46.116.

This guidance can be found at

http://www.hhs.gov/ohrp/humansubjects/guidance/invitrodev.html (HTML format) and

http://www.hhs.gov/ohrp/humansubjects/guidance/invitrodev.pdf (PDF format).

OHRP welcomes comments on this guidance document. Please send any comments to OHRP by e-mail at ohrp@hhs.gov, with "OHRP guidance on 21 CFR 50.23(e)" in the subject line.

Non-U.S. institutions must satisfy regs if doing HHS-supported studies

The Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services (HHS) is providing public notice to clarify a requirement contained in the Federal-wide Assurance (FWA) form for international (non-U.S.) institutions.

The clarification applies to institutions approved by the Office for Human Research Protections under the HHS protection of human subject regulations, 45 CFR part 46.

HHS said that the requirements of HHS regulations must be satisfied for all HHS-conducted or -supported research covered by an FWA, regardless of whether the research is conducted domestically or internationally. To date, HHS has not deemed any other procedural standards equivalent to 45 CFR part 46. The notice can be accessed as a pdf document at http://www.hhs.gov/ohrp/references/EPClarificationNotice.pdf

Protecting people "to death"?

Are people needlessly being kept from promising drugs? Alternative forms of access, combined with appropriate protective mechanisms may be needed

Have the gatekeepers sometimes gone too far in their efforts to protect human subjects? Have they crossed a line and now are in danger of protecting people "to death?"

Harvard Medical School Professor **George Demetri** said it is possible that "mindless regulations" may be keeping promising drugs away from people.

George Demetri

"We may be doing this if we're not designing and conducting the most relevant trials, including learning from every patient so that we can change what we do with the next patient," he said.

There may be choices that we as healthy people may not consider reasonable, but that very sick people may consider entirely reasonable.

Gatekeepers may be going too far as well, he said, "if we cannot provide alternative access to promising new agents for patients who might not fit stringent eligibility criteria strictly constructed only for regulatory approval. That bothers me a lot."

Demetri, Director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute, said it may be a mistake "if we do not recognize that autonomous patients may wish to take risks. Sometimes we should let them do so with appropriate mechanisms, including counseling, data, and informed consent. There may be choices that we as healthy people may not consider reasonable, but that very sick people may consider entirely reasonable."

He said his assertions are not intended to compromise efforts to protect research participants.

The work is important because "there are wild-eyed enthusiasts who will make exaggerated claims to vulnerable patient populations, and it is our IRBs that stand between them and good medicine.

"We need to protect our patients who are at their most vulnerable both from the untoward risks of their underlying diseases as well as from misinterpretation of data and bad science."

Compassionate access

He said there are serious questions related to making promising drugs more easily accessible to patients by way of mechanisms such as compassionate access programs.

"The conundrum is how early we should get drugs to people. How early can we have enough responsible information? If promising data exist, then autonomous patients are willing to take risks in the face of life-threatening diseases.

"They will sign anything to clear researchers and manufacturers of liability. They just want the drug," Demetri said.

Overly strict criteria

The problem becomes heartbreaking, he said, when no compassionate access mechanism is available because of overly strict eligibility criteria.

The FDA is supportive of allowing compassionate access by way of approving investigator-held new drug applications (IND), which allow

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George Demetri *discussed the concerns expressed here during his plenary address at the last PRIM&R meeting. He is the Director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School, as well as the Director of the Ludwig Center at Dana-Farber and Associate Director for Clinical Research at the Ludwig Institute.*

the study of an unapproved drug or an approved product for a new indication or in new patient populations, he explained.

Not every drug works

Nevertheless, researchers have to be cautious in employing this mechanism, because not every new drug is going to work. "Sometimes people hear about miracle drugs that aren't. So we have to be cautious about accuracy of information."

Sometimes people hear about miracle drugs that aren't. So we have to be cautious.

It is the rapid pace of drug discovery and development by employing the newest tools that will present a challenge for researchers and IRBs, he said. Some drugs will work and some will not, and before researchers begin too easily providing promising drugs to everyone who wants them, the data have to be in hand. "Nothing settles arguments as well as definitive data."

But when is it acceptable? "Is it when 12 of 13 patients rise like Lazarus from their deathbeds? Maybe." There is no black-and-white distinction, he said, because each drug and each situation are different.

Near-miraculous results

Demetri said some drugs truly do have near-miraculous results, including the recently developed Gleevec, which has had dramatic results in the treatment of one form of abdominal cancer.

"About 83% of the patients taking Gleevec are doing well. The overall survival rate has tripled, so it is clearly having an enormous impact for patients who would otherwise have died more quickly."

The difficulty that resulted from this was that when other patients at Dana Farber heard about this, they desperately wanted to be included in the study.

"But we had a limited number of slots" approved for the protocol, which meant that only some people could get the new drug.

As more of these "miracle" drugs are developed, Demetri said, the issue of when it is provided to patients will become more troublesome. If patients are overprotected, people will die who did not have to die. If they are not protected enough, other dangers will accrue. The key, he said, will be to find an appropriate balance.Δ

Useful Web sites

IRB resource links
http://www.peacehealth.org/IRB/links.htm

U.S. Department of Health & Human Services (HHS) Office of Research Integrity
http://ori.dhhs.gov/

Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule
http://privacyruleandresearch.nih.gov/pr_02.asp

HIPAA, Office of Civil Rights. Medical Privacy—National Standards to Protect the Privacy of Personal Health Information
Guidance on specific provisions of the regulation, including research rules is at:
http://www.hhs.gov/ocr/hipaa/privacy.html

Certification of IRB Professionals
Information is at the ARENA Web site:
http://www.primr.org/certification/certification.html

Professional Testing Corporation
http://www.ptcny.com/

The consortium to examine clinical research ethics
http://csmeh.mc.duke.edu/cecrelndex.htm

National Society of Genetic Counselors, Inc.
http://www.nsgc.org/

Tuskegee University National Center for Bioethics in Research & Health Care
http://www.tuskegee.edu/Global/category.asp?C=35026

The Collaborative Initiative for Research Ethics in Environmental Health
http://www.researchethics.org/

The President's Council on Bioethics
http://bioethics.gov/

The National Reference Center for Bioethics Literature: A specialized collection of books, journals, newspaper articles, legal materials, regulations, codes, government publications, and other relevant documents concerned with issues in biomedical and professional ethics.
http://www.georgetown.edu/research/nrcbl/nrc/bibliographies.htm

The National Information Resource on Ethics and Human Genetics
http://www.georgetown.edu/research/nrcbl/nirehg/index.htm

Bioethics Resources for Health Care Organizations
http://www.mcw.edu/bioethics/presentation.html

Informed consent

People tend to hear what they want to hear, and what they want to hear is that the research is going to help them.

Researchers and IRBs must continue trying to do a better job of grappling with the difficulties of getting informed consent, especially given the inclination of patients to hear mostly what they want to hear, according to bioethics professor **Nancy Kass**.

Patients often tend to believe that drugs offered by researchers are reasonably likely to help them and that the drugs wouldn't have been offered in the first place if that were not true, she said.

