IRB ADVISOR

*Your Practical Guide To Institutional Review Board Management*

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AMERICAN HEALTH CONSULTANTS

## IN THIS ISSUE



**MAY 2004**
**VOL. 4, NO. 5 • (pages 49-60)**

# Developing and assessing institutional conflict of interest policy can be tricky

*Here's some expert advice*

When the National Institutes of Health (NIH) recently became the target of intense public criticism and scrutiny over potential conflicts of interest (COI) among NIH directors and staff and clinical trials, it became apparent to the research world that this is an issue that could be a problem for any institution.

The best prevention strategy is to be proactive by having policies, procedures, and possibly a special committee that reviews COIs, experts say.

The reputations of some leading NIH officials were at stake when the *Los Angeles Times* published an article Dec. 7, 2003, that included information critical of outside consulting arrangements by Stephen I. Katz, MD, PhD, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSD), and John I. Gallin, MD, director of the Warren G. Magnuson Clinical Center at NIH. **(See story on NIH's COI problems and resulting guidance, p. 51.)**

"The whole point of a conflict of interest policy is objectivity in research," says **Wendy Baldwin**, PhD, executive vice president for research at the University of Kentucky in Lexington. "So the concern might be that if you have a competing interest, then the problem is that it would erode the objectivity of the research," she explains. "There's a fear that there is a competing interest there."

In some ways, a COI policy is more to address the perception of conflict than the actual conflict itself.

"We're concerned about actual conflicts of interest, but you have to be in a person's head to know whether a conflict is being created," says **Nikki Zapol**, JD, legal counsel for Partners Healthcare System Inc. of Boston.

"Because we depend on public trust, we can't afford to have a situation where the public believes our decisions are biased due to furthering our economic situation," Zapol says.

Baldwin and Zapol offer this advice about creating a COI policy:

• **Have an independent group or person review projects for COIs.** Partners Healthcare System has a COI committee that looks at the nuances related to institutional and individual conflicts of interest, Zapol says.

When forming a COI committee, it might be a good idea to make it an ad hoc group that spreads oversight among different experts because a standing group may have one person at various times who has a conflict of his or her own, Baldwin notes.

In addition, if there is one person on staff who is in charge of handling the management details related to COI, the process may be more efficient. For example, an institution's policy might allow certain institutional or individual COI so long as a management plan has been established to reduce the risk of having the research staff and institution influenced due to the COI, she notes.

"The point is to ensure objectivity," Baldwin says. "At present, I am reviewing management plans along with the head of sponsor projects."

• **Determine what the investigators' obligations are.** Investigators might list all of their potential COIs, whether they are covered by the institution's policies. Then if there is a COI that creates a problem, the COI committee can put together a management plan, Baldwin says.

"Investigators have to work with the management plan if a conflict is identified," she explains says. "If the oversight team thinks they're not getting access to the data, then they'll come to me."

• **Assess the walls established between an institution's financial interests and research.** Large institutions often will hold a portfolio of investments that might include companies that sponsor research conducted at the institution, Zapol notes. This typically does not pose a COI problem because money managers run the portfolio.

"There is a significant wall between general investments of the institution and what's going on in the institution," she says.

A COI policy should differentiate between these types of financial arrangements and arrangements that have a more direct connection to research-related activities, such as those financial arrangements involving technology transfer agreements.

• **Consider the conflicts inherent in ongoing relationships with companies that license new technologies and products.** Often, companies will sponsor basic research and obtain the right to license out the inventions of that research or the federal government may fund the research and the institution doing the research is permitted to license rights to the technology made in that research to private companies, Zapol says.

A private company that licenses technology from a research institution may reward the institution with stock and/or cash payment, and this type of financial arrangement definitely poses a

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COI that needs to be addressed in a COI policy, she notes.

Often in cases of technology transfer relationships, an institution has been involved with the private technology company for a number of years, and key people have had a relationship with the company's management, Zapol says.

"So it's not possible to say that any decisions they make are made without an awareness of that relationship," she adds. "That's when we might worry about whether decisions will be made for either personal or institutional financial gain."

