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## IRBs—their purpose and relationships

This edition of Protecting Human Subjects focuses on issues related to the evolving understanding of regulations designed both to protect human subjects and encourage research. Many of these issues were discussed during the 2008 Public Responsibility in Medicine and Research Annual Advancing Ethical Research Conference.

Several articles are expanded and updated examinations of questions raised at the conference about Institutional Review Board (IRB) effectiveness and the relationships between IRBs and investigators, institutional administrators, and the public, as well as the relationships among board members.

Other articles consider the issue of whether IRBs need more or less rigid oversight and whether flexibility is a virtue or a vice. Keynote speaker Ivor Pritchard's article, for example, continues the conversation on this topic. Still other articles raise questions about whether some assumptions about human subjects protection should be reconsidered and whether there are better ways to protect the vulnerable. Also included are updates on recently issued National Institutes of Health stem cell guidance, a summary of DOE's spring workshop, and DOE's plans to expand the scope of its Central IRB.

## Rule flexibility

*The regulated community does not always exercise the flexibility that the regulations allow*



Ivor Pritchard

*by Ivor Pritchard, Office of Human Research Protections -*

In the December 30, 2007, *New York Times*, Atul Gawande wrote an op-ed piece that contained several serious flaws.

First, it misrepresented the Johns Hopkins University Keystone Project in Michigan that was the editorial's focus, describing the project as if the research intervention consisted simply of introducing the use of a checklist to ensure that intensive care unit (ICU) staff follow recommended practices in the placement of catheters to avoid infections.

In fact, the research intervention included education of ICU staff, provision of a central-line cart, the use of the checklist, the introduction of a stopping order, daily discussion of catheter removal, and feedback to teams regarding the frequency of infections. Indeed,

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## *Is exploitation sufficient cause for IRBs to reject studies?*



Alan Wertheimer

*by Alan Wertheimer, National Institutes of Health*

The notion that we want to avoid exploitation is regarded as a unifying principle for human subjects research.

Concern about exploitation came to the fore with respect to vulnerable populations, prisoners being the standard example. Even more so, research in less developed countries has become the epicenter of worries about exploitation.

The most common example is placebo-controlled trials when a treatment already proven effective is available. Another is the situation in which an intervention being studied is likely to be used for the benefit of advanced countries rather than for the countries in which the studies are conducted.

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## Pritchard: *Rule flexibility*

(Continued from page 1)

the study did not reach any conclusions about whether the checklist by itself did anything.

Second, the editorial misrepresented the nature of research. In hindsight we can say that the research intervention was successful and that lives and economic costs were saved. But that wasn't proven when the study was begun; its purpose was to find out whether the intervention decreased the rate of infections, increased it, or had no effect. The editorial implied that unlike trials of experimental drugs, where the outcomes are unknown, the outcomes of research involving organizational interventions are entirely predictable and risk-free.

*A consequence of this fear is that the regulated community does not exercise the flexibility that the regulations allow.*

Third, it implied that the Office for Human Research Protections (OHRP) and its regulatory enforcement practices stand in the way of medical practitioners' delivery of good care based on sound scientific evidence. This is wrong. If an ICU has sound evidence to support implementing an intervention and decides to do so on that basis, this is a matter of good, evidence-based practice and does not involve the regulations for the protection of human subjects in research.

Gawande's editorial precipitated a vehement public response. OHRP was sharply criticized in the media and received numerous expressions of outrage from both organizations and private individuals.

There are genuine questions regarding how the regulations for the protection of human subjects in research may apply to some quality improvement activities. And within the regulated community some fear what OHRP might do when it judges that regulatory noncompliance has occurred.

A consequence of this fear is that the regulated community does not exercise the flexibility that the regulations allow, wasting people's time and efforts, impeding promising research, and possibly even

compromising the quality of human research subject protections. So how should we go forward?

What is this regulatory "flexibility"? The regulations provide discretion to adjust our approach to the activity in question. The regulations sometimes allow more than one option, and some regulatory provisions are open to interpretation in ways that allow us to deal with one research study differently from another. Exemption decisions, expedited or convened meeting review by the institutional review board (IRB), and informed consent or waiver of informed consent are common examples of flexibility.

The largely positive attitude toward flexibility typically contrasts flexibility with rigidity, implying that flexible guidelines are preferable to rigid rules. If flexibility were evaluated in terms of the Aristotelian scheme for moral virtues, however, flexibility as a virtue would have to be a mean between two extremes, one extreme being a vice of excess and the other a vice of deficiency. Rigidity would be the vice of deficiency in flexibility, while too much flexibility would be the vice of excess.

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*Some regulatory provisions are open to interpretation.*

## Web sites

### **Bioethics wire**

<http://www.thehastingscenter.org/BioethicsWire/Default.aspx>

### **Research ethics resources**

<http://www.ethicsweb.ca/resources/research/>

### **Corporate research ethics**

<http://www.researchethics.ca/business-ethics.htm>

### **Research in social sciences and humanities**

<http://www.researchethics.ca/social-science-humanities.htm>

### **Bioethics news**

<http://bioethics.net/>

Many criticisms of the current human research subjects system seem to arise from its excessive flexibility: One institution says a research activity falls under the regulations, while another does not; one IRB waives informed consent, while another refuses; especially in multi-site research activities where multiple IRBs are involved, complaints arise precisely because the exercise of regulatory flexibility led to varying results. Valuable time and effort are spent sorting things out before the research gets under way.

Having rules, and following them, can be desirable. Imagine having no rules and needing to invent ethical procedures and standards for each new research

project. Or imagine having rules but nobody following them (like driving in Rome, Istanbul, or Boston). It would be chaos. Rules enable us to repeatedly make use of constructive ways of proceeding, and make our behavior in cooperative activities predictable to ourselves and to each other. Knowing the rules allows us to anticipate whether a project will need to undergo review, what criteria will be used to evaluate it, and so on.

*Rules are never sufficient to answer all of our questions about how to carry out ethical research.*

Rules are never sufficient to answer all of our questions about how to carry out ethical research. The successful use of rules requires practical reasoning in addition to the rules themselves. We have to identify the salient features of the given activity. Sometimes we have to choose among several conflicting rules in a given situation. And rules are often subject to multiple interpretations.

Consider the notoriously thorny question of whether or not an activity is “research.” The answer determines whether IRB review and approval and the other requirements must be satisfied. Often the problem here appears to be too much flexibility: Different people have different conceptions of research, leading to different conclusions about whether an activity is or isn’t research, even in light of the existing regulatory definition of research.

The appropriateness of some flexibility in the definition of research is understandable. Quantitative or qualitative, experimental or observational, basic or

applied, there is some merit in the claim that there is no such thing as “the scientific method,” making it difficult to identify necessary or sufficient conditions for being research. Research is an evolving human artifact. For those activities that do fall within the evolving boundaries of contemporary research, new challenges emerge for the ethical administration of the system for the protection of human subjects in research.

***Underutilization of multisite flexibility***

For example, many more multisite clinical or field trials are taking place than 30 years ago, involving many institutions. The current regulations allow considerable flexibility for cooperative arrangements to secure appropriate review on behalf of the institutions involved. The apparent underutilization of this flexibility may signal the need for more direction as to how that flexibility may be used. OHRP is currently developing a proposal about the accountability of external IRBs to address this need.

Consider three more areas where the rules of research regulation and ethics are being challenged. First, recently the American Psychological Association passed a resolution opposing psychologists’ participation in national security interrogations that violate international standards for the protection of human rights.

*Underutilization of this flexibility may signal the need for more direction.*

An underlying scientific issue here is the difficulty of discerning when interrogated subjects are revealing the truth and when they are lying or inventing what they say. Should research be conducted to address this shortcoming? Would the current regulations allow it?

