

# IRB ADVISOR

Your Practical Guide To  
Institutional Review  
Board Management

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**AUGUST 2005**

VOL. 5, NO. 8 • (pages 85-96)

## How much is too much? Many IRBs lack guidelines for paying research subjects

*Studies show wide variance in how much participants are paid*

When an IRB reviews a proposal to pay research participants, members often have little more guidance to go on than their own gut feeling of what is appropriate and what is too much.

That's the assessment of two researchers who have studied the payment practices of research institutions.<sup>1,2</sup> They say the amounts paid to study participants vary tremendously — from site to site, even for the same multisite studies, and from study to study, even at the same institution for similar tasks.

They argue that more concrete guidelines would help IRBs make consistent decisions about payment and more fairly compensate volunteers who sacrifice time, comfort, and more to help advance science.

"My view is, and has been for a while, that the best thing that IRBs or institutions could do is to put together guidelines that help people find out what's an acceptable way to calculate [compensation]," says **Christine Grady**, RN, PhD, head of NIH's section on Human Subjects Research in the Department of Clinical Bioethics.

"Just to say to investigators, 'Whatever you do, don't give me an amount [that could create] undue influence,' gives them absolutely no guidance in terms of how to figure out how much to offer," says Grady, who emphasizes that she is speaking for herself only and not for the NIH.

Grady and **Neal Dickert**, a doctoral student at the Phoebe R. Berman Bioethics Institute in Baltimore, surveyed 32 U.S. research institutions to discover their policies regarding payment of research subjects.

They found that only 12 had any written policies or guidelines regarding payment — all but one reported using unwritten rules of thumb to determine compensation. Few could even provide an estimate of the proportion of their studies that paid subjects.

A second study, analyzing 467 protocols approved by 11 IRBs, found wide variation in the amounts of money paid for relatively similar procedures, both across institutions and within individual institutions. In one case, one offered \$1,000 to participants at one site and \$2,000 at

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another for the same study.

Dickert describes one study, on treatment of attention deficit hyperactivity disorder in children, where there were variations not only in how much was paid, but in who was paid.

“Payment went anywhere from zero to \$275 to

the teachers who were filling out the assessments for the kids,” he says. “And some sites that didn’t pay teachers paid children and parents a fair amount of money — from nothing to over \$300.”

The amount offered for a subject to undergo an MRI varied among 12 studies from \$25 to \$120; in fact, the dollar amount for an MRI sometimes differed within one institution.

“It just shows that for whatever reason, investigators are coming up with different ways to pay people,” Dickert says. “And all these different strategies were submitted to the IRB and the IRB probably looked at them and decided on a case-by-case basis whether each was reasonable rather than looking at whether they were all the same.”

Some argue that IRBs need flexibility in assigning payment for studies, based on the population they’re working with, the specifics of the study involved and other factors that can’t be foreseen by a set of guidelines.

“I would be concerned if one tried to adopt a very formulaic approach to it,” says **Richard Mattes, MPH, PhD, RD**, chair of the biomedical IRB at Purdue University in West Lafayette, IN. “Ethical questions are not black and white; they’re not scientific questions where you have a hypothesis, you do a test, and it’s yes or no. It’s all interpretation and it’s subtlety and it’s sensitivity. That would be very difficult to capture in a rigid system.”

But developing more concrete guidelines would create advantages, including keeping researchers at an institution from competing for volunteers on the basis of payment, Dickert says. He says it also would promote simple fairness, the idea that two people doing the same amount of work — for instance, submitting to a fingerstick or visiting a clinic four times — would be compensated equally.

## Developing guidelines

Dickert and Grady say an institution should start with the most basic question: Whom do we pay, and what are we paying for? Does the institution believe in paying only to cover a subject’s expenses, such as child care or taxi fare? Does the IRB believe in providing money as an incentive, or to compensate people for the time and effort it takes to participate in the study?

They argue for a sort of wage payment system — calculating the amount of time the subject must spend, and then paying something close to the local rate for unskilled labor.

Grady notes that IRBs often don’t see the

**IRB Advisor** (ISSN 1535-2064) is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to **IRB Advisor**, P.O. Box 740059, Atlanta, GA 30374.

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## Editorial Questions

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situation from the point of view of a study volunteer, who must give up time from work and deal with other problems to participate.

"I've heard from research participants, 'They offered me \$25 for each visit. But it cost me \$15 to get here; by the time I added up all the buses and subways, and now I've got to take two or three hours off work. I'm losing money on this deal. To offer me \$25 feels disrespectful to me.'"