Nancy Kass

Kass, Professor of Bioethics and Public Health at Johns Hopkins University, said regulations requiring informed consent have been helpful but that more is needed.

Words such as "treatment," "therapy," and "working" may inadvertently lead to unjusfied hope.

When a researcher explains a protocol to potential subjects, it is common to use words such as "treatment" and "therapy" and "working," all of which are typically construed by patients to mean that if they join the trial, the purpose is to treat their disease, using a therapy they hope will "work."

When those words are used, she said, there is a danger that patients will not fully understand that there may actually be no benefit that will accrue to them, that the purpose of the trial, for example, may be only to determine whether there are side effects. What they want is hope, and the words can inadvertently lead them to hope without justification.

Legal development

Requirements for informed consent have existed for a relatively short time, she said. The right of an adult of sound mind to determine what will be done with his or her own body was not established until 1914, and the requirement for informed consent was not required by a court until 1957.

In 1974, the first U.S. law requiring informed consent was approved, but at the time most consent forms were written in ways that were too difficult for most people to understand.

Since then, research has suggested various ways to improve the process, but the barrier is often the patients' inclinations to hear what they want to hear, rather than what is being said.

The barrier is the patient's inclination to hear what they want to hear rather than what is being said.

Misconception

This is especially true, she said, for the so-called therapeutic misconception, which can take the form of patients believing that they are going to get treatment for their conditions even when they are told they have a 50% chance of getting a placebo.

In a 1985 study of randomized double-blind trials using placebos, 32% of the patients reported believing they were in the group that is best for their own therapeutic needs. The same study found that 44% of the participants did not know that some patients in the trial who wanted treatment would not get it. ⇛

Nancy Kass *discussed some of her informed consent research during her keynote address at the last PRIM&R meeting. She is the Phoebe R. Berman Professor of Bioethics and Public Health in the Phoebe R. Berman Bioethics Institute, and Professor in the Department of Health Policy and Management at Bloomberg School of Public Health, Johns Hopkins University. She is also faculty associate of the Kennedy Institute of Ethics, Georgetown University, and a fellow of the Hastings Center.*

"They believed this," Kass said, "even though they were told the participants were being randomized."

In research she conducted during the mid 1990s, Kass said, 1882 patients at 16 hospitals around the country, including private and public institutions, were asked about their perceptions. Some were involved in research studies, some not.

"Experiments" seen as riskier

One of the findings was that when asked about the words "research," "experiment," and "study," people tended to believe that experiments were riskiest and that studies were the least risky form of research.

People tended to believe that the word "experiment" implied something more risky than "research" or "study."

The results suggest that the words used to ask for informed consent should be chosen carefully, she said. For example, it could be that investigators should deliberately use the word "experiment" in those studies that are riskier. This would convey to potential participants the real force of the risk.

The patients interviewed tended to have relatively common beliefs about research studies, she added. Their comments were typically like the following:

"If there's something new on the market that might be better than the traditional program, why not try it?"

"I was interested in something more advanced and potentially better."

"I don't believe they would offer me anything that isn't beneficial to me in my condition."

"I read some of the literature and it didn't mean a hill of beans to me because I didn't know anything about medical science. But, like I say, if it's to help me, I'll go in."

These and other comments, Kass said, indicate that people believe that "new equals better" and that "research equals treatment."

Why hold these beliefs?

Why do patients hold these beliefs? "Is it what they are told or what they need to believe?"

Kass said that she and Johns Hopkins University Professor Jeremy Sugarman designed a study to learn more about what oncologists say to patients eligible for phase I and II trials. Taped interviews between researchers and potential subjects found that the scientific intention was clearly discussed and that people were told about safety issues, although typically that comprised only one sentence and the "rest of the dialogue was about how the treatment was good for one's health."

For example, in one interview, the researcher said:

"The usual way we go through this is to see whether or not it's helping you. We look at the CAT scan about every two months. If things look like they're helping, we keep going. If it looks like the cancer is growing despite the treatment, clearly we don't want to continue that, and we'll sort out what other options make sense."

Believing it will work

Kass said that given this explanation, "it's no wonder the patient believes it will work" because of the use of words like "helping" and "treatment."

When patients were asked what they thought the purpose of the study was,

- 52% said it was to see if the drug works,
- 14% said to see if the drug helps me,
- 11% said to cure my cancer,
- 9% said to figure out the best dose, and
- 6% said to see if the drug is safe.

Asked what benefits they expected:

- 3% said their cancer would get worse,
- 3% said there would be no change,
- 33% said a short-term improvement in their cancer,

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"It is hard to go to a patient whom you have been treating for a long time and say there are no other treatments on the market, but you can go into a study that probably won't help you but might benefit others . . ."

Informed Consent

(Continued from page 7)

- 39% said a long-term improvement, and
- 21% expected a complete cure.

Some of this result, Kass said, may be because "it is hard to go to a patient whom you have been treating for a long time and say there are no other treatments on the market, but you can go into a study that probably won't help you but might benefit others, because the truth is that for you it's not going to be much help."

Trying an intervention

Because they believed it would be unlikely that oncologists would want to change what they are saying, Kass and Sugarman designed another study to learn what would result from an intervention.

They developed a touch-screen computer program that would explain to patients about the different phases of studies. It included video clips of patients who had been in trials, talking about the good and bad aspects. It also included clips of oncologists explaining a study.

Patients were randomly assigned either to get the computer program or a pamphlet developed by the National Cancer Institute called "What every cancer patient should know about clinical trials." All patients got one or the other and then went into a regular interview with the oncology researcher.

"The good news is that people who saw our intervention were more likely to say the purpose of the trial had to do with safety or dosing.

It is possible to teach prospective research subjects the real scientific purpose of a study.

"But we also found that it had no outcome on their expected outcome, that is, whether they thought it would help me, cure cancer, or help others."

The conclusion, she said, was that the intervention suggested that it is possible to teach prospective research subjects the real scientific purpose of a study, something that might enhance researchers' ability to give people a more accurate picture of what they are getting into when they agree to participate.Δ

News notes

■ *FDA consent exemption tied to terrorist threat*

The Food and Drug Administration (FDA) has issued an interim final rule amending regulations to exempt from informed consent certain diagnostic devices.

Effective since June 7, 2006, the ruling exempts in vitro diagnostic devices to identify chemical, biological, radiological, or nuclear agents.

The FDA said it is is acting because of concern that during potential terrorist events or other public health emergencies, delaying the testing of specimens to obtain informed consent may threaten the life of the subject.

"In many instances," the FDA announcement said, "there may also be others who have been exposed to, or who may be at risk of exposure to, a dangerous chemical, biological, radiological, or nuclear agent, thus necessitating identification of the agent as soon as possible.

"FDA is creating this exception to help ensure that individuals who may have been exposed to a chemical, biological, radiological, or nuclear agent are able to benefit from the timely use of the most appropriate diagnostic devices, including those that are investigational." The link to the new regulation, 21 CFR 50.23(e)is:

Medical Devices; Exception From General Requirements for Informed Consent. 21 CFR 50.23(e) FR Doc E6-8790. See: http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-8790.htm

Conflicts of interest threaten trust

Who should discuss which conflicts? When? Where? How?

