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Evaluate conflicts of interest both among investigators and IRB members

More public scrutiny is paid to issue

Media attention on research conflicts of interest has made it imperative that IRBs be aware of a wider variety of potential conflicts of interest than what they may have considered in the past, experts say.

Recently, a study published in the *New England Journal of Medicine* (NEJM) highlighted issues with IRB members having relationships with pharmaceutical companies, notes **Heather Fields, JD**, a shareholder in the health care department of Reinhart Boerner Van Deuren in Milwaukee. Fields spoke about conflict of interest issues at the 2006 annual Human Research Protection Program Conference of the Public Responsibility in Medicine & Research (PRIM&R), held Nov. 15-18, 2006, in Washington, DC.

One of the challenges IRBs face in managing conflicts is that often IRB members also serve as researchers or have other ties to the research industry.

It would be difficult for many IRBs to make quorum if they were required to find only IRB members who lacked all ties to the research industry, says **Elizabeth Bankert, MA**, assistant provost, Dartmouth College in Hanover, NH. Bankert also spoke at the PRIM&R conference about conflicts of interest.

Fields and Bankert discuss various aspects of conflicts of interest relevant to an IRB with these examples:

- **Conflicts of interest among IRB members:** Often the individuals most qualified to serve as IRB members are researchers, and they are typically obligated to disclose only those conflicts of interest pertaining to protocols with which they are directly involved, Fields says.

"There is a lack of federal guidance for addressing and managing IRB conflicts of interest," Fields says. "There are guidelines and standards for investigators and the National Institutes of Health guidelines, but very little specific to IRB members."

When asked to disclose their conflicts of interest, IRB members think about the type of conflicts that would impact their ability to be impartial when reviewing a certain protocol, and often do not think about other industry financial ties that may create a conflict, she adds.

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The recent study in *NEJM* found that 36 percent of IRB members had one or more relationships with industry within the past year.¹

Of the nearly 900 IRB members surveyed from 100 academic institutions, 85.5 percent said they never thought that these types of relationships with industry affected an IRB member's protocol review decisions inappropriately.¹

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• Fax: (800) 284-3291 • E-mail: stephen.vance@ahcmedia.com
• Address: 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: **Suzanne Koziatek** and **Melinda Young**.
Senior Vice President/Group Publisher: **Brenda Mooney**,
(404) 262-5403, (brenda.mooney@ahcmedia.com).
Associate Publisher: **Lee Landenberger**,
(lee.landenberger@ahcmedia.com).
Managing Editor: **Leslie Hamlin**, (404) 262-5416,
(leslie.hamlin@ahcmedia.com).

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Editorial Questions

Questions or comments?
Call **Leslie Hamlin** at (404) 262-5416.

About 15 percent of those surveyed said they had reviewed a protocol within the past year that was sponsored by a company with which they had a relationship or with that company's competitor, and close to 60 percent of these IRB members said they always disclosed this relationship to an IRB official.¹

Of the IRB members who disclosed the potential conflict, nearly 65 percent said they never voted on the protocol.¹

The study concluded that relationships between IRB members and industry are common.¹

• **Conflicts of interest among investigators:** Most academic and research institutions do not require investigators to report conflicts of interest more than annually, and this annual reporting process may not be linked to the conflict reporting process that occurs at the time information is submitted for a grant or a protocol is submitted for IRB review, Fields notes.

"Many institutions have a separate conflict of interest committee to evaluate conflict disclosures provided in connection with an IRB submission," she says. "But, no universal standard exists with respect to disclosure thresholds, and institutions are increasingly aware that the federal disclosure requirements may create an inadequate reporting threshold to safeguard subjects and preserve the integrity of the IRB review process."

Larger organizations typically have some kind of organized process for medical staff members to report annually their financial interests. When the investigator submits a protocol to the IRB, he or she checks on the box for financial interests, and the conflict of interest committee reviews the conflicts of interest to decide whether the interest needs to be managed, Fields explains.

"Then the conflict of interest committee forms a management plan which is communicated to the IRB," she says. "It is typically the responsibility of the IRB to determine what language should go in the informed consent form regarding an investigators' relationship with the sponsor of the study."

The drawback to most policies is that they only require disclosure of financial conflicts of interest, Fields notes.

"Most institutions don't have a process to identify and track non-financial conflicts of interest, such as promotions and tenure dependent on a person having x number of papers to publish or family relationships, like having a husband on the head of a company's board," Fields says.

The Association of American Medical Colleges

has published guidelines suggesting that the informed consent form have some disclosure on it when the principal investigator has significant financial conflicts of interest, she adds.