Other issues that institutions should consider when developing guidelines for compensating subjects:

- **Risk** — Should riskier studies pay more?

In Grady and Dickert's survey of IRBs, nearly a third paid subjects for incurring risk. But paying for risk raises ethical issues as well as issues of science, Dickert says. Because people's risk tolerance varies, paying extra for riskier studies may result in a study population that is riskier than the norm, he says.

"From a more systemic point of view, I think we spend a lot of time trying to minimize risk in studies, and if you can just raise payment for riskier studies, then there's a sense that it removes an incentive on investigators to minimize risk," he says.

- **Healthy subjects vs. patients** — The vast majority of organizations surveyed (90%) reported paying healthy subjects and patient-subjects similarly when similar procedures were involved and there was no apparent difference in the likelihood of direct benefit.

Grady says paying patients could help address the problem of therapeutic misconception, the inability of patients to differentiate research from therapy.

"It's at least possible that if you started to pay people for a certain study, it would help them to see the difference between what's research and what's not," she says, "because they don't get paid for being taken care of."

Dickert says paying a patient might actually help avoid undue influence because it changes the dynamic between doctor and patient.

"If you're offering money, you're changing the nature of the relationship," he says. "It's easier to say no — you're not asking for a favor, it's a different transaction entirely."

- **Children and others who cannot consent** —

Dickert says special concerns accompany payments to children and others who can't make the decision to participate in a study themselves.

"The biggest concern in my view with paying children is that you might create incentives for

parents to make decisions based on what's good for them rather than what's good for the children," he says.

That problem can be mitigated by keeping payments reasonable and minimal.

Dickert notes that IRBs already strictly regulate children's research, especially with an eye toward keeping risk levels lower.

- **International research** — Grady notes that there are tremendous differences from culture to culture regarding the role of money in a society. In some, paying research subjects would be unheard of, while in others, it would be expected. And of course, a sum of money that would be considered fairly minimal in the United States could be overwhelming, even an undue influence, in a poor nation.

Grady points out that these types of studies would have to be dealt with on a case-by-case basis. "My view has been that at least at this stage in our evolution of understanding this issue, the most appropriate locus for making those determinations is the local IRB," she says. "Maybe there should be at a central level for a multinational study — a decision about whether we offer money to anybody, and if we do, on what basis and what kind of amounts are we prepared to offer. Then, let the local IRBs determine whether that's appropriate in their setting."

- **Completion bonuses or escalating payments** — Most organizations (84%) in the survey of IRBs reported requiring prorated payments to subjects, rather than requiring them to finish the entire study in order to be paid. More than half had rules on the use of completion bonuses, usually limiting the amount or advising against excessive completion bonuses as an undue influence to continue in a study.

"I think small completion bonuses to encourage people to complete the study are reasonable," Dickert says. "But I think it's important that payment be prorated, if people are to withdraw."

He says completion bonuses or escalating incentives — increasing the size of the payments over the course of the study — can be useful, especially if there are important study endpoints, or if the study is a particularly long one.

"You just need to make sure that the amount is appropriate, where you're not putting people in a position where they feel like they have to stay in the study and do things they really don't want to do," he says.

There are other steps that IRBs can take to help minimize the possibility that compensation will

become an undue influence on participants.

**Rebecca Pentz**, PhD, a clinical ethicist at Emory University's Winship Cancer Institute who has served on a number of IRBs, says an IRB can require stricter screening to ensure that a person doesn't lie about eligibility to participate in a trial.

"If this study has pretty stringent eligibility requirements and you're relying on self-report, but you're also paying the patient, then you probably want to require that there actually be a test to make sure volunteers are eligible," she says. "There are cases in the literature of people lying about eligibility for relatively small amounts of money and having bad outcomes."

Pentz says when she is serving on an IRB and sees a study that raises concerns, she suggests an ethics companion study to collect data on why people volunteered for it.

"How did they view the money? Would they have done it if there was another way to get the exact same money that didn't involve any risk at all?" she asks. "Then, you can use that preliminary data, on that very study, if you're finding out that you're getting some really odd results."

The results also could be used to make determinations about future similar studies, she says.

Dickert says it's important to focus first on the study itself, and then decide whether the payment is appropriate.

"If a study is ethically problematic to start with, no amount of payment or nonpayment is ever going to make it acceptable," he says. "Similarly for studies that pose no risk — a fingerstick blood glucose test, or listening to someone's heart or asking what their favorite color is — I really don't think most of us have a worry about how much you're paying.