From left, the panelists for the informed consent discussion were Mary Faith Marshall, Kevin Weinfurt, Mark Barnes, and Jeremy Sugarman.

Conflicts of interest in conducting and reporting research can harm necessary relationships of trust. But whether that harm occurs and how to prevent it is a far more gnarly problem than is often assumed.

That is the conclusion of researchers who for the past few years have been trying to learn more about how conflict of interest issues are handled by institutions and researchers, and how the issues are viewed by human research subjects.

Johns Hopkins University Professor **Jeremy Sugarman** said he and his colleagues have been examining issues related to who should discuss which conflicts, when to disclose them, where to do it, and how.

With funding from the National Heart, Lung and Blood Institute, they have developed a project called Conflict of Interest Notification Study (COINS). The project is gathering data aimed at examining issues related to conflicts of interest at each stage of the research process, hoping to find ways to minimize conflicts consistent with fiduciary obligations.

The main reason people participate

"Trust is the main reason people agree to participate in research," Sugarman said during a panel discussion on the topic at the last PRIM&R meeting. "Because of that trust, it's our obligation to make sure we're trustworthy. Financial and nonfinancial conflicts threaten that trust, and we've got to fix it."

> *Investigators tend to believe disclosure might "detract from what really needs to be decided."*

Duke University Assistant Professor **Kevin Weinfurt**, who is a colleague of Sugarman's on the COINS study, said during the panel discussion that in surveys, investigators typically "say they should not have to disclose the amount of financial interest because of the complexity of the disclosure." They also tend to believe that disclosure "might detract from what really needs to be decided."

In one phase of the study, Weinfurt said, 3520 research subjects with diabetes and asthma were asked about the effects of disclosing potential conflicts of interest. "People in general were quite willing to participate, and most said it didn't increase or decrease trust in the researchers."

In focus groups held in New York, Chicago, and Durham, N.C., some people said financial disclosure might decrease trust and others said it would increase trust. "Some who said it would increase trust felt that way because of ⇛

Jeremy Sugarman *is the Harvey M. Meyerhoff Professor of Bioethics and Medicine and Deputy Director for Medicine of the Phoebe R. Berman Bioethics Institute at the Johns Hopkins University.* ***Kevin Weinfurt*** *is Assistant Research Professor of Psychiatry and Behavioral Sciences in the Duke University School of Medicine and Deputy Director of the Center for Clinical and Genetic Economics at Duke Clinical Research Institute.* ***Mark Barnes*** *has practiced and taught law and has administered government programs in the healthcare field for 20 years. He is one of the leading attorneys in the field of research compliance, the practice and ethics of clinical trials, and medical privacy.* ***Mary Faith Marshall*** *is Associate Dean for Social Medicine and Medical Humanities and Professor of Family Medicine and Community Health at the University of Minnesota Medical School.*

the transparency, being up front. Others said that knowing about financial interests would be perceived as a good thing. They said that if the researchers are getting paid enough, they will do a good, ethical job and won't be cutting corners." Others, Weinfurt added, said that they wouldn't want to know about conflicts such as instances when physicians are given money to enroll patients in studies.

Sugarman said conflicts arise throughout the research process. "It starts with the kind of research being done. Is it a drug to treat wealthy people or those less well off in the developing world? How many drugs are being developed to treat malaria versus those to treat hypertension?"

Trouble in the recruitment process

Trouble also arises in the recruitment process. "People's jobs require them to get people enrolled. They receive bounty payments, which can lead to conflicts."

Sugarman said possible solutions include divesting of financial interests, minimizing them, or disclosing them. "But it's not possible to divest, because research takes money, and I don't think there is a meaningful difference between industry-sponsored, federal-sponsored, and foundation-sponsored research." Whatever the source, he said, when money is involved, conflicts follow.

If researchers are to disclose financial interests, it would be helpful to know whether the information is important for potential subjects to have and whether they know how to interpret the information, he said. The COINS project is designed to get more understanding about that, he said, along with learning about ways to deter researchers from getting caught in the middle of avoidable conflicts of interest.

"If researchers are expected to disclose conflicts, we need to know how the information will be used. We also need to know what are the effects on trust and what are the effects on research.

Physicians as investigators

Attorney **Mark Barnes** said during the discussion that when physicians are acting primarily as investigators, conflicts of interest tend to arise. When investigators fail to disclose conflicts in situations when disclosure is required, he said, it is important that institutions discipline offenders. "If that doesn't happen, it is unfair to colleagues who have disclosed, and it will undermine the process."

Barnes also said IRBs should not be responsible for poring over the financial records of investigators. "IRBs do need some method of getting insight into conflicts of interest, but that should be obtained by having someone brief them about it. IRBs don't have the expertise for this."

Concluding the discussion, University of Minnesota Professor **Mary Faith Marshall** discussed non-financial conflicts, including the ghost-writing of articles. She said there are too many instances of medical research reports being co-authored by people who have not contributed substantially to the study but who have instead been hired merely to lend an air of credibility to the results.

This also occurs, she said, when people are paid to give talks about a drug when they have no knowledge of the raw data and haven't actually used the drug with their patients.

"This is a serious conflict of interest problem. As a result, the World Association of Medical Editors is prohibiting ghostwriting because it is "dishonest and unacceptable."Δ

Related publications

The COINS team has published these articles related to confllicts of interest:

"Disclosing conflics of Interest in Clinical Research: Views of Institutionnal Review BBoards, Conflict of Interest Committees, and Investigators," **Kevin P. Weinfurt**, et al., *Race & Ethnicity*, Fall 2006.

"Views of Potential Research Participants on Financial Conflicts of Interest—Barriers and Opportunities for Effective Disclossure," **Kevin P. Weinfurt**, et al, *Journal of General Internal Medicine*, v. 21, 2006.

"Policies of Academic Mediical Centers for Disclosing Financial Conflicts of Interest to Potential Research Participants," **Kevin P. Weinfurt**, et al, *Academic Medicine*, v. 81, No. 2, February 2006.

Endocrinologist **David Shaywitz** of Massachusetts General Hospital has published in the *Boston Globe* an article discussing issues of conflict of interest involving research studies. See **http://www.boston.com/news/globe/editorial_opinion/oped/articles/2006/07/27/science_and_shams/**

News notes

Science *reports results of students reporting misconduct at Wisconsin*

A lengthy report in the September, 2006, issue of *Science* discusses the difficulty a group of University of Wisconsin graduate students have encountered after turning in their adviser for scientific misconduct (*Science*, September 1, 2006: (Vol. 313. no. 5791, pp. 1222 - 1226. See http://www.sciencemag.org/cgi/content/full/313/5791/1222?etoc).

As a result of the students' reporting that they believed their adviser, tenured geneticist Elizabeth Goodwin, lied about laboratory results, the university cancelled three of her grants. The university also released a report saying it found "evidence of deliberate falsification" in the three applications for the cancelled grants, totaling $1.8 million in federal funds. The case has since been referred to the federal Office of Research Integrity (ORI) in Washington, D.C.