• **Outline black-and-white areas and leave gray areas to a committee to decide.** "We are a somewhat unusual institution in that we have a lot of black and white areas where most institutions would have a gray area," Zapol reports.

Most institutions will take COI on a case-by-case basis, with the COI committee reviewing each. However, the Partners Healthcare approach is another viable option, she says.

"We have a rule for individual conflicts of interest that says you can't conduct clinical research when you hold equity in a company," Zapol says. "Our question is, 'When is the clinical conflict over?' and our answer is, 'When you publish results.'"

So, at least in this case, the institution has eliminated the gray area for individual COI.

"There is another area of institutional conflict, which is one we're struggling with right now," she says. "It's when some senior person who is not involved with the actual research at all, but is a senior person to the people who are involved in the clinical research, holds equity.

"The public perception will be that whatever decision was made was influenced by the potential for a great upside gain," Zapol adds.

For now, Partners Healthcare has handled the issue with an interim decision that requires a management individual owning the equity to hold the stock until two years after the clinical trial is completed, she says.

"That's a temporary measure to prevent problems," Zapol says.

• **Follow the money.** It's important to address the financial flow to an institution, Baldwin notes.

While most people would say that only the financial flow tied to research is important, others would argue that any type of financial flow could be significant, she says.

"A financial flow that comes in through an endowment, are we worried about that too?" Baldwin adds. "If you have a sports promotion from a food company that is part of a conglomerate that is supporting research, do you care that you have the chicken tender franchise?"

The problem is that the issue of institutional COIs is not as well defined as individual conflicts of interest, so it's important that any institutional COI policy address these money issues, she explains.

• **Outline behaviors that could pose COIs.** Consulting arrangements are yet another way that researchers and/or institutions might trigger a COI issue, Zapol notes.

"We have a policy of reviewing all individual consulting agreements," she says. "We ask individuals if they are being given equity in a company in exchange for a consulting arrangement."

Another good policy is to require all CEOs and members of the board of trustees to complete financial disclosure statements, Zapol notes.

Also, it's important to outline an institution's internal processes for sharing objectivity, Baldwin says. "I think if you're going to think about this at the institutional level, then state which institutional behavior could impede objectivity and which would cause you to look at things like the deal cut on intellectual property or publication or access to data or data safety monitoring," she explains.

An institution needs a policy that outlines what will happen when these types of relationships are discovered, Baldwin adds.

Now is the time for institutions to pay attention to institutional COIs, Baldwin says. It's better to develop their own policies, procedures, and definitions because before too long a regulatory agency will do this for them. ■

# NIH changes COI policy in response to scrutiny

*Here's a quick look at new initiatives*

As National Institutes of Health (NIH) officials learned the hard way, sometimes it takes little more than the suggestion of a conflict of interest to cause a major upheaval and media scandal.

IRBs and institutions might take away two important thoughts from the NIH's recent experience: First, it doesn't take more than the appearance of a conflict to harm one's reputation. Secondly, some of the measures NIH has taken in response might guide institutions in their own conflict of interest (COI) policy-making.

On Dec. 7, 2003, the *Los Angeles Times* published a report that led to public concern over NIH's ties to research companies and resulted in a hearing before the U.S. Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education on Jan. 22, 2004.

The article raised questions about consulting activities on the part of **Stephen I. Katz**, MD, PhD, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases at NIH. Specifically, the article showed ties between Katz's consulting activities and a research sponsor of a lupus nephritis study in which one subject died.

Katz testified to the Senate Subcommittee that he followed all NIH rules and regulations regarding consulting work and other outside activities, including having made no decisions affecting any company for which he consulted.

In one instance, he had not recused himself from matters relating to one subsidiary of Schering AG, from which he had accepted consulting fees, because he and other NIH officials were unaware that the subsidiary, Berlex, was affiliated with Schering AG, Katz testified.

Berlex was the company that supported the lupus study.