Second, considerable media attention has been devoted to the use of anthropologists embedded in military units in Iraq and Afghanistan. Several federal agencies are supporting social science research efforts designed to investigate topic areas directly related to national security concerns and our ability to address them in different social and cultural contexts. How should we evaluate the risks and benefits of such research, and the relevance of the political relationship between the United States and the

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## *Is exploitation sufficient cause for IRBs to reject studies?*

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So the underlying question is whether to allow studies to be conducted in underdeveloped countries that would never pass ethical muster in the sponsoring country.

### **Three questions**

The major premise has become that if a trial is exploitative, it shouldn't be permitted. I have three questions about this. One, when is a trial exploitative? Two, should we accept the premise that an exploitative study should not be permitted? Three, are we worried about exploitation of communities or individuals or both?

*Is a transaction unfair when we take advantage of vulnerability?*

It is usually thought that person A exploits person B when A takes unfair advantage of B. But what constitutes unfair advantage? Consider four examples.

1. A Nazi researcher places a death camp inmate in freezing water to test how long a person can remain alive.
2. An affluent person pays a poor person for a kidney. The poor person consents.
3. My car gets stuck in a ditch during a snowstorm. A tow-truck driver offers to pull me out for \$200, which would take him about five minutes.
4. A psychotherapist offers to have sex with a patient, who agrees.

### **Two types of exploitation**

Many would think that all of these are exploitation. But we should contrast two types of exploitation. One is harmful and nonconsensual. The second is mutually advantageous and consensual.

In the first type the exploiter benefits, even if it is merely to produce knowledge, but the exploitee is harmed and does not give valid consent. The Nazi and the psychotherapist fit this form of exploitation. The psychotherapist's patient may consent, but it is not a valid consent.

By contrast, in the second type the exploiter benefits but so does the exploitee. The exploitee in the kidney case might regard the \$25,000 she is paid

as well worth her while. Similarly, if I am stuck on the side of the road I might think it's worth \$200 to get pulled out. I give consent and I benefit.

We know that the harmful and nonconsensual cases are wrong. The others are more complicated and more interesting. If both parties are benefiting, what harm accrues?

### **Appearances deceive**

U.S. Supreme Court Justice Potter Stewart said about pornography that it might be hard to define, but "I know it when I see it." I think that is not true about exploitation. Appearances can be deceiving.

Consider the tow truck driver. It might be that he roams the road all night long looking for people who need to be rescued. He might drive for 10 hours before finding one person to rescue. In that case I am paying for the security of his being available all night. I am not paying merely for the five minutes it takes to pull me out of the ditch.

So when is a transaction unfair? When we take advantage of someone's vulnerability? That cannot be correct. All kinds of legitimate occupations earn their living by taking advantage of other people's vulnerabilities. The director of a homeless shelter makes her living off other people's disadvantage.

### **Sometimes exploitee gets more**

Is it unfair when the exploiter benefits more than the person being exploited? That is not true either. It is counterintuitive, but sometimes the exploited person gains more than the exploiter.

Consider – patient A needs surgery or he will die. Surgeon B says he wants \$25,000. I think patient A gets more here; he gets his life. The surgeon just gets money. This suggests that benefits cannot easily be compared.

Now return to the first premise, that IRBs should not permit trials that are exploitative. Perhaps we should sometimes allow people to do things that appear wrong. Consider the example of a person wanting to give a speech denying the holocaust. It is wrong to do that, but it might also be wrong to interfere if we take free speech seriously.

An activity that is wrong is relevant to, but does not solve the question of, whether we should stop it. So, should we prohibit exploitation that is consensual and is mutually advantageous?

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## Poster session

The DOE Human Subjects Program's poster display for the PRIMR poster session showed examples of research projects with human subjects at DOE national laboratories.

Poster displays included:

**Human Subjects Protection Program Website**  
(<http://humansubjects.energy.gov/>)

**Human Subjects Protection Resource Book**  
(<http://humansubjects.energy.gov/doe-resources/humsubj-resourcebook.htm>)

**Human Subjects Research Database**

**Protecting Human Subjects Newsletter**  
(<http://humansubjects.energy.gov/doe-resources/default.htm>)

**Protecting Human Research Subjects – Are You Conducting Research Using Human Subjects?**  
(Brochure)  
<http://humansubjects.energy.gov/doe-resources/files/hs-researcher-brochure.pdf>)

**“From Paper to People: After IRB Approval of Research Studies”**  
(<http://humansubjects.energy.gov/doe-resources/files/P2Pbook.pdf>)



Protecting Human Subjects Program poster session

Manning the poster display for DOE's Human Subjects Protection Program is Peter Kirchner, MD, the program's Senior Medical Scientist, and at right is Peter Lichty, MD, IRB Chair and Site Occupational Medical Director of Lawrence Berkeley National Laboratory. (Photo by Gloria Caton)

## Exploitation (Continued from page 4)

Assume a researcher has no obligation to do research with subject A. Assume subject A gains from participating in research and consents to it but does not receive what we consider fair benefit. This makes it exploitation. Should we prohibit it?

I do not think there is a good answer. If prohibiting the research is worse for the exploitee, we should not prohibit.

We should not protect people's participation in research when they gain something. If protecting me from exploitation means I do not get my car pulled out of the ditch, then leave me alone and let me be exploited.

We need to be careful before describing research as exploitation. It cannot be because we are taking advantage of people's vulnerabilities or because one party is getting more than another.

I am not suggesting that we should never protect people from exploitation. Rather, we must withdraw some of the heavy rhetorical artillery and tread carefully before citing alleged exploitation as justification to prohibit participation in research.Δ

## New books

### ■ Medical research for hire

*Medical Research for Hire—The Political Economy of Pharmaceutical Clinical Trials*, by Jill A. Fisher, Rutgers University Press, January 2009.

More than 75% of drug trials in the U.S. are now conducted in the private sector, not by academic researchers. She assesses the risks and advantages.

### ■ The benefits/risks of research

*Everyday Practice of Science*, by Frederick Grinnell, Oxford University Press, January 2009.

This book explains why society cannot have the benefits of research without the risks. It discusses what should be done, who should do it, who should pay, and how much.

# New NIH guidance on stem cells

Informed consent must be a robust process rather than merely a form

New guidelines from the National Institutes of Health (NIH) for human stem cell research require viewing informed consent as a robust “process” rather than merely a consent document.

*Necessary details must be explained and understood by embryo donors*

“Therefore,” according to NIH acting director Raynard Kington, “exact wording for an informed consent form is not provided in the guidelines.” Researchers should view this, he said, as a process “where all necessary details are explained to and understood by embryo donors.”

### **NIH Record**

Kington’s views were discussed in an article about the new guidelines published in the *NIH Record*, vol. LXI, No. 16, August 7, 2009. (see [http://nihrecord.od.nih.gov/newsletters/2009/08\\_07\\_2009/story3.htm](http://nihrecord.od.nih.gov/newsletters/2009/08_07_2009/story3.htm)).

Information about human embryonic stem cell (hESC) research must be provided to donors during the consent process. In addition, donors cannot have been offered payment in cash or in kind.

The final guidelines were released July 6. They are posted on the NIH web site (<http://stemcells.nih.gov>).

The primary stipulation in the guidelines is that NIH will fund research only if it is conducted on human embryonic stem cells derived from embryos created by *in vitro* fertilization (IVF) for reproductive purposes only. The cells must come from embryos that are not needed by the donors for reproductive purposes.

### **Donor requirements**

Donors must have received reproductive treatment and must have voluntarily consented for the embryos to be used for research.