The university's investigators also raised questions about three published papers in *Nature Structural and Molecular Biology*, *Developmental Biology*, and *Molecular Cell*.

Goodwin resigned from her position at the university, but the *Science* report said the repurcussions have damaged the careers and the work of the graduate students.

"Although the university handled the case by the book," the *Science* article said, "the graduate students caught in the middle have found that for all the talk about honesty's place in science, little good has come to them. Three of the students, who had invested a combined 16 years in obtaining their Ph.D.s, have quit school. Two others are starting over, one moving to a lab at the University of Colorado, extending the amount of time it will take them to get their doctorates by years." The five graduate students who spoke with *Science* also described discouraging encounters with other faculty members, whom they say sided with Goodwin before all the facts became available.

Fraud investigators told *Science* that this result is typical. "My feeling is it's never a good career move to become a whistleblower," says Kay Fields, a scientific investigator for ORI, who depends on precisely this occurrence for misconduct cases to come to light. ORI officials estimate that between a third and half of nonclinical misconduct cases—those involving basic scientific research—are brought by postdoctoral fellows or graduate students like those in Goodwin's lab. "And the ones who come forward," admits ORI's John Dahlberg, "often suffer a loss of time, loss of prestige, [and a] loss of credibility of your publications."

Science said that none of the published articles questioned by university investigators has been retracted or corrected so far. "We are considering the implications" of the university report, said Lynne Herndon, president and CEO of Cell Press, which publishes *Molecular Cell*, in a statement. The editor of *Nature Structural and Molecular Biology* said she was awaiting the results of the ORI investigation, and the other authors of the *Developmental Biology* paper are reviewing the relevant data, says the journal's editor in chief, Robb Krumlauf of the Stowers Institute for Medical Research in Kansas City, Mo.

OHRP Web site adds "Frequently Asked Questions (and Answers)"

The Office for Human Research Protections (OHRP) has added a Frequently Asked Questions (FAQ) page to its Web site. It includes a new set of FAQs on Investigator Responsibilities. Other topics include: Assurance Process; IRB Registration Process; 45 CFR part 46; and Research with Children. These FAQs should be viewed as recommendations unless specific regulatory requirements are cited.Δ

Surprises? How researchers view IRBs

Report suggests that the way review boards see themselves and the way researchers see them may be very, very different

A perhaps not-so-surprising gap seems to exist between how IRBs see themselves and how researchers see them. A similar disjunct exists regarding the IRB qualities considered important by typical review boards and those considered by the researchers to be important.


Gerald Koocher

In a national sampling of 886 researchers by American Psychology Association (APA) President **Gerald Koocher, Patricia Keith-Spiegel** (See related article by these researchers on page 14), and **Barbara Tabachnick**, the common complaints expressed by investigators included that IRBs are unprepared, focused on unnecessary tasks, superficial and hasty in their reviews, arrogant, uncommunicative, lacking expertise, overly conservative, prone to favoritism, and paranoid.

No gender differences were found in the survey results. No differences were seen between less experienced and more experienced investigators.

The good news from the survey is that 38% of the researchers expressed satisfaction with their IRBs. The bad news is that 62% were less than satisfied and that 10% of the 886 were "very dissatisfied."

No gender differences were found in the survey results. Neither were there differences between those whose research requires full review and those whose research is primarily exempt.

Similarly, no differences were seen between less experienced and more experienced investigators (the majority surveyed were more experienced), nor between those who have served on IRBs and those who have never served.

Funded by the U. S. Department of Health & Human Services, Office of Research Integrity, the survey was part of a project titled "The Relationship Between Perceived Organizational Justice and Scientific Dishonesty." Some of the resulting data were reported by Koocher at last year's PRIM&R meeting. The study is the basis for an IRB researcher assessment tool he created to assist review boards in their efforts to be more responsive to investigators' concerns. (The tool, called the IRB-RAT, can be found at http://www.ethicsresearch.com The site also includes a variety of other documents and research reports related to human subjects protection.)

Many of the comments reported indicated general satisfaction with what is recognized as a difficult task. Many others, however, Koocher said were disturbing, including one researcher who said, "Don't tell anyone, but my IRB is so picky that I don't put everything I am actually going to do in the protocols I submit to them."

Among the results of the larger project examining scientific misconduct was that when investigators believe their review board is inadequate, they are more likely to violate standards of ethical research conduct.

Including more community members on IRBs has been a focus of many institutions and the topic of much discussion in the human subjects protection community. The investigators surveyed, however, reported little interest in expanding the role of community members. They said that having more than one public member on the board is the

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Gerald Koocher *is Professor and Dean of the School for Health Studies at Simmons College. Until 2001 he was Chief of Psychology at Boston's Children's Hospital and Associate Professor of Psychology at Harvard Medical School. He is President of the American Psychological Association.*

least important characteristic of an IRB. Of 45 IRB functions listed on the survey, this ranked 45th in importance.

Similarly, investigators said they are not especially concerned about whether an IRB has a diverse membership. They listed this as 42nd of 45 important characteristics.

The good news from the survey is that 38% of the researchers expressed satisfaction with their IRBs.

Among the overarching findings, Koocher said, are that issues related to how the IRB treats investigators are especially important. Does the researcher feel that the IRB listens? Does it indicate a respect for investigators? Does the board adequately explain what members like and don't like about a protocol? Does it give the investigator adequate opportunity to respond to objections?

"When the IRB tells an investigator that you're not taking appropriate care of human subjects, that is a narcissistic wound that is very hurtful—especially if it's coming from people whom you feel don't understand you or haven't given you a chance to respond or are disrespecting you in some way," Koocher said.

In eliciting information about investigators' views, Koocher and his colleagues asked them to rate how their own IRB compared to their ideal IRB. They were also asked to rate the importance in their own work of 45 IRB functions on a 7-point scale. Following are the 12 most important IRB characteristics, beginning with what they collectively said is the most important:

1. An IRB that reviews protocols in a timely fashion

2. An IRB with members who do not allow personal biases to affect their evaluation of protocols

3. An IRB that does a good job of upholding participants' rights while at the same time facilitating the conduct of research

4. An IRB that does not use its power to suppress research that is otherwise methodologically sound and in compliance with federal policy whenever it perceives potential criticism from outside the scientific community

5. An IRB with members who are very knowledgeable about IRB procedures and federal policy

6. An IRB that conducts a conscientious and complete review of protocols, including being prepared by having thoroughly read the protocol before meeting to discuss it

7. An IRB that views protection of human participants as its primary function, i.e., the scientific merit should have been adjudicated before the protocol reaches the IRB

8. An IRB that responds in a timely manner to investigators' inquiries about its processes and decisions

9. An IRB that gives a complete rationale for any required changes to or disapprovals of protocols, i.e., they provide a rationale and are willing to engage in a dialogue on the disputed point

Among the overarching findings are that issues related to how the IRB treats investigators are especially important.