"I think that in the absence of strict policy guidance, it's important to really contextualize payment and to worry about it in the cases where it's important to worry about it, which in my view are studies that are particularly risky or studies where you have reason to believe a good number of people might have good strong reasons not to participate," Dickert says.

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# HIV study involving foster children raises questions

*What was the IRB's responsibility?*

Recent revelations that hundreds of HIV-positive foster children may have been signed up for clinical trials without advocates assigned to ensure their safety have stirred the latest controversy regarding pediatric clinical research.

The practice appears to have been most prevalent in the 1990s, when treatment options for HIV-positive children were limited. Those who conducted the research say special advocates for the children were not necessary because the treatments involved in the clinical trials were therapeutic. But the debate already has led OHRP to issue a letter to Columbia University Medical Center/New York Presbyterian Hospital in New York City, making determinations of noncompliance.

In a statement, Columbia officials stressed their belief that advocates were not required for this research, but acknowledged the need for improvement in documenting its decisions regarding review of pediatric research.

In addition, the New York City Administration for Children's Services (ACS), whose wards were among the children who participated in the research, has arranged for an outside review of its actions in the matter.

The episode points out the need for IRBs and researchers to become more conversant with all of the relevant regulations regarding research participation of children in foster care, says one investigator who did research with HIV-positive foster children during the 1990s.

"I talked to a number of pediatric HIV clinical investigators around the country after this broke, and I could not find one who had ever heard of an independent advocate," says **Mark Kline**, MD, professor of pediatrics at Baylor College of Medicine in Houston.

"That includes some who had been HIV clinical investigators for more than 20 years — they had never even heard the term 'independent advocate.' This has been a little bit of a painful episode, but I think it has served a useful purpose," Kline says. "Personally, I'm very happy to have a better understanding of what the rules are. I have to say I was amazed at how this could have existed for such a long time and so few of us were really up to speed with what the requirement was."

The Code of Federal Regulations (45 CFR 46.409) does allow for the inclusion of wards of the state in research only if the research is related to their status as wards or conducted in settings where the majority of children involved are not wards.

The regulation goes on to state: "If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization."

However, Kline, and other researchers and institutions involved in the HIV research say that the advocate requirement does not apply to research that offers the potential for benefit to the subjects.

In testimony before the U.S. House of Representatives, **Alan Fleischman**, MD, a medical ethicist and professor of pediatrics at Albert Einstein College of Medicine in New York City, stated that his understanding was that research that involved the potential for benefit was governed by a different section of the regulations, 45 CFR 46.405, which requires only the permission of the parent or legal guardian to enroll a foster child.

Kline says Baylor's attorneys reviewed his research and similarly concluded that advocates weren't required. "The reason is that all of the studies offered potential benefit," he says. "I was not doing purely academic research, I was doing therapeutic research."

### **Context of AIDS research**

Kline says it's important to remember the context in which this research was conducted. In the late 1980s and early 1990s, therapeutic treatments for HIV were very limited, particularly for children. Children in foster care also were affected by the disease at a greater rate than the general population — many had parents who had died of AIDS, or who were unable to care for them because of illness or drug abuse.

He says that while there was some debate as to whether to include such a vulnerable population in research at all, the lack of other options led him

to believe that it was necessary.

"There were those — and I fell toward this end of the spectrum — who took the position that because of the primitive state of HIV therapeutics at the time, the only way for children to access potentially lifesaving therapy was through clinical trials," Kline says. "And so that it was wrong to exclude foster children as a group from participation because it was, in fact, a death sentence."

He says that his research never targeted foster children and that in fact, they only represented a small percentage of his research subjects. When asking permission for a particular child to participate, he usually contacted the child's caseworker, and then dealt with a supervisor to whom he described the details of the trial — "the potential benefits, the potential risks, the alternatives to participation in the trial, all the usual basic tenets of informed consent."

Usually, Kline says, a supervisor for the Texas Division of Child Protective Services would approve the child's participation. Occasionally, he says, a judge would sign the consent form.

As far as Kline can remember, no one ever raised the question of appointing special advocates at any point in the process, including IRB review.

"Thinking back, it was something I would have been happy to do then," he says. "I didn't *not* appoint special advocates because I thought it was onerous or unnecessary or unimportant or anything. I would have been happy to do it at the time, if it had been a requirement."