Stem cells created by somatic cell nuclear transfer, or cloning, are not eligible for NIH funding.

An advisory committee to the director has been formed by NIH to consider funding requests that are outside the norm. This could include research using stem cells that existed before July 7, 2009, that do not meet the new guidelines. It could also include research using lines developed from embryos in countries that do not have requirements identical to those of NIH.

Investigators can get help in identifying eligible cell lines by way of a new NIH Stem Cell Registry that replaces the previous one. As lines are approved, they will be noted in the registry. Once in the registry, those cell lines can be used without seeking further federal approval.

Kington said the rules could be revised as the evolution of the science and the debate changes.Δ

## Bioethics resources

- Bioethics blog, written by the editors of *The American Journal of Bioethics*  
<http://blog.bioethics.net/>
- The Hastings Center bioethics forum  
<http://www.bioethicsforum.org/whatis.asp>
- Women’s bioethics project  
<http://womensbioethics.blogspot.com/>
- Business ethics (includes discussion of the bioethics industry in the developing world)  
<http://www.businessethics.ca/blog/>
- The Alden March Bioethics Institute maintains a comprehensive listing of conferences, educational programs, and other activities related to research ethics and related issues. See  
<http://www.bioethics.net/events.php?page=1>
- Human research bibliography from the National Library of Medicine  
[http://www.nlm.nih.gov/archive//20061214/pubs/cbm/hum\\_exp.html](http://www.nlm.nih.gov/archive//20061214/pubs/cbm/hum_exp.html)

# Genetic technologies

*Privacy and confidentiality can no longer be ensured for genetic specimens in data banks. What are the implications for IRBs and repository managers?*



Nancy King

*by Nancy King, Wake Forest University School of Medicine -*

When specimens are provided to a biobank, individuals' expectations of privacy and confidentiality are becoming increasingly difficult to honor.

In part this is because technological advances using genotypic and phenotypic information are occurring so rapidly that there is no consensus about the answers to key questions, including What do biospecimen providers need to know about giving specimens to a biobank? What should they be told? Should they play a role in how their specimens are used?

*Expectations of privacy and confidentiality are becoming increasingly difficult to honor.*

There are several important issues to address in answering these questions.

**Privacy, confidentiality**  
The first is privacy and confidentiality. How can we ensure privacy when data-sharing plans spread information widely and large data sets continually link new data with existing data?

The second is risk of harm. Is the concern risk to individuals, or is it also harm to groups?

The third is information and consent. Is getting informed consent the goal? Providing information only, without consent? Consent without information, as in blanket consent to all future uses of the specimen and the information derived from it? Both, or neither?

**Deidentified?**

Part of the problem for privacy is that what we used to consider deidentified information really is not deidentified. It is increasingly possible to identify the source of a biospecimen, using only a small amount of genetic information.

Even when researchers attempt to protect the identities of individuals by pooling together the genetic information from many biospecimens, it has recently been demonstrated that it is possible to work back to identify individuals.

In fact, the Personal Genome Project (<http://www.personalgenomes.org/>) assumes that there is no longer any such thing as genetic privacy.

**Unrealistic expectation?**

Privacy is the right to keep information about us from being accessed by others. But if there is no privacy, can there at least be confidentiality, which is the expectation that those to whom we have entrusted information, such as managers of data banks, will protect the information they control from access by others? This expectation may also be unrealistic, especially in large-scale studies that continually link existing data to new information.

So what are the responsibilities of data managers and biobanking stewards? What do IRBs need to think about in their efforts to protect confidentiality of information when deidentification may be a mirage?

Should we be concerned about improving data security or about improving risk disclosure? Or is it neither of these? Is it something completely different?

**Risk of harm issues**

The inability to ensure privacy and confidentiality means there is a risk of harm both to individuals and to groups, especially given the way information is now gathered and reported. And yet, according to the Common Rule, IRBs are not supposed to consider harms to groups.

*Dissemination and discussion of research should concern IRBs because study results can be described in ways that perniciously affect groups.*

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## Genetic technologies

(Continued from page 7)

I do not advocate that certain types of research be limited because of their implications for group harms. Nevertheless, the dissemination of research results and the way they are described in publications should concern IRBs, because it can be surprisingly easy to describe study results in ways that perniciously affect groups.

Who should have the duty to communicate with the public about the meaning and limits of genetic information? Who should have the duty to monitor how results are disseminated, described, and discussed? Is it the IRB? The investigator? Members of the affected groups?

Indeed, what kind of voice should groups have in research?

### **Stigmatize, Discriminate**

We know that reporting and dissemination can stigmatize and foster discrimination against groups.

A well-known example is the study that took blood samples from members of the Havasupai tribe in Arizona to look for genetic associations with type 2 diabetes.

According to the tribe, however, without their permission, researchers later used the blood samples to look for genetic associations with schizophrenia and to identify ancestral migration patterns. The research purportedly showed that the Havasupai came across the Bering Strait, rather than originating in the Grand Canyon as their creation story holds. The tribe objected, because they believe their blood was used without permission in ways that harmed them.

A more common example is when research results describe genetic associations according to racial and ethnic categories. Race and ethnicity are social and cultural categories without genetic significance. Using them to report genetic research results perpetuates stereotyping and can stigmatize minority groups.

Informed consent remains problematic in biobanking research, as OHRP guidance states that secondary use of coded private information is not human subjects research if identifying information is not provided to the researcher. But the risk of reidentification is now known to be considerable, which means the IRB may need to play a more active role than OHRP contemplates. The Common Rule also exempts already existing data, but when new data are linked to existing data, the possibility of reidentification increases.

If the consent requirement is waived, what then? Individuals need and deserve to know when they are contributing to research. It is increasingly common, for example, for extra blood to be taken in clinics and stored in a genetic repository for use in future studies. Consent for this is often inadequate, yet information about it is essential.

Ethical concerns also arise when biobanks merge, creating ever-larger specimen collections and allowing kinds of research not previously contemplated. Various models have been proposed to ensure that oversight is adequate and that specimen providers' rights, interests, and welfare are addressed.

### **Which model?**

Most biobanks and data repositories use either a protection model or a utility model. The protection model limits research to that which is directly addressed by the consent originally obtained. This is giving way to the utility model, which maintains that blanket consent is sufficient because risks of harm to individuals are low and potential benefits to public health from the research are great.

Another model has been proposed by philosopher Vilhjálmur Árnason: the citizenship model. In this model there is democratic engagement with the steward of the repository.

It allows people to be as interested and engaged in the process of giving permission or opting out of future research as they wish to be. The opportunity for engagement also increases science literacy and makes the database more transparent.

Like the utility model, the citizenship model also utilizes broad consent but includes an opt-out mechanism. And it permits specimen providers to keep track of how their specimens are being used and to decide whether to participate in additional studies.

Because informing and involving the public can help researchers understand their concerns, a more transparent system can increase public trust. Besides, it simply makes sense to involve the people who are contributing the information from which researchers are learning so much about the genetic components of disease and health.Δ

*Risk of reidentification is considerable. . . . The IRB may have more of a role than OHRP would suggest.*

# Drug trials shifting to private sector

Investigators, who are not academics, not designing trials and publishing, and not getting tenure, now supervise most research



Carl Elliott

by Carl Elliott,  
University of Minnesota

The complex regulatory system for human subjects research was built around the assumption that the main threat to research subjects comes from academic researchers who

are arrogant or ambitious and might be tempted to gamble with the health of their subjects.

That is no longer the case. Drug research has become an almost completely commercial industry that includes an approval process by commercial ethics boards operating as a private, for profit enterprise.