A study of academic medical centers and their financial conflicts of interest policies found that 58 percent included verbatim language regarding conflicts of interest to be included in informed consent documents.²

The same study found three chief goals for disclosure of conflicts of interest, which are as follows:

1. Providing research participants information:

This goal is to give people sufficient disclosure to allow them to make an informed decision about participating in a trial.²

2. Meet regulatory/legal requirements:

Regulations do not require informed consent documents to disclose financial conflicts of interest, but there is precedent for investigators and institutions being sued when there is insufficient disclosure.²

3. Deter significant conflicts of interest:

Having a conflicts of interest policy requiring disclosure to research participants might discourage investigators from having conflicting interests.²

Another recent study found that research participants want to know about financial interests, but they do not always view them unfavorably.³

Some research participants said they felt a great financial interest would make the investigator do a better and more ethical job.³

• How IRBs can assess conflicts of interest:

“IRB members are so conscientious they sometimes won’t vote on a protocol if they’re unsure about their own conflict of interest,” Bankert says.

“They might say, ‘My son works for the company that provides the analysis of the x-rays for the study,’ and I tell them, ‘That is not a conflict,’” Bankert says.

Part of the problem is the ambiguity in federal regulations. For example, the FDA form that is completed when an investigational new drug is submitted for IRB review asks the investigator to list all of the people who might be part of the treatment team, Bankert explains.

“This could involve the whole oncology department if you’re a small place,” she says.

If all of the people listed were to recuse themselves from voting, there might be no oncology experts left on the IRB to review the protocol, Bankert adds. “So you can’t recuse everyone who is listed on the 1572 form,” she says.

It’s a challenge for institutions to come up

with a conflict of interest standard that works for all cases, Fields says.

“There’s no one-size-fits-all,” Fields notes.

When Fields visits research sites, she asks about additional conflicts of interest, including non-financial conflicts, such as family relationships, in order to see how sensitive an IRB is to the issue.

“I look to see if they have procedures in place to address various types of conflicts,” Fields explains. “And if they do, I look to see if they follow their standards.”

For example, at Dartmouth College the process is to remind IRB members at the beginning of the meeting: “Please recuse yourself if you have a potential conflict and leave the room when we vote,” Bankert says. “We have been working on guidance and have made some recent progress.”

One of the goals is to come up with a standard that doesn’t require IRB members to complete a disclosure form every time they meet, but to have clear guidance in place to remind members of the obligation to disclose potential conflicts of interest,” Bankert says.

“It’s something we’re all thinking about right now,” she says.

The lack of regulatory guidance on this issue means that each IRB and institution will have to find its own balance.

“You need people with the expertise and knowledge in the room to make decisions about studies, but at the same time you want a process that minimizes the potential for inappropriate bias,” Fields says. ■

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IRBs and discussions over commercial tissue banking

IRBs expertise makes them the go-to board for approval

Commercial tissue repositories looking for sources of human tissue, and hospitals that discard tissue from surgeries daily, could appear to be a match made in heaven.

But a hospital’s decision to enter into a rela-

tionship with a commercial repository is a complicated one — one that often draws in the IRB, with its existing experience with privacy and consent issues.

“There really wasn’t any other ethical board within the hospital that we felt had the expertise to review it ethically,” says **Jan Trott**, director of the Office of Research Affairs at Maine Medical Center, in Scarborough, ME, which began a collaboration with a commercial repository four years ago. “So the IRB took this on, even though it really didn’t fit the usual guidelines.”

Maine Medical Center’s experience not only resulted in a successful tissue banking program there, it led to an online guide to working with commercial tissue repositories, created by **Julien Murphy**, PhD, a professor of philosophy at the University of Southern Maine, in Portland, ME.

Murphy, who heads up the university’s Bioethics Project, also served on the medical center’s clinical ethics committee and is currently on the center’s tissue banking steering committee.

“As we worked on it, it occurred to a couple of us that if we were confronting this matter, then other hospitals were probably confronting it as well,” Murphy says. Her hope is that other IRBs will use the online guide as a resource when discussing similar collaborations at their own institutions.

“We wanted to do this so that every site that was approached wouldn’t be starting from scratch in trying to think about these issues,” she says.

A new kind of arrangement

Murphy says that in the early 2000s, when the medical center was approached, commercial companies were just beginning to try to enlist public and private hospitals to provide tissue samples for research.

“After the genome was mapped, genomic research was developing, and it appeared that there was a great need to make available to researchers large amounts of human tissue from a variety of different patients, primarily to determine different gene functions,” she says.

The companies thought that hospitals’ surgical departments, who were disposing of these types of tissue remnants every day, might be a useful source of tissue for researchers.

“This was a really new idea in 2001 or 2002,” Murphy says. “Many hospitals, when they were confronted with this proposal, knew that they needed to take it to some sort of ethics committee.”