In New York, ACS officials have estimated that about 465 foster children participated in clinical trials between 1988 and 2001. The Associated Press reported that New York City could find records showing that only 142 were assigned independent monitors.

The city has asked the Vera Institute of Justice, a nonprofit research institution, to look at ACS policies and determine whether necessary consents and monitoring were conducted. The agency also has proposed a new policy for enrolling foster children in clinical trials. It would require an individualized, independent medical review concluding that enrollment offered a child a "significant potential treatment benefit not available outside of the clinical trial, while posing a concomitant minimal risk of harm." The proposed new policy is currently awaiting state review.

In May, OHRP issued a compliance oversight determination letter to Columbia/Presbyterian, laying out the following determinations of non-compliance regarding pediatric HIV studies:

- Columbia's IRB records demonstrated "a failure of the IRB to obtain sufficient information" regarding the selection of wards of the state and foster children as research subjects.

- The documents showed the IRB failed to obtain sufficient information regarding the process for obtaining permission of parents or guardians for those children.

- The documents showed the IRB failed to obtain sufficient information regarding additional safeguards for enrollment of those children as required by federal regulations.

OHRP noted that Columbia planned to take several corrective actions, including reviewing IRB procedures and appointing a task force to develop a training program on the participation of children in research.

**Patricia El-Hinnawy**, a spokeswoman for OHRP, says the Columbia/Presbyterian case is the only one open at this time in connection with the HIV trials.

Columbia spokeswoman **Marilyn Castaldi** says the institution is in the process of responding to the OHRP letter.

In a statement issued in response to a query about the matter, she says Columbia "has acknowledged to OHRP the need for improvement in how information is collected and decisions documented in its review of research involving children. Standard practice in this regard at leading research institutions has changed significantly since the early 1990s. The University is committed to meeting current and evolving standards for protection of all research subjects, including children."

New York Presbyterian referred questions to Columbia, saying they fell under the university's jurisdiction.

### ***Document discussions***

How should IRBs deal with proposals for this type of research involving wards of the state?

Kline contends that they won't see many such proposals in the future regarding HIV and AIDS research, thanks to the evolution of medical care for the disease.

"We have such a large menu of treatment options right now that I think it would be an extraordinary circumstance where I would enroll a foster child in an HIV clinical trial, because we have prescription drugs that do a very good job of suppressing the virus and maintaining the child's health," he says.

There are few other diseases Kline can think of to which foster children might be particularly vulnerable, but he says the controversy related to the HIV trials represents an opportunity for IRBs to better understand the regulations regarding care of children in vulnerable situations.

For one thing, IRBs may not even realize they have foster children involved in the clinical trials they approve.

"On the IRB applications, we don't tell whether we're enrolling foster children," he says. "When we file our annual reports and tell them how many patients were enrolled, they don't ask whether they were foster children. There's no line in the informed consent document that says anything about foster children. There's nothing in any of the materials I've ever seen that says, 'If you plan to enroll foster children, check the box here.'"

He says IRBs should familiarize themselves with the pertinent federal regulations, as well as any restrictions that individual state governments place on the inclusion of foster children in research. International research would require dealing with those governments involved as well.

When an IRB is dealing with a study that does require an independent advocate, Kline says it should alert the investigators about the requirements. And follow that up with diligent documentation, Fleischman says.

"It appears that the most important issue for IRBs is to document their discussions and assure that the children are adequately protected, regardless of the section of the regs under which the proposal is approved," he says. ■

## **Future insurability is an issue for genetic subjects**

*New study reveals fears about discrimination*

The largest study yet of public fears about genetic discrimination found that 40% of people undergoing testing for a particular genetic disease were concerned that their participation could affect future access to insurance.<sup>1</sup>

The finding could have implications for people's willingness to participate in genetic research, although fears of discrimination did not appear to be a deterrent in the group tested, says **Mark Hall, JD**, a professor of law at Wake Forest University in Winston-Salem, NC.

Hall, who specializes in health care law and public policy, notes the group being studied already was involved in genetic testing, and so could be seen as biased in favor of it.

The researchers also noted that a subject's participation in a social insurance program such as Medicare or Canada's national health care system had fewer concerns about genetic discrimination.

Hall had previously studied the issue of genetic discrimination by health insurers, concluding that it wasn't occurring often, and that public fears of such discrimination exceeded the reality.

His group decided to learn more about those fears, piggybacking on an existing screening program for hereditary hemochromatosis, a metabolic disorder in which too much iron accumulates in the body, leading to organ damage and other health problems. The Hemochromatosis and Iron Overload Screening (HEIRS) Study was designed to discover how many people in the general population had the genetic condition.