## **Lots of money**

Investigators, who are not academics, not designing trials and publishing, and not getting tenure, now supervise most research. They are getting lots of money.

The market has changed the game for universities, which now have to compete for trials with private business on terms set by the market.

So, what can we expect when we turn pharmaceutical trials into a business?

One result has been development of a subculture populated by professional guinea pigs, usually young people living on the margins, surviving by way of the underground drug testing economy.

## **Few willing unless paid**

Few people are willing to test the safety of new drugs in phase one trials unless they are paid for it. This is in part because it is no picnic. One must have time to be in a research unit for a prolonged period, be willing to take untested drugs, and submit to all the invasive procedures that go along with these studies.

Who is willing to do that? College students, undocumented immigrants, unemployed people, homeless people, contract workers, guys just out of jail, and professional guinea pigs.

Thirty years ago, if a drug company wanted to do a trial, it had to come to a university, partly because it

needed academic expertise but also because that's where the subjects were.

Now that the industry has grown and is producing more drugs requiring more complicated studies, they need more subjects. They are bypassing universities. Fourteen years ago, two of three studies were in universities. Now, three of four are in the private sector.

## **Former Holiday Inn**

The trial sites vary considerably—some good, some not so good. Until it was closed recently, the largest drug-testing site in the country, with 675 beds, was in Miami. Operated by SFBC International, it was located in a former Holiday Inn that Miami-Dade County determined is unsafe for human habitation and should be demolished.

What led to its demise? A report in *Bloomberg Markets* magazine found that SFBC was testing drugs on poor undocumented immigrants from Latin America and the Caribbean. The medical director did not have a medical license. It obtained ethics approval from a commercial IRB owned by the wife of the company's vice president.

## **Keeping payment low**

We have traditionally sought to keep payments low for people participating in drug trials, largely because we feared that paying too much would tempt subjects into joining trials that might be risky. Too much money might compromise their informed consent. People living in desperate financial situations could be persuaded to participate in almost any study no matter how dangerous.

What we've done by allowing some, but not much, payment is to make sure that only the poorest and most desperate people will participate. It's not worthwhile for the ordinary middle-class white

*Fourteen years ago, two of three studies were in universities. Now, three of four are in the private sector.*

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## Drug trials *(Continued from page 9)*

American to do a phase one trial. But if you're an illegal immigrant with no work permit, it sounds like a good deal. That's exploitation. We are using the poor to test a drug that they will never get.

Further, while IRBs sometimes think that subjects could be paid too much and ask that the payment be

lowered, IRBs do not ask if investigators are paid too much. They do not ask whether the money investigators are making in drug trials might tempt them to enroll patients in studies when it is not in the patient's best interest.

(Carl Elliott is a professor in the Center for Bioethics and the Departments of Pediatrics and Philosophy at the University of Minnesota.) $\Delta$

## DOE expands role of Central IRB

Central Beryllium IRB adds Former Worker Medical Screening Program; name changes to Central DOE IRB



Elizabeth White

Human subjects research is conducted at multiple DOE sites, and each either has its own site IRB or contracts with another DOE site IRB or an outside (university) IRB to serve as the IRB of record.

*by Elizabeth White, DOE  
Human Subjects Protection  
Program Manager*

Additionally, in 2001 DOE, under the leadership of human subjects protection program manager Susan Rose, established a Central Beryllium IRB (CBeIRB) to bring expertise and consistency to the review of DOE-funded and conducted beryllium-related human subjects research and medical screening.

The CBeIRB is funded jointly by the DOE Office of Science and the DOE Office of Health, Safety, and Security. It has been tremendously successful in ensuring that the studies develop and use informational materials and consent forms that provide clear, accurate information about chronic beryllium disease.

The same effort is made to provide information about the benefits and risks of participating in screening (given that the beryllium sensitization test is not a very good predictor of who will develop the disease) and about the availability of follow-up medical screening and compensation for those who do.

Beginning in January 2010, DOE will expand the scope of the CBeIRB. It will also serve as the IRB of record for the entire Former Worker Medical Screening Program (FWP). David Wehrly is chair of the CBeIRB and will continue in that role with the Central DOE IRB (CDOEIRB).

To date, the DOE site IRBs have reviewed all but the beryllium sensitization screening portion of the

protocols and consent forms for ongoing FWP projects serving former workers from their sites. Now, in an effort to streamline the review process, DOE will not require that its site IRBs conduct a separate review of the non-beryllium-related portion.

The CDOEIRB will, however, ensure that the site IRBs receive copies (via IRBNet) of all materials submitted by principal investigators for initial and continuing reviews, as well as letters sent by the IRB to investigators following the reviews.

Because of this change in scope, it will be important to expand membership in the CDOEIRB, which currently includes experts in occupational medicine, industrial hygiene, immunology, bioethics, epidemiology, and public health, as well as two community members.

The number of representatives from DOE site IRBs on the CDOEIRB will be increased, as will the number of DOE worker representatives. Additionally, representatives from the FWP screening provider organization(s) and an expert in the protection of personally identifiable information will be added.

It is also anticipated that the scope of the CDOEIRB will be expanded in the future to include topics such as nanotechnology-related human subjects research and other research that presents challenges for multiple DOE sites. $\Delta$



David Wehrly,  
M.D., IRB chair

# Innovative programs

*African Americans often mistrust the research community because of their experience with neglect and abuse. In Pittsburgh, that is beginning to change.*



Stephen Thomas

*by Stephen Thomas,  
Graduate School of Public Health,  
University of Pittsburgh -*

We have made great progress in improving the health of the American people over the last 50 years, but not everyone has benefited, especially racial and ethnic minority populations.

I believe that racial and ethnic health disparities are both scientifically and morally unacceptable. For this reason, the mission of our Center for Minority Health at the University of Pittsburgh is to eliminate racial and ethnic health disparities by implementing community-based health promotion and disease

prevention interventions for African Americans at risk for preventable chronic disease.

**Closing the gap**

Compared to whites, higher disease rates in blacks in the United States are persistent over time. Disparities between the health status of African Americans and whites are well documented in my city of Pittsburgh.

For example, diabetes death rates for African American females and males are nearly two times white rates. In addition, Pittsburgh has the highest

rate in the nation of African Americans progressing to end-stage renal disease, according to the 2008 report from the U.S. Renal Data System.

These and other facts guided our vision to build a community-based infrastructure focused on closing the racial gap that has been apparent since the first collection of epidemiological trends for morbidity and mortality in the United States. We know now more than ever about how to prevent chronic disease. Now is the time to take action to improve the health of racial and ethnic minority populations.

*I believe that racial and ethnic health disparities are both scientifically and morally unacceptable.*

**Beyond the biomedical model**

To eliminate health disparities we must move beyond the biomedical model with its focus on organ systems and biological pathways. We must also gain a better understanding of the social context that fuels the disparities.

The aim must be to find the cultural and environmental factors that lie beyond the biomedical model. These include breaking the cycle of poverty, increasing access to quality medical care, eliminating environmental hazards

in homes and neighborhoods, and implementing effective prevention programs tailored to specific community needs.

We must also recognize that when we enter the African American community, the burdens of race and history must be confronted.

Because of the historic inequalities in the health care system, many African Americans may delay seeking care. Additionally, their beliefs about health and illness have been shaped by the experience of discrimination, which will also influence the black community's response to public health methods designed to improve their health. This is the context in which "trust" matters.

**Cultural memory**

African American distrust of the medical care and research establishment is well documented. Some of these challenges result from the cultural memory passed on by word of mouth that makes people wary of us when we go into a community and say we're from the university and we're here to help. That's the same thing people working in the Tuskegee study said. As a result, when in 1991 the Centers for Disease Control and other agencies were disseminating information about AIDS prevention, people in these

*The aim must be to find the cultural and environmental factors that lie beyond the biomedical model.*

*(Continued on next page)*

## Innovative programs

(Continued from page 11)

communities did not believe them even though these communities were suffering disproportionately.