IRBs, which often already handle privacy issues for hospitals, were an obvious choice, she

says, although many IRBs declined to take the issue up, saying it was outside their purview. At other hospitals, particularly smaller ones where the IRB serves as a sort of “one-stop shop,” IRBs did review the proposals.

A proposal for providing tissue to a repository is different from the type of research protocol an IRB is used to reviewing, Murphy says. It’s impossible to identify at the outset who eventually will be using the tissue, and for what purpose. Researchers from all over the world could potentially end up with tissue donated from a hospital in one corner of the United States.

“The question was, could you conduct informed consent appropriately, when you could basically tell the tissue donor next to nothing about who would use the tissue, or where or what would be done with it?” she says.

She also notes the regulatory environment for collaborations is murky. Regulations are inconsistent and many basic questions, such as ownership of human tissue, remain unanswered.

Trott says her board also was concerned with the impact on the public if the hospital entered into a commercial tissue banking arrangement.

“We were worried about how people would react if it ended up on the front page of the newspaper that the medical center was selling tissue,” she says.

And she notes that there weren’t many institutions to consult about their own experiences, since the practice was so new. Murphy says there is a dearth of published information about commercial collaborations for tissue.

The Maine Medical Center set up a steering committee to oversee the project, and asked Murphy and others to look at the ethical issues involved.

Those issues included the privacy of genetic information derived from the tissue and whether tissue would be linked with medical records. Clinical data about a tissue sample — everything from the patient’s medical history to the eventual outcome — can greatly increase its usefulness to researchers.

Murphy says her group also looked at issues of institutional integrity — how a commercial proposal would fit with the hospital’s mission, the ethics of investing in commercial repositories and potential conflicts of interest.

“The big difference between an IRB looking at a commercial collaboration from any other banking protocol is just thinking clearly about that commercial piece,” she says. “How to protect the integrity of the collecting institution, if the collaboration has any commercial aspects to it.”

Consent, confidentiality key

In her discussions with IRBs, Murphy says their biggest issues tend to center around informed consent and confidentiality, and maintaining a link between tissue samples and patient medical information.

Consent was an important concern at Maine Medical Center, Trott says, leading to a long process in writing the consent form, and a plan to hire two nurses, at the repository's expense, to administer the consent to patients. The nurses work through the clinical trials office to allow for greater oversight of the process.

"We wanted to make sure that the nurses who were consenting people knew how to really consent people and they weren't just signing them to get their tissue taken," Trott says.

The IRB also carefully examined the company's encryption program, which enables some coded information to travel with the tissue samples. Although the medical center is unable to tell donors exactly where their tissue will go or what it will be used for, the IRB insisted that the company guarantee tissue would only release tissue to a researcher who could show evidence of an IRB's approval for his or her project.

The company provided infrastructure for the tissue banking process at the hospital, including the encryption software and a freezing process to preserve the tissue. The Maine Medical Center's own researchers were given first rights to the tissue if they wanted it for their own research, Trott says.

"Another policy of the steering committee was that any money that was received back from this that didn't just pay for the infrastructure would be used to fund a community project," she says. "We knew we may have some bad publicity from this and we wanted to show that every angle had been covered."

One area the Maine Medical Center chose not to pursue was banking tissue from deceased patients, Trott says.

"It seems to be something that the community just doesn't want to deal with," she says. "They're open to the (tissue banking) if you consent people well and you really explain what you're doing and what you're asking for and where this tissue may go, and you give them the opportunity to ask questions.

"Taking tissue from newly expired people just leaves a bad taste in people's mouths," she says. "And right now, we're just not willing to wrestle with that piece."

In the end, Trott says, the IRB approved the

structure of the tissue banking program, including policies, the encrypting procedures, the makeup and policies of the steering committee and the consent form.

After the medical center decided to go ahead with a commercial collaboration, Murphy and her colleague, geneticist **Karen Rasmussen**, PhD, obtained a grant from the Greenwall Foundation to build an online guide that IRBs could use as they navigate the unfamiliar waters of commercial agreements for tissue banking.

"We thought it might be useful to apply for a grant and build a national conversation about the ethical issues involved in collaborating with commercial tissue repositories."

She says they faced some challenges in researching the subject, because the idea was so new and the commercial tissue industry was changing rapidly.

"It really felt like we were researching a moving target," Murphy says. "We interviewed a number of commercial companies, as well as hospital IRBs that were collaborating with them. Even in the very short time of the grant, companies were folding or redesigning themselves and changing their objectives.

"It surprised me how volatile the commercial research repository business is," she says. "I think many companies are struggling to find a niche and I really assumed that the market would be very stable. It's still rapidly changing."