Subjects were recruited for the screenings in Alabama; California; Washington, DC; Hawaii; Oregon; and Toronto. Once people were recruited for the screening, they were asked to fill out a questionnaire that asked their general attitudes regarding genetic testing.

More than 86,000 subjects filled out the questionnaire. Of that group, about 40% agreed with the statement: "Genetic testing is not a good idea because you might have trouble getting or keeping your insurance."

Among the possible reasons for concern about genetic testing, it ranked first, above concerns relating to genetic determinism (a feeling of helplessness that a genetic predisposition can't be changed), impact on the family or feeling less healthy.

"The level of concern was broadly consistent with what we had expected and what has been found in other studies," Hall says. "But we were interested in going beyond just the surface level of concern to see where there were pockets of greater or lesser concern — whether the concern varied according to the legal landscape."

On the one hand, he says, people who were covered by Medicare or by Canada's social insurance program, which covers all of its citizens, had less concern about genetic discrimination. For example, among those older than 65, who are covered by Medicare, only 31% believed that genetic testing could lead to discrimination.

"Legally, if you're part of a social insurance system, you're not going to be discriminated against," Hall says. "That's part of the whole idea

of a social insurance system." However, in looking at the differences between states that had specific laws prohibiting genetic discrimination and those that did not, there was no real difference in people's attitudes, Hall says.

"Within that system of [state-specific] laws, the legal environment did not appear to matter," he says. "To the extent we were able to tell, it was no different in states with or without these legal protections."

### ***Offering reassurances***

One of the more unusual findings of the survey was the correlation between levels of education and concerns about discrimination. High school graduates had the lowest level of concern (36% agreeing with the statement), while respondents with both more and lesser education had more concern (of those with no high school diploma, 51%; of those with a college degree, 44%).

Authors described the finding as "puzzling," and warned that the education levels were guessed at from zip codes rather than measured directly in the study. "I think it needs further exploration," Hall says.

In interpreting the results of this survey, Hall says he's tempted to say that the level of concern is excessive, given the demonstrated low incidence of actual discrimination by insurers on the basis of genetic testing.

He does think the results should cause research institutions to carefully review their informed consent processes when genetic testing is involved. Hall says that while it's important to fully disclose the possible risks of testing, a good informed consent document should balance that with a description of the safeguards in place to protect subjects.

The consent form that participants in the HEIRS study saw stated that: "We will keep your identity . . . your blood test results, and anything you tell us confidential to the best of our ability. . . . To help insure your privacy, the National Institutes of Health has given us a Certificate of Confidentiality. This means that we cannot be forced to give any information about you to people who are not connected with the study, including courts, without your written consent. However, we cannot guarantee absolute confidentiality."

"I think it's proper to note the risks and not downplay it," Hall says. "But it would be inappropriate not to tell people that there are protections in place."

He says his group plans to follow up with the

participants in the HEIRS study to see if they have encountered any discrimination problems in obtaining employment or health insurance. So far, he says, most studies have supported his original research that showed very little actual genetic discrimination by insurers.

"The real concern is whether in the future it might get worse," Hall says.

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# Lack of information may be behind low participation

*Study says public just doesn't know*

Many people willing to participate in clinical research trials never do because they simply don't know about them or misunderstand the obligations involved, says a leading expert on supporting public research participation.

"From what we've seen, people are really hungry for information, they want to know about clinical research, but they don't know where to start," says **Roni Thaler**, president and co-founder of the Center for Information and Study on Clinical Research Participation (CISCRP), a nonprofit advocacy organization dedicated to improving public understanding of the benefits and obligations of research participation.

Started in late 2003, the center recently produced a public service announcement in conjunction with the FDA and has developed several brochures and other information products in both English and Spanish, explaining what clinical research is and how people can participate.

In May, the center and 40 co-sponsors held a one-day symposium on clinical research participation at Boston's Northeastern University. Of the 300 people who attended, more than 95% were interested laypeople, not health care professionals.

"We were very surprised at the interest of the public," she recalls. "As we expected, the sessions on informed consent and patient protections were popular, but we also had 'Meet the Doctor' sessions, where experienced investigators came to talk about their work. These sessions were filled to capacity."

Sessions featuring former and current research participants, who offered their perspective on the trial experience, were very popular as well, Thaler reports.

The center hopes to repeat the success of the first symposium in other large cities later this fall, she says.