### **Anthrax scare**

Similarly, during the anthrax scare a few years ago, black postal workers saw themselves as lab rats. They feared the government was using them in an experiment and wondered if it was another Tuskegee — now a metaphor for the abuse of science.

It was out of the ashes of Tuskegee that we reinvigorated our human subjects protections, balancing autonomy, beneficence, and justice with informed consent and confidentiality.

At the University of Pittsburgh, we have laid a foundation for trust by increasing the participation of African Americans in research as a result of several initiatives.

One was that we turned around the federal government's "Take a loved one to the doctor day" and made it "Take a health professional to the people day," which we've held for seven years.

In 2008 we had 250 health professionals stationed in 10 community barbershops who screened 700 people in one day. We also have created grants for training people to work in barbershops to do screenings, including the use of nurse practitioners to perform prostate screenings and other services.

### **Can barbers have more credibility than doctors?**

It is an example of what can be done if you reach people in their settings. A barber sometimes can have more credibility in this community than a doctor. We have done things such as bringing echocardiograms on laptops into the barbershops and establishing programs to reduce the onset of type 2 diabetes.

Our Healthy Black Family Project (HBFP) has enrolled 7000 people in a program giving them free access to the university's health facilities, which has created a sense of family for them. They spend the day there, going to yoga classes, body toning, water aerobics, and other activities.

So we are bringing the science of public health into the communities, and one of the results is that we have been able to embed our clinical trials into the effort. When trials conclude, people do not feel abandoned because they realize this is an ongoing process of which we are all a part. They realize that they are working with health professionals inter-

ested in improving their health for their health's sake, not just in completing a clinical trial.

This has also allowed us to establish a Community Research Advisory Board (CRAB). It is not an IRB or a regulatory body.

It is a forum for building relationships so that we could overcome the far-too-common label "drive-by research."

CRAB began in response to demands from the black community and increasing pressure on investigators to establish advisory boards.

### **Permanent board**

Rather than re-creating a group each time another study was proposed, we wanted a permanent board consisting of university faculty and community stakeholders. It serves the university research community across all the schools of the health sciences.

Among other things, we have been able to allay concerns in the African American community that signing a consent form is not akin to signing away their rights.

### **Diversity in research teams**

We have also sought to diversify the research teams so that they are not all white, and we require the principal investigator to attend meetings so that questions can be asked.

Among the most productive results of CRAB is that the board is now identifying problems in the community that should be addressed with research.

This solution created in Pittsburgh is very fragile, but I have hope.Δ

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### *Protecting Human Subjects E-version*

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](mailto:humansubjects@science.doe.gov).

# Social sciences and behavioral studies

*The way forward to resolve issues about IRB review is with flexibility, so that the relationship between investigator and reviewer is collaborative*



Andre Ivanoff

*by Andre Ivanoff, Columbia University -*

Much ferment exists around the difficulties, tensions, and adversarial relations between investigators and IRBs, especially in the social sciences and behavioral disciplines.

Recently, the oral history group designated its methodology as separate and distinct, specifying rules for exemption from the IRB process.

To begin working toward resolution of these issues, I outline several approaches to how the relationship between investigators and reviewers may function, and then I suggest some ways this relationship might be more productive.

### **Top-down approach**

The first is the top-down approach: Let the feds handle it by changing the regulations.

The feds would determine whether there should be specific regulations for social sciences and whether to change the definitions of risk and vulnerability.

Should we reduce local or idiosyncratic interpretations so that IRB decisions are standardized? Should we reduce the flexibility and interpretative power IRBs have? Should we thwart mission creep by clearly prescribing the activities of IRBs?

### **Revel in idiosyncracies**

The second approach is bottom up: Start at home.

In this, investigators should learn to revel in the idiosyncracies and flexibility their IRB possesses. It's a strength that allows us to develop personalized IRBs that address particular concerns of this community of researchers and the research they are trying to carry out.

Should we be inviting, if not mandating, investigators to come to the table and have face-to-face, direct interaction with their boards?

### **Historical approach**

The third approach is historical: Remove social sciences from consideration. When these regulations were established, the social sciences were not considered, a soon-to-be published article suggests. The regulations were written to deal with biomedical issues.

Another approach is evidence based. Three years ago a survey of 866 researchers revealed the top four things scientists wanted from their IRBs: timely review, personal biases to stay out of protocol evaluation, a balance between protecting human subjects and facilitating research, and IRB autonomy that protects against nonscientific issues suppressing scientific research.

### **Openness and objectivity**

In my language, timeliness means that you are there to respond to the needs of investigators. Withholding personal bias means openness and objectivity. Balance is upholding subjects' rights while facilitating research.

But there is a missing quality here—willingness. It is the willingness to use data when available to support our decisions and to listen to investigators present the data.

It is also the willingness to use local discretion to serve subjects and science, that is, to look at the relationship as a collaboration. This might mean using different recruitment procedures useful for a particular setting or obtaining expert consultants

*Regulations were written to deal with biomedical, not social-science and behavioral issues.*

*A survey of 866 researchers indicated the top four things scientists wanted from their IRBs.*

*(Continued on next page)*

## Ivanoff: Social sciences and behavioral studies

(Continued from page 13)

when needed. In some cases there is a huge reluctance to do that.

### **No one-size-fits-all**

Finally, IRBs must use function to determine need. There is no one-size-fits-all. Every IRB has its own issues with investigators, and there are specific issues in different kinds of institutions.

For example, certain issues present themselves in large institutions quite differently than in small institutions. One is resources for staffing to enhance the capacity to do timely review, such as meeting

over the summer when researchers have time away from teaching.

Another is to provide resources to recruit and sustain skilled board members so that we have qualified researchers to review protocols.

Especially important is the ability of an IRB to function autonomously, away from the pressures that come from nonscientific or administrative factions.

And when all else fails, there must be the capacity and procedures for an appeals process.Δ

## News notes

### ■ Holocaust Museum focuses on implications for informed consent

The continuing impact of the Nuremberg Code is illustrated in exhibits and Web sites at the United States Holocaust Memorial Museum in Washington, D.C.

The museum's Web site (<http://www.ushmm.org/museum/exhibit/focus/aftermath>) examines the development of principles of informed consent that resulted from

the Holocaust and the subsequent Nuremberg trials.

On-line exhibitions include *The Doctors Trial* (<http://www.ushmm.org/research/doctors/>) and *Deadly Medicine: Creating the Master Race* (<http://www.ushmm.org/museum/exhibit/online/deadlymedicine/>).

### ■ Updating DOE's HS database

The DOE Human Subjects Research Database (HSRD) is being modified to include more information about the extra work done by IRBs.

The next report will include numbers of exempt protocols along with numbers of inquiries about whether projects should be submitted to an IRB, are exempt, or require complete review.

HSRD includes all research projects involving human subjects that 1) are funded by the DOE, 2) are conducted in DOE facilities and performed by DOE or contractor personnel, or 3) use DOE workers as subjects.

### ■ *Protecting Human Subjects* wins award of excellence

The newsletter *Protecting Human Subjects* has received an "Award of Excellence" from the Society of Technical Communications (STC) Middle Tennessee Chapter.

The award was for the Periodicals category in the 2008–2009 Annual Technical Publications and Online Communication Competition. The newsletter is prepared at Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Department of Energy.