Patient support

Trott understands that volatility very well. The company that originally worked with the Maine Medical Center pulled out of tissue banking, and the hospital has since contracted with two other companies to handle the work.

After the first company fell out, "we did have a period of reconsideration," Trott says. But the hospital's research institute decided to continue the program, even supporting the project financially until new companies could be found.

"Now the tissue bank is self-supporting again from these other companies," she says. "But we're using the same infrastructure and the same policies and they're agreeing to that."

In fact, Trott says, the medical center got the new companies to agree to use the Maine Medical Center's existing consent form, rather than using their own forms. Trott says that enabled the tissue to be potentially used by more than one company without requiring patients to sign multiple forms.

“One thing we didn’t want is to have our patients consented over and over and over again just to have a patient’s tissue,” Trott says.

She says response from patients to the tissue banking project has been better than she expected.

“We’ve been very pleased that most people want to do it,” she says. “We really were afraid that people would be very resentful of this.

“In most cases, these are people who have just been told they have cancer and they’re being asked to give up a piece of their tumor. Most people at that point, even that early on, want to help and think this is a way of helping. We’ve been very pleased with that reaction.”

And she believes that the collaboration will help other patients in the future, as researchers are able to do more and more studies using tissue, rather than human subjects.

“That’s going to change research,” Trott says. “You won’t have to use animals and humans as much if you can actually use tissue from people who have this specific disease and see how well it’s going to work. We really believed in that journey and we still do. We still think that that will happen.”

Since writing the guide, Murphy and her colleagues have been giving presentations on the ethics of collaborating with commercial tissue repositories at medical conferences around the world. Now, she says, they are focusing on writing journal articles that will disseminate the information they gathered in creating the guide, and they’ll be updating the site with new information. ■

To view the online guide to collaborations with commercial tissue repositories, go to <http://usm.maine.edu/bioethics/biobank/>

Online guide can help IRB with tissue banking review

Administrative support, knowledge of company key

When an IRB is confronted with reviewing an unfamiliar commercial collaboration to collect human tissue, it doesn’t have to work in a vacuum.

The online guide created by **Julien Murphy**, PhD, a professor of philosophy at the University of Southern Maine, in Portland, ME, can help clear confusion about the process, and lead to a more informed decision.

The guide (see editor’s note above for URL) is laid out in a question and answer format, covering everything from the basics of tissue banking

(Is there a need for clinical data to be associated with a tissue sample?) to legal, regulatory and ethical issues (How does the Privacy Rule apply to repositories? Is open-ended consent ethical?)

In addition, Murphy, and **Jan Trott**, director of the Office of Research Affairs at Maine Medical Center, Scarborough, ME, say there are a number of key steps IRBs need to take when considering a proposed commercial agreement:

- **Gaining institutional support.** Trott says it’s important to bring all the potential players on board as soon as possible. When her medical center was approached, the first step was to take it to the president and chief executive officer for approval, she says.

“You have to make sure that the senior administration has bought into this, even including the public relations department,” Trott says. “They have to understand what this means and agree to it.”

In addition, she says, the hospital’s surgeons should be consulted, since the project would affect them.

“Knowing you have all these internal approvals in place before it comes to the IRB makes it easier to get through the IRB,” Trott says.

- **Learning about the company.** “Is this a reputable company? Is this company taking the high road when it comes to ethical issues? How much assurance do we have that this company will take every opportunity to put up the right mechanisms to protect donor confidentiality?” says Murphy, who serves on the Maine Medical Center’s tissue banking steering committee. “There are some very good companies that care very much about the community and donors and doing business in the right way. And then there are others.”

- **Creating an appropriate consent form.** Murphy says it’s not enough to simply amend the standard research consent form; commercial tissue donation requires a specific sort of consent. “You have to disclose the usual things, including the commercial nature of the repository,” she says. “And you also must clearly explain the nature of the collection protocol — that the tissue will be banked, that protocols usually are not specified at the time of collection, and that there may be many end-users, research projects, etc.

“Because of the open-ended feature of tissue repositories, it is important to make sure patients know how to withdraw from a collection protocol,” Murphy says. “The risks of privacy and confidentiality should be clearly explained, as well as the mechanisms the hospital uses to protect donors.”

She says the online guide provides a number

of talking points regarding what needs to go into a consent form.

- **Confidentiality concerns.** The IRB must carefully review any protocols for unlinking identifiable patient information from tissue samples.

Murphy says some IRB members she's spoken with have suggested that researchers should be able to contact donors if significant advances are obtained from working with that patient's tissue. The contact could serve as a benefit to the donor for agreeing to have his or her tissue collected.

But she says that would be next to impossible, given the confidentiality mechanisms in place.