10. An IRB that works with investigators to find mutually satisfying solutions whenever disagreements exist, i.e., they are not simply gatekeepers

11. An IRB whose members fully understand and act within the scope of their function, i.e., they focus on human protection as their key issue

12. An IRB that includes a complete rationale when it denies or mandates changes in a protocol based on criteria that are more stringent than or different from federal research policy (i.e., application of "local standards")

Following are what researchers say they believe are the five least important of the 45 IRB characteristics. The list begins with what they collectively said is the single least valuable characteristic.

1. An IRB that is composed of more than one public member

2. An IRB that offers editorial suggestions regarding consent documents and protocols (typos, grammar, clarity, etc.)

3. An IRB that offers investigators opportunities to be educated about federal research policy

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4. An IRB that has a diverse membership (i.e., includes women, minorities, and junior and senior members of the institution)

5. An IRB that offers consultation during the development of research protocols and grant applications. (Koocher said this is among the least important characteristics because investigators will have previously consulted with their colleagues and done literature reviews before a protocol gets to the IRB.)

Results and other details of the survey are available at http://www.ethicsresearch.com.Δ

Do IRB efforts sometimes encourage deceit?

Studies suggest perceptions of excessive protective zeal lead to scientific misbehavior. Are there ways colleagues can intervene to prevent fraud?

It may be that IRB efforts perceived as too zealous encourage scientific misconduct, according to an article by psychologists **Patricia Keith-Spiegel** and **Gerald Koocher** ("The IRB Paradox: Could the Protectors Also Encourage Deceit?", *Ethics & Behavior,* vol. 15, no. 4, December 2005).

"The efforts of some IRBs to exercise what is viewed as appropriate oversight may contribute to deceit on the part of investigators who feel unjustly treated," the psychologists asserted.

Using an "organizational justice paradigm," they explored why certain IRB behaviors may lead investigators to believe that they have not received fair treatment.

"These feelings may, in turn, lead to intentional deception by investigators that IRBs will rarely detect. Paradoxically, excessive protective zeal by IRBs may actually encourage misconduct by some investigators."

Optimizing compliance

The authors contend that by fostering a climate in which investigators perceive that they receive fair and unbiased treatment, IRBs optimize the likelihood of collegial compliance with appropriate participant protections.

Similar observations have been reported elsewhere, including an article by **Jim Giles**, which claims that when researchers believe IRBs are acting unfairly, they sometimes find ways to circumvent the boards. See: Jim Giles, *Nature* **435,** 718–719; 2005, and **B. C. Martinson** *et al., Nature* **435,** 737–738; 2005).

Koocher said during a presentation at the last PRIM&R meeting that the best way to prevent the kind of research misconduct that results from perceptions of mistreatment is a combination of efforts by IRBs and by institutions to create an institution-wide atmosphere that encourages discussion about ethical behavior.

He said that he and Keith-Spiegel have begun developing what they call a "collegial" model for intervening to head off research fraud. The model is based on one developed by **Bernard Whitley** of Ball State College explaining why people engage in dishonest academic behavior.

Surveying 12,000 investigators

Koocher and Keith-Spiegel are surveying 12,000 investigators in an effort to determine whether their collegial model has merit and how it might be implemented.

When cheating occurs, Koocher said, the investigator tends to say something like, "My cheating won't make a difference" or "This is going to get me something important, whereas my lying won't affect much" or "this can get me the results I need to get refunded." Willingness to engage in misconduct, he explained, depends on what the researcher feels an obligation toward: the research, colleagues, subjects? It also depends on perceived chances of getting caught.

To improve chances that a researcher will not engage in misconduct, Koocher said, it is necessary to create situational constraints, including development of a collegial atmosphere that encourages discussion among investigators. "If your colleagues are paying attention to what you're doing, if they're not afraid to talk to you privately if they have a concern, and if you fear rapid and serious disapproval, then that would likely improve behavior."Δ

Suspicion and distrust

A history of scientific abuse has led too many African-Americans to believe government scientists created AIDS, a belief that led to distrust and reluctance to participate in research

African-Americans are very often skeptical of the motives and standards of health care researchers, harboring suspicions that could dangerously threaten attempts to control disease, according to **A. Cornelius Baker**, a health care policy consultant who primarily works on issues related to AIDS.

Their skepticism, he said, is partly the result of the still-painful legacy of Tuskegee, but is also the result of various other real and perceived harms that the African-American community believes it has suffered.


A. Cornelius Baker

Only guinea pigs

It is possible to allay the misapprehension, but it will take a significant effort by the research community to alter the perception by African-Americans that the research community is interested in them only as guinea pigs.

A study reported last year by the Rand Corporation and Oregon State University said nearly half of the 500 African-Americans surveyed believe HIV is man-made, 15 percent said AIDS is a form of genocide against black people, and 54 percent said a cure for the disease is being withheld from the poor, Baker said.

The lesson to draw

What matters, he added, is not whether their beliefs are justified. Rather the important lesson to draw from their suspicion is that 20 years into the AIDS era, too many African-Americans "embrace a belief that government scientists created the disease" and that as a result, they are significantly less likely to be willing to participate in human subjects research.

Responses to the survey did not vary by age, gender, education, or income level, Baker noted, which means it is a generalized belief throughout the community. "During the interviews, people said consistently that one of the main reasons for their distrust is the belief that government scientists used tainted needles to infect the Tuskegee men with syphilis."

The problem has far-reaching implications, he said, because the world is increasingly interlocked. "At this very moment, the world is poised to eliminate the scourge of polio, and yet many people in India, Africa, and some in the United States don't trust the vaccination process. This threatens progress toward eliminating the disease."

> *Half of the 500 African-Americans surveyed believe HIV is man-made; 54% said a cure is being withheld from the poor.*

Less likely to get flu shots

In addition, studies through the last decade or so have found that African-Americans are far less likely than others to receive influenza immunization.

"This could be dangerous. Scientists are rushing to develop a vaccine to prevent widespread outbreaks of avian flu in humans. But wouldn't it be to our lasting horror if lives were lost because millions of people don't trust the government or the medical establishment to act in their interests," he said.

Citing the work of University of Wisconsin medical researcher **Vanessa Northington Campbell**, Baker said her studies demonstrated that Tuskegee and other harms

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***A. Cornelius Baker** discussed the concerns expressed here during his keynote address at the last PRIM&R meeting. He is a consultant on health policy, working primarily in areas related to AIDS. He was until 2004 Executive Director of the Whitman-Walker Clinic, which provides prevention, treatment, research, and social services to people living with HIV disease and the gay and lesbian populations of Maryland, Virginia, and the District of Columbia.*

"predisposed many African-Americans not only to distrust medical and public health authorities, it also led to critically low black participation in research studies and organ donation."

A promising result

While much of the information gathered in the Rand/Oregon study is cause for concern, Baker said there was also a more promising result. The people surveyed said that despite their suspicions, they believed that the medical and public health communities are searching for tools to slow the spread of HIV in black communities.

"So while there is distrust, there is not a complete rejection of the promise that results from the best forms of public health work."

From the beginning of the slave era to the present, we find repeated documentation of bad experimentation on vulnerable populations.

Baker said informed consent requirements and IRB reviews have developed in ways that are more honoring of the diversity in communities and are more sensitive to those communities' attitudes.