# Research in the developing world

Peter Lurie: *This is an example of why we should not change scientific standards when we move from one part of the world to another*



Peter Lurie

Research in the developing world increased dramatically between 1980 and 1998, creating important questions about exploitation and appropriate methods of research with human subjects.

One of these questions is whether it is ethical to undertake placebo-controlled trials for new drugs when effective existing treatments are available. Is this a form of unacceptable exploitation?

## **Trial designs**

There are different ways to structure randomized trials. One is a superiority trial, employed when the question is “is A better than B,” a special form of which is when B is a placebo.

A second form is a non-inferiority or equivalency trial, which determines whether a new treatment is not too much inferior to the existing treatments.

Clinical trialists also use the term active controlled trial, which is any trial (superiority or non-inferiority) that compares one or more interventions but does not use a placebo.

An example of the issues involved here regarding placebo controls occurred at a U.S.-based laboratory that proposed to test a surfactant it developed.

Surfactants reduce surface tension, especially in premature neonates with difficulty

expanding their lungs. Surfactants allow them to breathe properly.

Four surfactants have been approved in the United States. The approval of one was based upon an active controlled trial. The products have reduced neonatal mortality by 34%, which is extraordinary effectiveness. Placebo-controlled trials on surfactants would therefore be unethical in the United

States, according to internal Food and Drug Administration (FDA) documents.

## **Resisted by FDA**

In developing its new product, one option was a non-inferiority trial, but this was resisted by the FDA. That left the company with the option of superiority or placebo trials. They may have been reluctant to perform superiority trials because of fears that such trials would not demonstrate that their product is superior to others. But the placebo-controlled trial would not be considered ethical here.

The lab therefore proposed a placebo-controlled trial in Latin America. They could not do this study in the most sophisticated Latin American institutions because patients there would tend to be more affluent and hence may already have been receiving surfactants. Neither could they do trials in a completely deprived area with little available medical, making it difficult to upgrade services to include intensive care units and ventilatory support. They needed mid-level hospitals, where there is care but the patients tend to be less affluent.

## **Turning back the clock**

In fact, no one had conducted a placebo-controlled surfactant study in the previous five years; all had been active controlled. Thus, the company was trying to turn back the ethical clock.

The proposal was rejected after Public Citizen objected to the placebo design. The study was conducted as a superiority trial in both developed and developing countries.

The company claims that the trial demonstrated superiority to one of the approved surfactants, but it has yet to reach the market. This case demonstrates how researchers planned to exploit the inequitable distribution of wealth. It is an example of why we should not change scientific standards when we move from one part of the world to another.

If we change standards, we could unjustly open up the developing world to studies such as the one this company proposed.Δ

*The FDA says that placebo-controlled trials on surfactants would be unethical.*

*This is a summary of a longer presentation by Peter Lurie at the Advancing Ethical Research Conference in Orlando, Fall 2008. -*

## Report questions globalizing clinical trials

*Duke researchers cite potential for exploitation and whether data can be extrapolated to other settings*

Duke University researchers have completed a large study analyzing the ethical and scientific consequences of globalizing clinical trials.

The report, published in *The New England Journal of Medicine* (vol. 360: 816–823, no. 8, 2-19-2009), expresses concern about conducting studies outside the U.S., especially in underdeveloped countries, for new drugs that require approval by the U.S. Food and Drug Administration (FDA).

Among other concerns, the investigators question the practice of using money and free medical care as incentives, suggesting that in some circumstances this may be coercive.

### **Who benefits?**

The report, "Ethical and Scientific Implications of the Globalization of Clinical Research," says that globalization of trials by pharmaceutical and device companies is a phenomenon that "raises important questions about the economics and ethics of clinical research and the translation of trial results to clinical practice: Who benefits from the globalization of clinical trials? What is the potential for exploitation of research subjects? Are trial results accurate and valid, and can they be extrapolated to other settings?"

They found that about a third (157 of 509) of FDA-regulated trials for the 20 largest U.S.-based pharmaceutical companies are conducted outside the country and that a majority of study sites (13,521 of 24,206) are outside the country.

### **Risks**

The risks they cite include "Wide disparities in education, economic and social standing, and health care systems may jeopardize the rights of research participants.

"There may be a relative lack of understanding of both the investigational nature of therapeutic products and the use of placebo groups. In some places, financial compensation for research participation may exceed participants' annual wages, and participation in a clinical trial may provide the only access to care for persons with the condition under study.

"Standards of health care in developing countries may also allow ethically problematic study

designs or trials that would not be allowed in wealthier countries.

"In one study, only 56% of the 670 researchers surveyed in developing countries reported that their research had been reviewed by a local institutional review board or health ministry.

"In another study, 90% of published clinical trials conducted in China in 2004 did not report ethical review of the protocol and only 18% adequately discussed informed consent."

### **Conclusions**

Among the conclusions drawn by the authors was that "Improved international collaboration among academic investigators would increase the quality of multinational trials.

"Investigators in developing countries would benefit from rigorous training in the design, conduct, and ethical oversight of trials, which would allow them to engage more fully in multinational clinical research at a leadership level.

"These programs could be structured as courses of study in either residence or distance offerings through academic institutions and jointly funded by industry and clinical research organizations. . . . An international mechanism for tracking investigators who are trained through such programs or, conversely, who have been prohibited from conducting clinical studies is needed."

The full-text PDF of the report is at <http://content.nejm.org/cgi/content/full/360/8/816>

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# Inviting researchers to IRB meetings

The benefits of goodwill, effectiveness, and faster reviews outweigh the logistical and scheduling difficulties



Laura Stark

by Laura Stark, National Institutes of Health

As every researcher and administrator knows, there are serious logistical and scheduling difficulties involved in inviting investigators to IRB meetings where their protocols are being reviewed. The benefits of doing so, however, are immense.

Presently, only about 9% of IRBs in the U.S. invite researchers to attend meetings. While in the past the number has been higher, it has always been low. In 1978 about a quarter of IRBs invited researchers to meetings, and in 1998 about a third of boards did so.

*One clinical-IRB member called this the peanut butter and jelly test.*

After that time, the practice declined in part because of concerns related to conflicts of interest. Having investigators at IRB meetings was also thought to make board members less open, discouraging them from criticizing studies and developing useful suggestions for how researchers should modify proposals. Now that many IRBs are in the habit of meeting without investigators, it has become routine.

My research as a sociologist, ethnographer, and historian at the National Institutes of Health has focused on the social history and practices of IRBs. My goal has been to understand and improve the review process by studying IRBs from the inside to see how the groups actually work.

Based on my observations of IRB meetings and my analysis of meeting transcripts, I advocate that IRBs do everything they can to encourage investigators to attend meetings. For their part, I urge researchers to make IRB meetings a priority in their schedules. In the long run, it pays off.

## **Reduces mistaken impressions**

I encourage IRB members and investigators to talk face-to-face because, my research shows, they tend to communicate more effectively and efficiently in person. It reduces mistaken impressions and, as a result, it also enhances goodwill. Talking in person makes reviews faster in the long term, although it might require more time in the short term.

I observed the meetings of three IRBs for one year and I was interested in answering the question, what sorts of things do board members actually take into account when deciding whether a protocol is good or bad?

I found four basic considerations. The first was whether the research was valid. The second was whether the subjects were adequately informed. And the third was whether the researcher was following the nuts-and-bolts of regulations. These first three considerations were not very surprising.

## **Indispensable part**

The fourth consideration that IRB members took into account was fascinating. I call it “housekeeping work.” This included the paper-oriented tasks of correcting typos, noting formatting problems, and marking other details that one could argue will not affect the study’s outcome.

Housekeeping work is not very exciting, but for IRB members I observed it was very important. They took this to be an indispensable part of their work because it allowed them to evaluate how careful the researcher is in general.