To her knowledge, CISCRP is the only group dedicated to getting information about clinical research to the public and studying why people decide to volunteer and why so many don't, she says. Numerous studies indicate low volunteer participation is becoming a serious problem. Data collected by the center from numerous sources indicate:

- There are approximately 50,000 clinical trials currently taking place in the United States, but 80% are delayed at least one month because of unfulfilled enrollment.

- One out of every four volunteers drops out of a study after they have begun participation.

In the 1960s, it took 8.1 years to develop a new drug. In the 1990s, it took researchers 15.3 years, or nearly double the time.

- From 2001 to 2004, the number of people who stated that they had the opportunity to participate in a clinical research study increased by almost 50% from 13% to 19%.

- An overwhelming majority of people (77%) say that they would consider getting involved in an appropriate clinical research study if asked; yet only 10% of those eligible to participate in clinical trials do so in the United States.

- Very few patients are even aware that they are eligible to participate. And surprisingly, only 30% of participants report that they first learned about a clinical trial from their primary/specialty health care provider.

- In a recent poll, 94% of people recognize the importance of participating in clinical research in order to assist in the advancement of medical science. Yet 75% stated that they have little to no knowledge about the clinical research enterprise and the participation process.

The data indicate that people want to participate, but need to be better educated about the process, and what to expect of participation, and need information about research trials they are eligible for, Thaler says.

CISCRP's role is not to recruit trial participants or encourage people to be research subjects, but to help educate members of the public so they can make informed decisions, she says.

The center's brochure explains what clinical

trials are, lists 10 questions for potential subjects to ask trial coordinators, and contains a list of organizations that provide more detailed information.

"We have provided the brochures to investigators, to research institutions, and at medical conferences, and we are working on getting them in doctors offices and other public places," Thaler says.

In addition to education, it's also important to encourage societal recognition of the contributions and sacrifices of research volunteers, she adds.

"One thing we did at the meeting, which I think was really important, was ask people who had been research participants to stand up at the opening session," Thaler says. "We recognized them for their efforts. And, that needs to be done more. We recognized and honor people who donate blood or tissue, or agree to be organ donors, but people who participate in clinical research are not acknowledged at all. If they are, it is often in a stigmatizing way — they are called guinea pigs in the media, etc. That should change."

More information about CISCRP and its programs, as well as copies of the brochure and other materials, can be found on the web at [www.ciscrp.org](http://www.ciscrp.org). ■

## OHRP effort rubs some the wrong way

*Social/behavioral researchers feel left out*

The new public outreach campaign by the OHRP is a much-needed step in the right direction, say many clinical researchers. But the campaign's centerpiece — an educational pamphlet designed to answer basic questions about research participation — is leaving nonclinical researchers feeling left out in the cold.

"There are statements in the brochure that would not apply to the research that we do here," says **David Kreiner**, PhD, professor of psychology and associate dean of the graduate school at Central Missouri State University in Warrensburg. "I wouldn't want to distribute this here because I think it would be confusing to people who would volunteer for our studies."

The pamphlet is titled "Becoming a Research Volunteer: It's Your Decision." Under the first heading, "What Is Research?" a bullet point states that

"Scientists do research because they don't know for sure what works best to help you." Other items refer to possible side effects and all of the benefits of research studies listed are medical treatments.

CMSU faculty often conducts social and behavioral studies, with students frequently serving as subjects, but there is no biomedical research on campus. Concerns about experimental treatments and side effects are not relevant.

"I think the OHRP intends this to be used in the context of clinical and biomedical research, that's the way I am reading it," Kreiner says.

It's unfortunate that the pamphlet is not applicable to his setting because basic education about research study design, ethics, informed consent and other tenets of human subjects research would be very welcome, he notes.

Students and others considering participation often have no prior knowledge of what research participation entails, he says. Individual researchers and study coordinators make efforts to educate subjects about the risks vs. benefits of their projects, but it would be helpful if people had some basic knowledge.

"There are issues to consider, even though the chance of someone experiencing any side effects or harm from participation in our research is very small or nonexistent," he says.

Federal officials have concentrated compliance and education efforts where they feel they are most urgently needed — in biomedical research — because of the increased risk of many clinical trials, he says.

As a result, most of the information they put out is targeted at centers conducting medical studies. The IRB at Central Missouri has to carefully read and tailor the compliance guidance to fit their setting, which is sometimes difficult.