The task would be easier if Tuskegee were the only experience of abuse. "But it isn't. From the beginning of the slave era to the present, we find repeated documentation of bad experimentation on vulnerable populations," he said.

Recorded history and folklore

"Through both recorded history and folklore, black communities have the memory of centuries of science gone wild—from slave girls forced into sterilization research to robbing of African American graves for cadavers in the post-Civil War era, to the current practices that evidence inferior treatment of blacks in health care.

"There is a pattern of ethical lapses that remain in the memory of the African-American community and that threatens the success of research progress."

Because the perception is that medical research often exploits people for financial gain or other sinister motives, Baker said, the distrust is deeply embedded and will take a concerted effort to alter.

"When President Bill Clinton was still in office, he spoke about Tuskegee, saying that 'The legacy of the study at Tuskegee has reached far indeed in ways that hurt our progress and divide our nation.'

There is a pattern of ethical lapses that remains in the memory of the African-American community.

"Ten years after he spoke those words, much has to be done to right the wrongs of Tuskegee, of the Nazis, of thalidomide, and of all the other examples of poor science. But it can be done, not least because the consequence of not achieving trust would be too great a cost."Δ

Recent books

Gert, Bernard; Culver, Charles M.; and Clouser, K. Danner, *Bioethics: A Systematic Approach*, Oxford/New York: Oxford University Press, 2006, 2nd ed.

Mappes, Thomas A. and DeGrazia, David, *Biomedical Ethics*, Boston: McGraw-Hill, 2006, 6th ed.

Bankert, Elizabeth; and Amdur, Robert, *Institutional Review Board: Management and Function*, Sudbury, MA: Jones and Bartlett, 2006, 2nd ed.

Athanassoulis, Nafsika, ed., *Philosophical Reflections on Medical Ethics*, Basingstoke [England]/New York: Palgrave/Macmillan, 2005.

Cahill, Lisa Sowle, *Theological Bioethics: Participation, Justice, and Change*, Washington, D.C.: Georgetown University Press, 2005.

Walters, LeRoy; Kahn, Tamar Joy; and Goldstein, Doris Mueller, eds., *Bibliography of Bioethics*, vol. 31, Washington, D.C.: Kennedy Institute of Ethics, Georgetown University, 2005.

Lessons to be learned

Devastating illnesses for six research subjects "could happen again"

An online article by **Jeremy Sugarman** and **Carol Levine** about difficulties encountered during a British research study asserts that the nearly fatal problems suggest lessons that should be learned by IRBs and investigators.

The bad news, they said, is that the study "went forward on a 'business-as-usual' approach, and something like it could happen again."

During the study, which was conducted early this year, six British men suffered devastating illnesses after receiving the experimental compound, TGN1412, in the first phase of human testing. The drug was designed to treat chronic autoimmune/inflammatory disease. (*The Hastings Center Bioethics Forum,* **http://www.bioethicsforum.org/20060417clevinejsugarman.asp**)

The men are out of the hospital, but it is unclear whether they will suffer long-term health effects.

The study was the first test of the drug in humans. It was developed by a German company (which is now out of business) as a monoclonal antibody designed to treat chronic autoimmune inflammatory diseases. It mobilizes one part of the immune system specifically to attack another part. If it works, TGN1412 could have created a huge market for treating devastating diseases such as rheumatoid arthritis and leukemia.

The article said the study's problems were not the result of paying the subjects; nor was it that the study was not done at an academic medical institution. Paying research subjects for their time and inconvenience is "accepted practice," Sugarman and Levine said, noting, however, that "very high payments" raise serious questions about "undue inducements" to participate.

Further, they said, the three research subject deaths that occurred during recent years in the United States were at well-respected, large academic medical centers—the University of Rochester, the University of Pennsylvania, and Johns Hopkins University.

Critical aspects ignored

Instead, the basic problem, they said, was that "those involved ignored critical aspects of the research that should have warranted what we have called 'special scrutiny.'" The authors also argue that the traditional protections for human research subjects—such as informed consent and special protections for vulnerable populations—are necessary cautions, but they have never been sufficient to guard their welfare.

Sugarman and Levine propose as at least a partial solution a "special kind of scrutiny" for research that seems to involve serious moral issues. They also challenge IRBs, investigators, and sponsors to "recognize and respond to the moral complexities of a protocol before it is implemented, not after it is criticized in the scientific or lay press—nor, we might have added, after subjects have already been harmed."

Special scrutiny

Special scrutiny, they said, is called for when any of the following circumstances apply:

1. The research involves "initial experiences of translating new scientific advances to studies in humans, especially when the intervention is novel, irreversible, or both."

2. "Without potential for offsetting direct medical benefit, there is a known or credible risk for significant harm (death or serious disability are the clearest examples)."

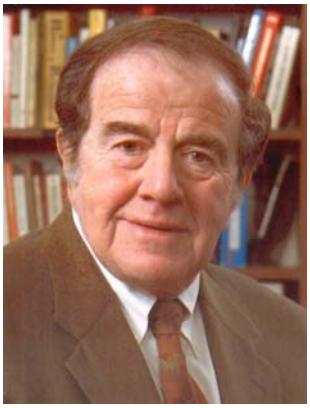
3. The protocol raises ethical questions "about research design or implementation for which there is no consensus or there are conflicting or ambiguous guidelines."

Based on information in newspaper and journal reports, they said, the study "seems to have met these criteria for special scrutiny. Had it been subjected to that process, it might have never gone forward as it was designed and implemented."Δ

Jeremy Sugarman *is Harvey M. Meyerhoff Professor of Bioethics and Medicine and Deputy Director for Medicine of the Phoebe R. Berman Bioethics Institute at Johns Hopkins University.* ***Carol Levine*** *directs The Orphan Project: Families and Children in the HIV Epidemic, which she founded in 1991. In 1993 she was awarded a MacArthur Foundation Fellowship for work in AIDS policy and ethics.*

Robert J. Levine

Lifetime Achievement Award for Excellence in Research Ethics



Robert J. Levine

Robert J. Levine has been given the Lifetime Achievement Award for Excellence in Research Ethics by PRIM&R.

A Professor of Medicine and Lecturer in Pharmacology at Yale University School of Medcine, where for 30 years he chaired the IRB, Dr. Levine is also co-chair of the Executive Committee of Yale's interdisciplinary Bioethics Project.

He is the author of *Ethics and Regulation of Clinical Research* and the founding editor of the journal *IRB: A Review of Human Subjects Research*.

In addition, he was chair of the Working Group for Revision of the Declaration of Helsinki at the World Medical Association.

In presenting the award, PRIM&R said it's possible to get "bleary-eyed" reading a catalog of his achievements and that he is "a very kind, very patient, very calm, very generous, and very smart man." The award was given, PRIM&R said, because of a lifetime seeking to "make research ethics a more principled and accessible endeavor."

Dr. Levine has been on the PRIM&R board of directors since 1986 and during that period gained a reputation as a one-man band in his work on the annual PRIM&R conferences.