For example, one clinician-IRB member I interviewed described what he called his peanut-butter-and-jelly test. When he looked at a submission, he noticed whether the investigator was careful enough to make sure the documents were clean and well cared for, and more importantly, whether the researcher was thorough enough to be sure words were spelled correctly and equations were accurate.

As he put it, if there is a misspelled word in the protocol, it makes him wonder whether the PI might also get a decimal point in the wrong place—making the doses incorrect. Through housekeeping work,

*(Continued on next page)*

## Inviting researchers

(Continued from page 17)

IRB members like him developed their first impressions of investigators, whether these impressions were fair or not.

### **Housekeeping work has real consequences**

Another board member told me that if the proposal were exceptionally sloppy, there would be more questions about the protocol and a higher likelihood that the board would audit that study. In her experience the IRB was more cautious with submissions that included factual errors and typos. In other words, they would question the character and ability of the researchers based on the appearance of the paperwork.

Conversely, investigators who attend the meetings are able to put to rest such concerns. This is why it is essential that investigators attend meetings. When investigators were at meetings, IRB members could engage and judge the researchers directly, rather than use housekeeping work as a proxy for their competence and conscientiousness.

When magnified throughout the IRB system, there are real advantages to having investigators routinely attend meetings.

A recent study by Taylor, Currie, and Kass (<http://www.thehastingscenter.org/Publications/IRB/Detail.aspx?id=930>) shows that when investigators attended meetings, IRBs' time to approval was shortened, the number of letters and emails was reduced, and the number of meetings before approval was cut.

My research explains why this is the case: IRB members do not have to give housekeeping work undue weight if they can talk through legitimate questions with the researcher.

Finally, the face-to-face conversations in meetings that I observed gave the IRB deliberations a different, more positive tenor. It is no secret that researchers can sometimes approach IRBs antagonistically. Talking in person was a productive way for boards to humanize the review process—and to improve their relationships with the research community.Δ

## New bioethics book available free online

*Hastings Center publication includes 36 comprehensive overviews of current issues*

A new bioethics book from The Hastings Center is available online for free.

*From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns* contains 36 overviews of issues.

It is at <http://www.thehastingscenter.org/Publications/BriefingBook/Default.aspx>.

The chapters are written by well-known ethicists such as Daniel Callahan, Bonnie Steinbock, Arthur Caplan, Timothy Quill, Wylie Burke, Thomas Murray, and others.

It includes two appendixes. One provides presidential campaign positions from 2008 on issues in bioethics. The second is a comprehensive overview of pending and recent legislation related to bioethics. The book includes a history of bioethics and policy as well as a section providing a journalist's perspective on why bioethics matters today, written by Nancy Gibbs, Editor-at-large, *TIME* magazine. Chapters include, among many other topics:

- Assisted Reproduction
- Biobanks: DNA and Research
- Clinical Trials
- Cloning
- Conflict of Interest in Biomedical Research
- Disaster Planning and Public Health
- Enhancing Humans
- Environment and Health
- Gene Patents
- Genetic Testing & Screening
- Health Care Reform
- Medical Error
- Multinational Research
- Nanotechnology
- Personalized Medicine & Genomics
- Physician Assisted Death

# Alternatives to conflict in the review process

Sources of problems between IRBs and investigators vary, and the solutions are worth learning



Hannah Rothstein

*by Hannah Rothstein,  
Baruch College of The  
City University of New York*

For most of us, conflict is an all-too-common occurrence in an IRB. Based on my experience, I would like to offer some practical advice on ways to handle conflict so that it yields win-win solutions for the parties involved.

There are many sources of conflict when it comes to IRBs and their constituencies. One major source is role-based differences in perceptions. Think about how your own perspective changes when you switch from the pedestrian role (drivers are crazy!) to that of the driver (why do those pedestrians cross so slowly?). Sometimes I joke that we could re-enact the

*The last thing you want to be is an IRB that resembles the Wizard of Oz, operating behind a curtain, issuing commands.*

Zimbaro prison experiment ([www.prisonexp.org](http://www.prisonexp.org)) by randomly assigning some of us the role of principal investigator (PI) and others the role of IRB member. I wonder how long it would be before we would have to shut down the experiment?

Roles establish our perspective; keep the person, change the role, and the perspective changes. That is why I like to bring in productive PIs to serve on the IRB, so that they can see things from both the IRB and researcher perspectives.

Another source of conflict is differences in goals, objectives, or priorities. The researcher wants to move the process along as quickly as possible; the IRB wants sufficient time to do a thorough review. Another source is personality differences.

These are all complicated by the fact that many decisions made by the IRB are judgment calls about which reasonable people can disagree.

While there may be conflicts within the board itself and between the board and institutional administrators, the number one conflict is between the PI and board members.

Each side thinks they are right and the other wrong, they're knowledgeable and the other is ignorant. This can create an "us versus them" battle in which it is all too easy to blame, belittle, ridicule, insult, threaten the other side, and get defensive.

### **Alternatives**

However, there are alternatives, such as these:

- Remember that you have shared goals based in the fundamental reasons IRBs were established, which is to protect human participants, researchers, and institutions.
- Take a collaborative, rather than confrontational, approach.
- Emphasize transparency. On our board, we make publicly available the criteria we use to evaluate protocols. We also provide constructive feedback that explains why we are asking for revisions and include targeted suggestions for how to fix things.
- Separate people from the problem. Instead of viewing the other as your opponent, view them as your partner in facing a common problem.
- Determine the relevant facts. Often, conflicts are generated by misperceptions of facts. When information is missing, discussions go askew. If you sort out facts from opinions and get all the facts, common ground can more easily be reached.
- Focus on interests rather than positions. A position is something you want. An interest is why you want something. A position is "This has to be approved by Thursday." The underlying interest is that the granting agency will not release funds unless I have IRB approval by Thursday.
- Create transparency. IRBs should go out into the research community, conduct workshops, invite investigators to meetings. The last thing you want to do is be an IRB that resembles the Wizard of Oz, operating behind a curtain, issuing commands. If you invite people in and listen to them, it will facilitate better working relationships.Δ

## News notes

### ■ DOE holds spring workshop in D.C. for its Human Subjects Working Group

DOE's spring workshop focused on continuous improvement, including 1) implementation of QA/QC programs at each DOE site to monitor ongoing projects, especially those that are high risk or of particular concern to the IRBs, between annual IRB reviews; 2) the IRBs' roles in ensuring that principal investigators protect personally identifiable information;

3) training and succession planning for the IRB chair and members; and 4) the expansion of the Central Beryllium IRB. Additionally, Julie Kaneshiro, Policy Team Leader at OHRP, spoke to the group about OHRP's new policy and guidance, including guidance on the implications of the new Genetic Information Nondiscrimination Act (GINA) on human subjects research.



Plaques for exemplary service to the DOE Human Subjects Protection Program were awarded to Terry Reser, in the photo at left, Administrator of the Human Studies Board at Sandia National Laboratories, and Peter Kirchner, M.D., in the photo on the right, Senior Medical Advisor in DOE's Office of Science. The awards were presented during DOE's Human Subjects Working Group Workshop, May 6, 2009, by Sharlene Weatherwax, Director, Biological Systems Sciences Division, DOE Office of Science.



Peter Kirchner, left, who will be retiring from DOE in September 2009, received a gift from members during its May workshop in Georgetown. Charles Pietri, center, and Terry Reser, right, made the presentation.

### ■ OHRP adds Subpart E to 45 CFR 46 concerning IRB registration with HHS

IRBs will be required to register with the U.S. Department of Health and Human Services (HHS), according to a new requirement from the Office for Human Research Protections (OHRP).