"Once it's delinked, it can't be traced back," Murphy says. "And even if you could locate the donor, how is the donor's physician supposed to really evaluate the finding of the research?"

- **Institutional integrity.** The board should review any financial incentives the hospital receives for its collaboration, as well as potential conflicts of interest. "They have to make sure there can be no conflict between patient care and tissue collection, so that one maintains the first priority of the hospital, which is quality patient care," Murphy says. ■

Study finds participation despite fears of exploitation

It's an accepted truism among many in biomedical research: Blacks won't participate at the same rates as other ethnic groups, because of fear of being exploited, thanks to the legacy of the infamous Tuskegee Syphilis Study.

But the truth is more complex, says **Ralph V. Katz**, DMD, MPH, PhD, a professor of epidemiology and health promotion at the New York University College of Dentistry, New York.

Katz is part of a team of researchers on the Tuskegee Legacy Project, a long-term project to understand and address issues related to recruitment and retention of blacks and other minorities in biomedical research.

After administering an extensive questionnaire to 900 people of different races in four American cities, Katz says his group learned a more subtle lesson — that while blacks are more likely to raise concerns about participation in research, they are just about as willing to volunteer as whites.

"One headline summed it up by saying: 'Blacks: Wary, but willing,' and I think that's a wonderful summation of what we found," Katz says. "I think

the African-American community would be very smart to be wary and reflective of history, but I think they participate in American life, they always have, as fully as they're allowed to in very positive ways."

And he believes the study carries a special message for researchers who struggle to achieve minority representation in their studies — and the IRBs who review them.

"I think people should have the confidence to actually hold the investigators' feet to the fire to come up with creative, active plans to recruit the diversity of population that we need scientific health answers on," Katz says. "In other words, don't cut them slack because you think it's an impossible task."

Katz's study was published in the November 2006 issue of the *Journal of Health Care for the Poor and Underserved*.¹

Conference spurred interest

Katz's introduction to the issue came at a 1994 conference he attended about the Tuskegee study, which ran from 1932 to 1972 in Macon County, AL. As part of a U.S. Public Health Service study on the effects of syphilis, nearly 400 poor black men were watched for years without being adequately treated for the disease, even after penicillin was established as the drug of choice for syphilis in 1947, according to the Centers for Disease Control.

The study was revealed by public health workers in 1972, to a huge public outcry. In 1973, the National Association for the Advancement of Colored People filed a class-action lawsuit, resulting in a more than \$9 million settlement for those who had survived the experiment. In 1997, President Clinton delivered a formal apology on behalf of the nation to the survivors and the families of the men who died in the study.

Katz says the 1994 symposium featured a number of speakers reflecting on the Tuskegee study and its legacy in health care research. Their message was a familiar one — that knowledge of the abuses of that study had soured African-Americans on participating in biomedical research.

"On the 12-hour train ride back, it just struck me that I didn't think academics could talk all day and not cite a reference — and there wasn't one reference cited" to back up the central premise that African-Americans were less likely to volunteer for research because of Tuskegee, Katz says.

At the time, Katz was director of the Northeastern Minority Health Research Center, which was conducting research into such condi-

tions as oral cancer, pediatric AIDS and baby bottle caries.

"We had all African-American cases, as it turned out, in New York, because we were based with the dental school there," he says. "I said, if we have this problem in the community we're trying to recruit, we've got to make sure they understand we're not operating that way. I decided to quickly make up a questionnaire and find out if that was in fact the story, that [blacks] were afraid of coming into studies."

As it turned out, that questionnaire took three years to develop, and became the Tuskegee Legacy Project (TLP), an attempt to quantify issues of recruitment and retention among minorities.

The 60-question TLP questionnaire asked subjects — white, black and Hispanic — about their knowledge of research abuses, including Tuskegee, and their willingness to consider participating in research, based on a number of factors.

Subjects were asked whether they might be more or less inclined to volunteer based on who was running the study — the subject's own doctor, a university medical school, the government, a nonprofit foundation, a tobacco company, a drug company or an insurance company.

They were asked how their decision might be influenced by what the study required — a blood draw, an IV injection, exercise, personal interviews, telephone interviews, dietary restrictions, oral medication or major or minor surgery.

Subjects also were asked about fears that might hinder them from participating, including fear of being a "guinea pig" or lack of trust in research.

The subjects were asked three times during the questionnaire about their knowledge of Tuskegee, including an open-ended probe asking about abuses in medical research, and two questions that identified the Tuskegee study by name, Katz says.

The telephone questionnaire first was administered to 900 adults in four cities: Birmingham, AL, Hartford, CT, San Antonio, TX, and Tuskegee, AL.