"He helped plan the meetings, identified and recruited many of the faculty, gave many of the talks, moderated many of the panels and debates, and edited the conference proceedings," PRIM&R said.Δ

Publications

ORI's experience with allegations of research misconduct

Chris Pascal, with the HHS Office of Research Integrity (ORI), has published a paper describing ORI's experience with people who allege research misconduct (*Experimental Biology and Medicine* 231:1264–1270, 2006).

Pascal describes the legal framework for complainant issues, the various roles of the complainant as the allegation of misconduct proceeds through the steps of investigation and resolution, how allegations of retaliation against the complainant are handled, the responsibilities of ORI and of the research institution where the alleged misconduct occurred, and ORI's experience with several cases of alleged retaliation.

In each of these areas, he provides guidance to prospective complainants, research institutions, and other interested persons on effective ways to approach the various problems and concerns that arise, while maintaining a balance between the needs of the complainant, the accused, the research institution handling the allegation, and ORI.Δ

Web sites

Code of Federal Regulations: IRBs
http://www.cfsan.fda.gov/~lrd/cfr56.html

FDA Information Sheets for IRBs
http://www.fda.gov/oc/ohrt/irbs/appendixc.html

The National Academies Institutional Review Board
http://www7.nationalacademies.org/irb/

National Jewish Institutional Review Board
http://www.nationaljewish.org/news/irb/index.aspx

Human Subjects Research Training, sponsored by The Collaborative IRB Training Intiative (CITI) and The University of Miami
http://www6.miami.edu/citireg/

Office for Human Research Protections (OHRP), Department of Health and Human Services
http://www.hhs.gov/ohrp/

Secretary's Advisory Committee on Human Research Protections (SACHRP)
http://www.hhs.gov/ohrp/sachrp/

Office for Human Subject Protections (OHRP)—IRB Guidebook
http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

Checklists?

Two views being debated: a dangerously comfortable substitute for protection or the best guarantee both to protect subjects and limit overzealous IRBs

IRB review checklists, when used badly, can become a dangerously comfortable substitute for actually ensuring the care and well-being of human subjects in research studies.

That is one possible conclusion.

The other is that if review boards routinely extend their purview beyond certain clearly defined and listed items, they risk unfairly and arbitrarily preventing needed research.


P. Pearl O'Rourke


Leonard Glantz


Nancy Dubler

The debate about which of these conclusions should be the mandate of IRBs will be a part of the agenda at the next PRIM&R meeting, which is to be held in November in Washington, D.C.

At the last PRIM&R meeting, a panel that included **Nancy Neveloff Dubler**, **Leonard Glantz**, and **P. Pearl O'Rourke** generally agreed that the first conclusion is more likely to fulfill the mandate of review board.

Checklists can't "put you in the shoes of the patient."

They argued that while checklists have value, they are not sufficient and should never be mistaken for the kind of review that, as Dubler said, "puts you in the shoes of the patient."

The discussion is about whether IRB reviews have sometimes become too zealous in efforts to ensure protections, and whether it would be best to have a more standardized review by employing a comprehensive and well-thought-out checklist.

O'Rourke said that while she seldom uses checklists, she knows they can be effective even though they may not be sufficient. They can demonstrate "that the task is completed, that loose ends are all tied up, and that when some oversight agency questions me, I can demonstrate compliance."

The danger

Glantz agreed that checklists have utility, but that they tend to belong to the world governed by laws and regulations, "which is not an ethical world." He said regulations, like checklists, set the floor, the required minimum, but they should not establish the ceiling. "The danger of checklists is that we routinely check the boxes and forget that mere compliance" often is intended merely to protect the institution.

"When I hear about a culture of compliance," he said, "it makes me shake, because that's the last thing you need. You need a culture of caring, of empathy."

Dubler 's position was that it is not possible for there to be enough checklists to encompass the wide-ranging inquiry that should characterize an ethics review.

"Checklists don't enable the reviewers to see all of the person who is a possible research subject. They don't allow for

(Continued on page 22)

P. Pearl O'Rourke *is Associate Professor of Pediatrics at Harvard Medical School and Director of Human Research Affairs at Boston's Partners HealthCare System.* ***Leonard Glantz*** *is Professor of Health Law at the Boston University School of Public Health and Professor of Law in the Law School.* ***Nancy Dubler*** *is Professor of Epidemiology and Social Medicine at Albert Einstein College of Medicine and Director, Division of Bioethics, Department of Epidemiology and Social Medicine at New York's Montefiore Medical Center.*

Database update shows funding is up

The annual update reports $23 million increase in funding from DOE for human-subjects-related projects

By **Don Watkins and Kathy Olsen,**
Oak Ridge Institute for Science and Education

The fiscal year (FY) 2005 update of the U.S. Department of Energy (DOE) Human Subjects Research Database (HSRD) is available at https://hsrd.orau.gov.

The database details research projects involving human subjects that were funded by the DOE, conducted at DOE facilities, performed by DOE or its contractors, or that used DOE workers as human subjects.

Funding
DOE funding for projects increased to $73 million in 2005 from $50 million in 2004 and $45.4 million in 2003. This represents an increase of 46 percent over 2004.

Funding from additional Federal sources also increased to $34.8 million in 2005 from $27.8 million in 2004 and $9.8 million in 2003. In 2005, funding for individual projects ranged from a low of $200 to a high of $14 million.

The average project received $470,800 compared with the median project, which received $150,000.

Projects
The FY 2005 database includes 285 active projects, with 72 percent conducted at DOE facilities and 28 percent at non-DOE facilities. Of these 285 projects, 56 percent were funded by DOE.

With 44 active studies, the national laboratories continue to have the most projects.

Although the number of active projects increased from 276 in 2004 and 255 in 2003, the percentage of DOE projects remained essentially constant.

Forty-five research organizations provided data in 2005. Twelve of these were DOE laboratories and 33 were non-DOE facilities.

These numbers are fairly consistent with the breakdown for 2004 and 2003. In 2005, six DOE facilities accounted for 61 percent of the active projects—Brookhaven National Laboratory, Lawrence Berkeley Laboratory, Lawrence Livermore National Laboratory, Los Alamos National Laboratory, Oak Ridge National Laboratory, and Oak Ridge Associated Universities. Lawrence Livermore National Laboratory continued to have the greatest number, with 44 active projects in 2005. This breakdown has been consistent since 2003, except for the addition of Oak Ridge National Laboratory.

Human Subjects
In FY 2005, 1,022,172 human subjects were involved in DOE-related projects with 33 percent at DOE facilities and the remainder at non-DOE facilities, compared with 24 percent at DOE in 2004 and 29 percent in 2003.

285 active projects, 56% of them funded by DOE and 72% of them conducted at DOE facilities

In 2005, 48 percent of subjects were involved in records-related and epidemiologic type studies, consistent with previous years.

The database continues to evolve, and in 2006, we expect to identify specific international projects.Δ

Journal

The academic journal *Accountability in Research* publishes analyses of systems for conducting research. It provides an international interdisciplinary forum for development of new policies and procedures for ensuring integrity of research data. A sample searchable issue is at **http://www.tandf.co.uk/journals/titles/08989621.asp**

News notes

Panel recommends loosening regs on human research in prisons

A report by the Institute of Medicine of the National Academy of Sciences recommends loosening restrictions on research conducted using prisoners. Current regulations, passed in 1978, say prisoners can participate in federally financed biomedical research if the experiment poses no more than "minimal" risks to the subjects. The new report said experiments with greater risks should be permitted if they had the potential to benefit prisoners. The report recommended that all such studies first be approved by an independent review board.