The educational pamphlet seems to focus almost exclusively on issues faced by subjects participating in clinical trials, which themselves are just a subset of biomedical research, says **Greg Koski**, MD, senior scientist at the Institute for Health Policy at Harvard Medical School and the former director of the OHRP.

"There's a wide variety of medical research studies that aren't clinical trials that this pamphlet would not be useful for, either," he notes.

This unfortunately contributes to the perception that the agency is focused only on clinical trials oversight. In reality, the agency's mission is to enforce the precepts contained in the Belmont Report on Ethical Principles and Guidelines for the Protection of Human Subjects of Research, which

was developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

If the commission saw fit to include biomedical and behavioral research together, then it is possible for OHRP to develop guidance that is applicable to a wide variety of research involving people, Koski says. "The overall guiding ethical principles are the same," he notes.

The new outreach effort is a long time coming, and is very much needed, but the agency needs to make more of an effort to broaden the scope to include research arenas other than clinical drug and device trials.

When he was head of the agency, Koski worked to form relationships with institutions focused on social and behavioral research as well as medical research in an attempt to include their perspective in the guidance and directives offered, he says.

Within the federal government, change often is slow. It took quite a while before OHRP was able to launch an outreach effort to potential research participants, something Koski wanted to do when he was there. Now that the initial effort has been made, the office needs to work on broadening its perspective.

"I don't think it's a case of needing separate materials for clinical research and social and behavioral research," he adds. "They were able to write the Belmont Report so that it covered all areas."

The pamphlet and other materials in the OHRP's new public outreach campaign can be found on the Department of Health and Human Services web site at: [www.hhs.gov/ohrp/outreach/](http://www.hhs.gov/ohrp/outreach/). ■

## South Korean team makes patient-specific stem cells

*American researchers talk ethics*

Last year, South Korean researcher **Woo Suk Hwang** and colleagues at Seoul National University stunned the world with news first published in *Science* on-line that they had developed stem cells from a cloned human embryo, using somatic-cell nuclear transfer.

In those studies, the scientists created 30 cloned embryos, using 242 eggs from 16 healthy women. The scientists were able to actually derive an embryonic stem cell line from only one of those 30 embryos, but proof of principle nevertheless

was achieved. The news made *Science's* top 10 list of breakthroughs for 2004.

In news published in May, again in *Science* on-line, Hwang might have assured his place on that list for 2005, as well. He and colleagues at Seoul National University, MizMedi Hospital, Hanna Women's Clinic, and Hanyang University (all located in Seoul), and the University of Pittsburgh School of Medicine, report that with improvement in their techniques, they have gone from proof of principle to deriving stem cell lines with what may be near-optimum efficiency; they now can consistently get a stem cell line in fewer than 20 tries. Furthermore, while last year's experiments involved using both skin cells and eggs from the same donor, here, skin cells from a patient were fused with an egg from a healthy volunteer donor.

**Gerald Schatten**, PhD, professor of obstetrics, gynecology and reproductive sciences and cell biology and physiology at University of Pittsburgh School of Medicine and senior author of the paper, told reporters at a press conference that the technology "is a way of deriving cells that grow in two dimensions and that may be nature's very best immune-matched repair kit." He added that Hwang's group is doing "some of the most important scientific work of our generation."

Hwang himself attributed the increased efficiency to several methodological improvements; among other things, improved micromanipulation and the use of human feeder cells, which originated with the patients themselves, rather than animal-based feeder cell lines.

The researchers generated disease-bearing stem cell lines from three separate populations: Nine of the 11 stem cell lines generated came from spinal cord injury patients, and one each from a juvenile diabetes patient and from a patient with a variant of so-called "bubble boy disease," a genetic immune deficiency. When asked about the specific patient groups they chose, Schatten said, "Dr. Hwang has a deep professional and personal commitment" to the study of spinal cord injuries, and that while the diseases differ with respect to whether they are genetic or environmental in origin, all three of them theoretically are curable by the transplantation of just one cell type (though in the case of genetic diseases, the genetic defect would first need to be treated for such transplantation to do any good). He also noted that each of the three cell types comes from one of the three basic body lineages. Beta-islet cells are derived from endoderm, blood-forming stem cells from mesoderm, and motor neurons from ectoderm.

The stem cells immunologically matched the donors of the skin cells, and spontaneously differentiated into major cell types. But transplantation is just one of the uses for the lines, and probably the one that is furthest in the future. Schatten stressed that spontaneous differentiation is a very different animal from directed differentiation — i.e., getting the specific cell type you want. To him, the major near-term implication is that “it is now possible to make disease-bearing stem cells to analyze the root causes of diseases.”