Effective July 14, 2009, the rule is in a new Subpart E to the HHS protection of human subjects regulations (45 CFR 46). The requirements will make it easier for OHRP to convey information to IRBs and will support the current IRB registration system operated by OHRP.

Under this final rule, the IRB registration system will be compatible with the IRB registration requirements of the Food and Drug Administration (FDA). Initial registration with all required information must be submitted

within 60 days of the effective date of the rule, by September 14, 2009.

For any IRB currently registered with OHRP, the institution or organization operating the IRB must submit all information required under this rule by the three-year expiration date previously assigned by OHRP or within 90 days of any changes regarding the contact person who provided the IRB registration information or the IRB chairperson.

The final rule is at <http://edocket.access.gpo.gov/2009/E9-588.htm>. The FDA's IRB registration final rule can be accessed at <http://edocket.access.gpo.gov/2009/E9-682.htm>.

## Pritchard: Rule flexibility

(Continued from page 3)

societies being studied? Again, is such research ethical, and do the current regulations allow it?

Third, the Johns Hopkins Keystone Project raises a wider issue regarding waivers of informed consent of the human research subjects in quality improvement research activities involving organizational procedures.

*The Keystone Project raises wider issues regarding waivers of consent.*

Some have argued that such studies should not require the informed consent of either health-care employees or patients; rather, employees are obliged to participate because they work at an institution whose mission is to improve health care, and patients are obliged to participate because they reap the benefits of the application of previous

research to the existing quality of care they receive. Is it ethical to waive informed consent for all such studies, and do the current regulations allow it?

### **Does beneficence trump respect?**

How can disputes be resolved concerning whether the existing rules are too inflexible in the context of the evolving research enterprise? One familiar strategy is to appeal to a higher principle. In contemporary American research ethics, the standard approach is to consider the **Belmont Report's** three principles of respect for persons, beneficence, and justice.

In the quality improvement research debate, one side is arguing that the principle of beneficence with its interest in increasing benefits should overrule the principle of respect for persons with its interest in preserving individual autonomy.

But to simply assert that one ethical principle is more compelling is an arbitrary assertion of preference. To be justified, such assertions require cogent explanations as to why one principle should carry more weight than it does in the current regulations. Of course, the current regulations also represent a fundamentally arbitrary compromise between the same principles.

Without a compelling justification for the current compromise, the current compromise may be no better than its rival, other than the fact that it represents the traditional consensus.

The quality improvement controversy also raises an important empirical question for research ethics and the system for the oversight of human subject protections. The Keystone Project reflects a hypothesis about how organizational culture influences individual decision-making within organizations.

The Keystone Project tested the hypothesis that deliberately changing the ICU's organizational culture by introducing measures to encourage the staff to behave in a more rule-governed way would lead to better health-care delivery outcomes. The project's success was attributable to the organizational decision to constrain the professional autonomy of staff health-care behavior.

The same hypothesis may also apply to human research protection program operations. Perhaps more consistent reliance upon adherence to a more extensive set of rules by IRBs and human protection programs would improve their operation. Like the Keystone Project's ICUs, managing the organizational culture of IRBs and human research protection programs might improve IRB review outcomes.

### **Remember Milgram & Zimbardo**

While the Keystone Project demonstrated the value of following rules in specific circumstances, it did not show that mechanical adherence to rules always achieves the best results. If human subject protection programs adopt this approach, they will have to determine when and how this approach produces not only greater uniformity in practice but also better practices, and where attaining greater efficiency carries with it significant costs. The exploration of this general approach should also keep in mind a lesson from the research tradition of Milgram and Zimbardo, who found that ordinary people are

*Should some studies not require consent of employees or patients?*

(Continued on next page)

## Pritchard: *Rule flexibility* (Continued from page 21)

prone to unethical behavior when they see themselves as simply “following the rules.”

### **Defy the regulations?**

Should people ever defy the regulations? Our rules and ethical principles reflect our best judgment to date about the right ways to behave towards one another. But progress is possible, implying that today’s best rules are still flawed and that those flaws may become increasingly problematic. The flaws should be identified, and the authorities should be petitioned to change them.

If the rules are not changed, and they direct people to behave unethically, then people may—or even should—disobey them. If they do so openly, then their actions will challenge the authorities to respond appropriately. This view of legitimate civil disobedience was offered long ago in Socrates’ *Crito* and also famously in King’s *Letter from a Birmingham Jail*.

When people defy the rules and principles, how should regulators respond? When noncompliance occurs and regulators demand corrective action, the regulators are affirming that the regulations still provide legitimate protections for human subjects. If the noncompliance occurs due to confusion, the regulators should determine if the confusion derives from poorly written regulations or policy guidance, and adjust their response accordingly; regulators should only hold people responsible for following

the rules if what the rules say is reasonably clear.

If the rules are clear but do not support the ethical treatment of human subjects, then the regulators should exercise the flexibility provided by enforcement discretion to avoid discouraging ethical behavior by investigators and IRBs. And the regulators should pursue regulatory reform.

Finally, in this conference’s discussions about guidelines, codes, regulations, and principles, and about flexibility and balance, we should not lose sight of why these discussions are so important: We’re talking about how people—including friends and children, as well as strangers—deserve to be treated when they serve society as subjects in research. The imperative to treat them ethically is not just a guideline.Δ

*We should not lose sight of why these discussions are so important: We’re talking about how people deserve to be treated as subjects in research.*

## News notes

### ■ New text-searching tool, eTBLAST, designed to find plagiarism in scientific articles

A new tool designed to spot plagiarism in scientific publications has been developed by researchers at the University of Texas Southwestern Medical Center.

The computer-based text-searching tool, called eTBLAST, was used to analyze millions of articles randomly selected from Medline, a database of biomedical research articles. It found nearly 70,000 highly similar citations.

A sample analysis identified 207 pairs of articles that suggested potential plagiarism.

The developers of eTBLAST reported their findings in the March 6 issue of *Science*. They also described the reaction when they sent their results to authors

of the original articles as well as those who seemed to have plagiarized from the original articles.

“Although our goal was merely to solicit information, our questionnaire triggered 83 internal investigations by editors, 46 of which have led to retraction,” said Harold “Skip” Garner, professor of biochemistry and internal medicine at UT Southwestern and senior author of the *Science* article.

“As it becomes more widely known that there are tools such as eTBLAST available, and that journal editors and others can use it to look at papers during the submission process, we hope to see the numbers of potentially unethical duplications diminish considerably.”

# Meetings

## ■ VIII Brazilian Congress of Bioethics

September 23–26, 2009.

*Hotel Atlantico Buzios Convention & Resort, Buzios, Rio de Janeiro.*

For information, see [www.congressodebioetica2009.com.br](http://www.congressodebioetica2009.com.br)

**Contact:** Roberta Braz at [roberta@rsvpress.com.br](mailto:roberta@rsvpress.com.br)

## ■ American Society for Bioethics and Humanities 11th Annual Meeting

October 15–18, 2009.

*Hyatt Regency Capitol Hill, Washington, D.C.*

For information, see <http://www.asbh.org/meetings/annual/index.html>

**Contact:** [program\\_committee@asbh.org](mailto:program_committee@asbh.org)

## ■ 2009 Advancing Ethical Research Conference

November 14–16, 2009.

*Gaylord Opryland Resort & Convention Center, Nashville, Tennessee*

For information, see <http://www.primr.org/Conferences.aspx?id=5917>

**Contact:** [info@primr.org](mailto:info@primr.org)



## 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., Senior Medical Advisor

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### **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.

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# PROTECTING HUMAN SUBJECTS

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