Katz says Birmingham was chosen because it was the closest city to Tuskegee that had a major medical center, and Hartford was chosen because of its comparable size and demographic similarities to Birmingham. San Antonio was selected in order to provide a sizable number of Mexican-American subjects, to balance Hartford's Puerto Rican population.

As for the fourth location, "I couldn't give up the epicenter of Tuskegee, even though it's a much more rural area and not likely to be invited to participate in studies," he says.

Study circumstances affect results

The results from the basic question on willingness to participate in biomedical studies showed that 20.6 percent of blacks were considered "likely" to participate, compared to 31.2 percent of whites. However, the authors note that when the question is broken down by who administers the study and what is asked of participants, the picture changes.

Blacks were only slightly more influenced than whites by who was running the study, and in fact reported being more likely to participate than whites in a few instances. On the question of what a subject would be willing to do in a study, there were fewer differences between the racial and ethnic groups.

Hispanics' responses were found to hover between the blacks' and whites' responses to the major questions studied.

"The in general differences between racial and ethnic groups . . . disappeared when subjects were given specific study circumstances as to who was conducting the study or what subjects were asked to do within the study," the authors write.

"Based on these study findings, the recruitment of Black and Hispanic minorities for biomedical studies appears to be a fully attainable goal for most types of biomedical studies, in addition to being highly desirable for ensuring diversity within study populations in biomedical research."

A few years later, the same questionnaire was administered to 1,100 adults in New York City, Baltimore and San Juan, Puerto Rico.

"Not only did we find the same direction of findings, but almost the same exact measurement level, and it was separated by three years in the field and different cities," Katz says. "It gives a hint that this is a stable phenomenon and we may have a reliable instrument that can replicate it."

The authors write that while some previous studies have linked unwillingness to participate in research on specific knowledge of the Tuskegee study, they have not shown a more general effect on the black population as a whole.

And they note that more recent studies have shown that minorities do enroll, proportionally, in biomedical research at expected rates when researchers make an effort to recruit them. The article cites the national Women's Health Initiative, which achieved 93 percent of its targeted minority goal and reported that recruitment yields for black and Hispanic groups surpassed those of white women.

Katz says many of the studies that achieved this success came after the 1994 National

Institutes of Health Guidelines for the Inclusion of Women and Minorities in clinical studies, which required that researchers do more to achieve diversity in their studies.

“Putting up notices just on posts in medical centers doesn’t necessarily attract everybody,” he says. “But if you work through medical centers, and you work through churches and community leaders and community organizations, you’ll get a full participation, as these studies are finding out.

“They meet their quotas, although it does take a little more planning and effort, and that’s what the 1994 legislation asks for,” he says.

Katz says his group is only beginning to sift through the large quantity of data collected through the TLP questionnaire.

“We have 18 manuscripts designed to be published that we can think of now, and we’ll find more as we get into it,” he says.

But he says the story that’s emerging about blacks’ attitudes toward research seems strong.

“I think I see a very solid and sane and understandable message here: Wary but willing, and the wary is understandable, and the willing is evidenced by the recent studies that have assessed participation in studies and have gone one step further to make sure that the community knows they’re welcome and in fact vital to the success of the [research] project.” ■

Reference

1. Katz RV, et al. The Tuskegee Legacy Project: Willingness of Minorities to Participate in Biomedical Research. *Journal of Health Care for the Poor and Underserved*. 2006;17:698-715.

Research geared toward specific groups/individuals

One drug was approved for one race

As studies become geared toward narrow research questions, targeting specific groups, IRB members will have an even more challenging time resolving ethical dilemmas and weighing risks and benefits.

Going back to the Belmont Report, one of the tenants of research is that society as a whole will share in the risks and benefits of studies, says **Heather Butts**, JD, MPH, regulatory specialist at Columbia University in New York, NY.

At the same time, investigators have been wary of including vulnerable populations in research, Butts says.

It’s a balancing act between the fear that there could be greater risks or the understanding that these same individuals should not be excluded from research that might benefit them.

But that is the old dilemma. The new one has even more ethical questions, such as this one: How do IRBs use the old risks-benefits measures when confronted with research that specifically targets one ethnic group, Butts says.

The drug BiDil, which treats heart failure, is the first drug that’s been approved for one specific ethnic group. It was approved on June 23, 2005, by the FDA for use with African-Americans, Butts says.

The FDA issued a press release when the drug was approved, saying it represented “a step toward the promise of personalized medicine.”

“It caused some controversy because there are questions in terms of what was their thinking behind this decision,” Butts says. “What are the genetics and biophysical aspects of this drug that make it seem to work better in African-Americans than in other populations?”

Two clinical trials of BiDil among the general population found no benefit from the drug, the FDA media release says.