In a lengthy analysis of the report's recommendations, *The New York Times* said "The proposed change includes provisions intended to prevent problems that plagued earlier programs. Nevertheless, it has dredged up a painful history of medical mistreatment and incited debate among prison rights advocates and researchers about whether prisoners can truly make uncoerced decisions, given the environment they live in." (*The New York Times*, August 16, 2006, **http://www.nytimes.com/2006/08/13/us/13inmates.html?ex=1313121600&en=8796300a5191346d&ei=5088&partner=rssnyt&emc=rss**)

"The current regulations are entirely outdated and restrictive, and prisoners are being arbitrarily excluded from research that can help them," said Ernest D. Prentice, a University of Nebraska genetics professor and the chairman of a Health and Human Services Department committee that requested the study. Prentice said the regulation revision process would begin at the committee's next meeting, on Nov. 2, according to the *Times* article.

Until the early 1970's, about 90 percent of all pharmaceutical products were tested on prison inmates, the *Times* reported, citing federal officials. But such research diminished sharply in 1974 after revelations of abuse at prisons like Philadelphia's Holmesburg, where inmates were paid hundreds of dollars a month to test items as varied as dandruff treatments and dioxin, and where they were exposed to radioactive, hallucinogenic, and carcinogenic chemicals.

In addition to addressing the abuses at Holmesburg, the regulations were a reaction to revelations in 1972 surrounding what the government called the Tuskegee Study of Untreated Syphilis in the Negro Male, which was begun in the 1930s and lasted 40 years. In it, several hundred mostly illiterate men with syphilis in rural Alabama were left untreated, even after a cure was discovered, so that researchers could study the disease. (*See related article in this issue, page 15.*)

"What happened at Holmesburg was just as gruesome as Tuskegee, but at Holmesburg it happened smack dab in the middle of a major city, not in some backwoods in Alabama," the *Times* said, quoting Allen M. Hornblum, an urban studies professor at Temple University and the author of *Acres of Skin*, a 1998 book about the Holmesburg research. "It just goes to show how prisons are truly distinct institutions where the walls don't just serve to keep inmates in, they also serve to keep public eyes out."

Alvin Bronstein, a Washington lawyer who helped found the National Prison Project, an American Civil Liberties Union program, told the *Times* he did not believe that altering the regulations risked a return to the days of Holmesburg. "With the help of external review boards that would include a prisoner advocate," Bronstein said, "I do believe that the potential benefits of biomedical research outweigh the potential risks."

(For another analysis of the issue, an article in the *Boston Globe* urges that the Institute's report should be cautiously considered. See **http://www.boston.com/news/globe/editorial_opinion/oped/articles/2006/08/17/testing_drugs_on_prisoners_the_easy_out/**)

Meetings

2006 Conference on Research Integrity
Dec. 1–3, 2006
Tampa, Fla.
This meeting is co-sponsored by the Office of Research Integrity, HHS, and the University of South Florida College of Medicine.
For information, see ***http://www.cme.hsc.usf.edu/research_integrity/***
The conference program is available at ***http://ori.dhhs.gov/conferences/rri2006_agenda2.pdf***

Biotechnology, Culture, and Human Values in Asia and Beyond
March 19–23, 2007
Bangkok, Thailand
For information, see http://www.stc.arts.chula.ac.th/ABC2007/
Also: Dr. Soraj Hongladarom, hsoraj@chula.ac.th (+66(0)2218-4756)

2007 Joint Ethics Conference
May 30—June 3, 2007
Bangkok, Thailand
The Joint Ethics Conference of the 18th Canadian Bioethics Society Conference and the 3rd International Conference on Clinical Ethics and Consultation is hosted by the University of Toronto Joint Centre for Bioethics.
For information, see http://www.bioethics.net/events.php?viewEvent=413
Also: Email the conference organizer at joint.ethics.conference@utoronto.ca (416/978-2709)

31st Annual Health Law Professors Conference
May 31–June 2, 2007
Boston University School of Law
This conference is intended for professionals who teach law or bioethics in schools of law, medicine, public health, health care administration, pharmacy, nursing, and dentistry. ASLME's Annual Health Law Professors Conference combines presentations by experienced health law teachers with the opportunity for discussion among conference participants.
For information, see **https://www.aslme.org/aslmesecure/info/description.php?conf_id=67**

9th Annual Ethical Issues in International Health Research Workshop
June 11–15, 2007
Boston, Harvard School of Public Health
For information, see **http://www.hsph.harvard.edu/bioethics/pdf/EIIHR_Brochure_2007.pdf**

Checklists (Continued from page 19)

sufficient complexity. We need to ask: Where is this person? In a nursing home? At home? Are there people with her who love her? Is she still something of an advocate for herself, able to say yes or no?

"There is no place on a checklist," she added, "that will allow you to truly develop an understanding for what this means to that person, what the change in life and condition will be for a prisoner, for an adolescent alone, for patients at the end of life."

She said regulations and checklists don't ask "that you go and stand in the shoes of the subjects. A reviewer not constrained by checklists can demand that we do exactly that."Δ

WHO: New standards for registering

The World Health Organization (WHO) is urging research institutions and companies to register all medical studies that test treatments on human beings, including the earliest studies, whether they involve patients or healthy volunteers.

The announcement from WHO in Geneva said the effort is part of the International Clinical Trials Registry Platform—a major initiative aimed at standardizing the way information on medical studies is made available to the public through a process called registration. The aim is to make clinical research transparent and to enhance public trust, WHO said.

Although registration is voluntary, there is growing pressure to register clinical trials. In July 2005, for example, the International Committee of Medical Journal Editors, a group representing 11 prestigious medical journals, instituted a policy whereby a scientific paper on clinical trial results cannot be published unless the trial had been recorded in a publicly accessible registry at its outset.

Some groups have raised concerns that these new requirements could jeopardize academic or commercial competitive advantage if they apply to preliminary trials of new interventions. Similar concerns have been voiced about the requirement to disclose certain items—such as the scientific title of the study, the name of the treatment being tested and the outcomes expected from the study—at the time of registration.

The planned Registry Platform will not be a register itself but rather will provide a set of standards for all registers. It also creates a global trial identification system that will confer a unique reference number on every qualified trial.

Currently, there are several hundred registers of clinical trials around the world but little coordination among them. The Registry Platform seeks to bring participating registers together in a global network to provide a single point of access to the information stored in them.

Later this year, the WHO Registry Platform will launch a Web-based search portal where scientists, patients, doctors, and anyone else who is interested can search among participating registers for clinical trials taking place or completed throughout the world.

For more information contact **Judith Mandelbaum-Schmid**, Communications Officer, WHO/Geneva, telephone: +41 22 791 2967, mobile phone: +41 79 254 6835, e-mail: schmidj@who.int.Δ

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.

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