### ***Could it have happened in U.S.?***

In the United States, the regulatory climate for stem cells has changed significantly since Hwang and his group made their February 2004 announcement. At the time, Advanced Cell Technology CEO **Robert Lanza** told *BioWorld Today* that there is “virtually no funding [in the U.S.]” for ESC work.

In the meantime, California has passed a \$3 billion funding initiative for stem cell research, Proposition 71, and a number of other states appear ready to follow suit. The Stem Cell Research Enhancement Act also is being considered on Capitol Hill; it would provide federal funding that would circumvent President Bush’s restrictions on such grants.

Indeed, when asked at the press briefing whether the research could have been conducted in the United States, David Magnus, a bioethicist at Stanford University and co-author of a policy forum that accompanies the research paper, answered, “It’s a moving target; and in the U.S., it also depends on which state you’re in. My guess is that if this had happened in California, there would have been a mandatory IRB review and there would have been some tweaks.”

Ethical concerns also were addressed in an accompanying editorial by Magnus and his colleague and co-author **Mildred Cho**, also a bioethicist at Stanford University. While the lay public’s greatest concern probably is whether the technology represents another step toward the feasibility of cloned embryos, neither the scientists nor the ethicists seemed to feel that that is

the most pressing concern.

Both Hwang and Schatten strongly reiterated their opposition to reproductive cloning, which Hwang called “unsafe and unethical.” He added, “I also feel that it may be biologically impossible.”

Schatten elaborated that the methods used in the paper were derived from pig cloning and “ethics aside, it is completely unfeasible ever to have that amount of oocytes to work with” in humans.

Both Hwang and Schatten stressed that they work with “nuclear transfer constructs” rather than embryos. Magnus echoed the scientists’ opinion and added that the new methods are actually preferable from an ethical standpoint to deriving stem cells from IVF eggs: “It’s impossible, given what was done to these cells and where the science is, that they could have developed into an embryo. So even for the people who believe that potentiality is the key to personhood, these things, whatever they are, are not people. That’s why I believe somatic-cell nuclear transfer is a better way to derive these cells than IVF eggs.”

For the experts, both scientists and ethicists, the bigger ethical problem lies in informed consent by donors, and assuring that donors understand both the risks and the remoteness of benefits, which possibly still are decades away. Magnus also said that “the risks to oocyte donors are not well captured by the current frameworks of informed consent,” adding that they “are not research subjects, nor are they patients.” He likened them most closely to live organ donors.

On the side of the somatic-cell donors, the bigger issue is making sure that donors understand that they personally should not expect to benefit from the discoveries made with their donated cells, since practical applications are most likely still decades away. “It is important that [donors] not be misled about how close we are to success,” Cho said.

Both Magnus and Cho pointed out that unrealistic donor hopes are not unique to stem cell research, and that the guidelines for informed consent forms contribute to the problem: The ethical guidelines of the National Academy of Sciences require that “all future uses” be mentioned in an

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## CE/CME questions

Physicians, nurses, and others participate in this continuing education program by reading the article, 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 certificate of completion. When your evaluation is received, a certificate will be mailed to you.

5. In a survey of research institutions, how many believed that research subjects should be paid for incurring risk?
  - A. Nearly a third
  - B. A little more than half
  - C. 90%
  - D. All of the above
6. Federal regulations allow for the inclusion of wards of the state in research only if the research is related to their status as wards or conducted in settings where the majority of children involved are not wards.
  - A. True
  - B. False
7. Why do researchers believe that Canadians and Americans older than age 65 were less concerned about the possibility of genetic discrimination based on their participation in a screening for hemochromatosis?
  - A. Because those groups are at low risk for the disease
  - B. Because those groups had more education about the disease
  - C. Because health care costs for those groups was covered by social insurance programs
  - D. None of the above
8. In a recent study, what percentage of respondents stated that they have little to no knowledge about the clinical research enterprise and the participation process?
  - A. 27%
  - B. 62%
  - C. 75%
  - D. 90%

**Answers: 5-A; 6-A; 7-C; 8-C.**

informed consent form. And therein lies the rub, Magnus said: "Putting in all future uses without making it sound like we are very close to therapies is very difficult." ■

## CE/CME objectives

For more information on this program, contact customer service at (800) 688-2421; e-mail: [ahc.customerservice@thomson.com](mailto:ahc.customerservice@thomson.com).

- 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. ■