“The approval of BiDil was based in part on the results of the African-American Heart Failure Trial (A-HeFT),” the FDA notice says. “The study, which involved 1,050 self-identified black patients with severe heart failure who had already been treated with the best available therapy, was conducted because two previous trials in the general population of severe heart failure patients found no benefit, but suggested a benefit of BiDil in black patients.”

The self-identified black patients in the A-HeFT study had a 43 percent reduction in death and a 39 percent decrease in hospitalization for heart failure when compared with placebo, the FDA notice says.

When Butts spoke about this drug at a national IRB conference, one doctor said that he has a white patient in his mid-50s who takes the drug and does well with it. The doctor felt obligated to let the patient know that the drug was approved only for use in African-Americans, and the patient was fine with this disclosure, Butts says.

“The doctor was essentially telling the patient, ‘I’m prescribing this to you off-label, and I think it will be of benefit for you because other things aren’t working,’” Butts says.

But questions still linger about how the research data came to the conclusion that it was

the demographic of being African-American that made the difference, rather than some other item, such as a comorbidity, Butts says.

“Another issue is that there’s a question of whether the drug interacts interestingly with patients with diabetes and congestive heart failure, and a lot of African-Americans have diabetes,” Butts explains. “So one thought is that the drug works better with the comorbid illness of diabetes than if someone doesn’t have diabetes.”

However, in the case of BiDil, it was the Association of Black Cardiologists who linked with BiDil’s sponsor, NitroMed of Lexington, MA, to conduct the A-HeFT trial to see whether the fixed dose of isosorbide dinitrate and hydralazine benefited blacks, who were selected based on self-identification, Butts says.

“What an IRB should do is be vigilant that groups of people aren’t being stigmatized based on what a study describes,” Butts says. “For example, if an IRB saw a protocol like the BiDil one, they should ask: Given what the outcomes of this study might be, how will this impact XY people, and will they be looked upon in a certain way that’s not favorable?”

Other questions for IRBs to ask are:

- Will there be untoward societal or legal or employment impacts because of the information being sought? “That’s especially important in genetic studies,” Butts says.
- Are there risks this group of people could suffer based on what you study, and are these balanced by the potential benefits?
- What are the risks you want to take into account as the study progresses?
- Should the study be monitored more frequently because these people may be harmed in ways that cannot be imagined yet?

“The area of genetic research is ever evolving, and there are certain risks you can’t wrap your head around in 2006, that you might see later,” Butts says.

The medical community and researchers are becoming more aware of what causes certain diseases, including genetic components and comorbid factors, she notes.

“There’s a whole area of medicine that looks at the rate at which individuals metabolize drugs,” Butts explains. “For example, if you have certain different pain medications and people metabolize them differently, then what works on one person might not work as well for another.”

Future medical research will be increasingly geared toward individualized medicine, and this includes individualized according to ethnic

group, although it’s not clear whether that is an answer or a crutch, Butts says.

“Race may be a pretext for less vigorous examination of why people respond to a specific treatment of drugs,” Butts says. “It may be easier to say people respond because of gender, race, and ethnicity.” ■

Weigh risks/benefits under component analysis model

SACHRP recommends its use in pediatric studies

IRB members and researchers are beginning to hear more about a new model for weighing risks and benefits in human subjects research. Called component analysis, it requires IRBs to weigh individual procedure risks and benefits against themselves.

“Component analysis is an idea that has been worked on and forming since the early 1990s,” says **Charles Weijer**, MD, PhD, an associate professor, philosophy and medicine and the Canada research chair in bioethics at the University of Western Ontario in London, Ontario, Canada. Weijer has promoted component analysis and spoke on the topic at the 2006 annual Human Research Protection Program Conference of the Public Responsibility In Medicine & Research (PRIM&R), held Nov. 15-18, 2006, in Washington, DC.

“My colleagues and I have been doing a lot of work on this concept,” Weijer says. “The aim of component analysis is provide a procedure for deciding when it’s acceptable and when it’s not acceptable to expose human subjects to risk for scientific ends.”

Typically, IRB members engage in collective analysis when they weigh the risks and benefits of a study.

“Collective analysis allows you to look at all the risks in total for the study and all the benefits in total, and if the potential risks are at least balanced by some of the potential benefits, then you can say the risk-benefit relationship of the research is acceptable,” explains **Ernest Prentice**, PhD, an associate vice chancellor for academic affairs and the chair of the Secretary’s Advisory Committee on Human Research Protections (SACHRP) for the U.S. Department of Health and Human Services. Prentice also spoke at the PRIM&R conference about component analysis.

With component analysis, it’s not the overall risks and benefits that are weighed, it’s the individual risks and benefits. In other words, each

procedure or intervention included in a trial protocol is weighed for its own risks and benefits.

SACHRP has recommended that component analysis be used in pediatric research so that different procedures in a single trial maybe approved or disapproved under different subpart D categories, Prentice says.

One of the reasons why IRBs increasingly are using component analysis is because it provides a clear ethical model for thinking through risks and benefits, Weijer says.

"IRBs struggle with how to think through whether there are acceptable benefits or harms in studies, and a major challenge in IRBs has been achieving consistency in reviews across IRBs," Weijer says. "It's hard to see how it can be consistent in a structured approach, and component analysis provides just such a structure, so it has been fairly widely accepted."

Prentice offers this example of how component analysis would work in the review of a protocol for studying two different drugs in a pediatric population:

- First, IRB members would break down the trial's procedures into separate units. One unit would be the administration of either drug A or drug B to diabetic children, ages four through 12 years.

- The IRB discussion might entail reviewing the prospective benefits of these drugs for the ill children, versus the risks of side effects and discomfort. IRB members likely would find that the potential risks balance with the potential benefits with regard to the drugs.

- Next the IRB would look closely at the protocol's add-on procedure of pharmacokinetic (PK) testing, which would require an indwelling, intravenous (IV) catheter, serial blood sampling, and an overnight hospitalization of the child.

- The risks of the PK testing might appear greater than minimal because of the hospitalization and the IV catheter. There would be no potential of direct benefit to the children because the procedure was added to the protocol purely to gain additional scientific knowledge about this population of patients.

Under component analysis, the risks of the PK

testing must be balanced by the potential benefits of the same procedure.

"It's very clear that we would say that the risks of the testing are greater than minimal, and there is no direct subject benefit," Prentice says. "So the PK component of the research cannot be approved under the 45 CFR 46 category."

The PK component could be considered under the more stringent category of 46.406 in which the IRB has to find that the risk represents a minor increase over minimal risk and that the procedure represents experiences to the subjects that are reasonably commensurate with experiences expected in medical, dental, psychosocial, etc. interventions, Prentice explains.

"Is sticking a kid with a needle and indwelling intravenous catheter and taking blood samples and hospitalizing overnight really commensurate with the experiences of a child from ages four to 12?" he says. "Some IRBs will say kids get shot, get blood taken, and end up in the hospital, so some would say 'Yes,' and some would say, 'No.'"

CE/CME Objectives

The CE/CME objectives for *IRB Advisor* are to help physicians and nurses be able to:

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **apply** the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

■ Children's Hospital guide educates parents about pediatric research

■ When is it ethical to give research subjects placebos?

■ Research participant and scientists discuss ethics from both perspectives

■ Take this advice on managing IRB staff

■ Streamline the IRB process, learning to prioritize

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CE/CME questions

5. True or False: It is feasible for an IRB to require that researchers using donated tissue from a commercial repository notify donors if significant advances are obtained from working with that patient's tissue.
 - A. True
 - B. False
6. Which of the following was not shown to be a factor in black subjects' willingness to participate in research?
 - A. Who is running the study
 - B. The race of the research staff
 - C. What subjects are asked to do in the course of the study
7. A recent study in the New England Journal of Medicine found that what percentage of IRB members had one or more relationships that could be seen by some as a conflict of interest with industry within the past year?
 - A. 17 percent
 - B. 36 percent
 - C. 52 percent
 - D. 56 percent
8. In weighing risks and benefits of studies that target specific populations, which of the following is not a good question for an IRB to ask?
 - A. Will there be untoward societal or legal or employment impacts because of the information being sought?
 - B. Are there risks this group of people could suffer based on what you study, and are these balanced by the potential benefits?
 - C. What are the risks you want to take into account as the study progresses?
 - D. All of the above are good questions to ask

Answers: 5. (False); 6. (b); 7. (b); 8. (d)

The PK intervention is likely to yield general knowledge about the subject's disorder or condition, which is of vital importance to the understanding of the condition Prentice notes.

So a key point in analyzing this scenario under component analysis is that the children have a medical problem, Prentice says.

"A totally normal, healthy child involved in this protocol would not qualify because you could not meet the condition of their having a disorder or condition under the regulations," Prentice says.

The IRB could not approve the PK procedure under 45 CFR 46.405 because the potential benefits don't offset the potential risks, he says.

However, under 46.406, the IRB might find that the PK procedure's risks represent only a minor increase over minimal risk, and the pediatric participants are sick, and so if assent and informed consent are adequately obtained, it could be approved, he says.

"I personally think that when using component analysis in this example the study could be approved under 46.406," Prentice says. "One would then have to judge whether or not whatever data they get from the PK testing is of significant importance, and how important it is to do this test on children." ■