"Notwithstanding this gap in the system and despite the sensational and wholly inaccurate impression the *LA Times* sought to create, I did not make any substantive decisions which affected Berlex or the lupus trial conducted on its drug," Katz told the Senate subcommittee.

John I. Gallin, MD, director of Warren G. Magnuson Clinical Center at NIH, also was mentioned in the newspaper article. The alleged COI that resulted in Gallin being forced to testify before the senate subcommittee was that he was an author on a study about a vector prepared by Somatix Therapy Corp. to be given to patients as gene therapy. In June 1997, 18 months after the gene therapy last was administered and after the manuscript was ready for submission, Somatix Therapy was purchased by Cell Genesys.

Several months later, Gallin was asked to join the Scientific Advisory Board of Abgenix Inc., a spinoff of Cell Genesys. Gallin testified that he was unaware that Abgenix and Cell Genesys had an affiliation when he accepted the advisory board position.

"But I should note again that Somatix Therapy Corporation and Cell Genesys were not affiliated at any time during our gene therapy study," Gallin testified. "Therefore, there was no conflict between my consulting work for Abgenix Inc. and the clinical research study that my laboratory did with Somatix Therapy Corporation."

Both these examples show how wrong public impressions can be created based on tenuous financial ties to research sponsors.

## New policies an outgrowth

NIH's response has been to develop new policies and initiatives with regard to financial COIs includes the following:

- NIH employees are required to submit outside activity approval packets for any outside activity they wish to pursue that involves consultative or professional services; these include teaching, speaking, writing, and nonfederal board service.
- NIH employees who already are engaged in such activities are required to complete these packets, listing the information regarding the amount and type of compensation they receive and expect to receive.
- Supervisors will be required to review and approve or deny these requests, seeking advice from deputy ethics counsel when needed.
- In considering requests for approval of outside activities, supervisors should consider whether a conflict will arise between the relationship the employee has with the outside organization and his duty to the NIH and whether the conflict will require a disqualification that will effectively prevent the employee from performing critical duties and thereby harm the efficiency of NIH.
- NIH has created the NIH Ethics Advisory Committee (NEAC), composed of members within NIH, to review certain activity requests where an NIH employee will receive compensation from an outside entity.

Activities reviewed by NEAC primarily will involve employees who are directors, and they will include one of the following:

— cash awards where compensation exceeds $2,500;

— outside activities with biotechnology or pharmaceutical companies;

— outside activities where total anticipated compensation exceeds $10,000 or is expressed as future income stream;

— activities for which the compensation proposed is stock, stock options, or other equity position.

NEAC's review criteria will include these questions:

— Does the proposed activity conflict with the employee's official duties?

— Does the proposed activity use the employee's government position for private gain?

— Does the proposed activity influence the employee in the performance of an official act, or induce the employee to take or omit an action in violation of the employee's official duties?

— Does the proposed activity use nonpublic information?

— Does the proposed activity involve the inappropriate use of government property? ■

# Lawsuit challenges use of blood samples

*Indian tribe claims other studies done*

The Havasupai Indian tribe of northwestern Arizona, and some of its individual members, have filed two federal lawsuits seeking a total of $75 million in damages against Arizona State University (ASU), the Arizona Board of Regents, and three university researchers, claiming that blood samples taken from tribe members as part of a diabetes study were destroyed, lost, or used in studies of schizophrenia, inbreeding, and population migration without the donors' consent.

The tribe alleges that nearly 400 blood samples were collected from more than 180 donors between the years 1990 and 1994 as part of a larger study of the incidence of diabetes among its members.

According to the lawsuit, the tribe was told the study consisted of three parts: diabetes education, collecting blood samples from members for research, and genetic testing to identify which genes in the Havasupai caused diabetes.

However, researchers later used their access to Havasupai medical records, in addition to the blood samples, to initiate studies of schizophrenia and inbreeding. They also transferred some of the samples to researchers at other institutions across the country, some of whom used the samples in research into theories of population migration.

"The material went from university to university, lab to lab,'" the tribe's attorney, **Robert Rosette**, JD, of the Sacramento, CA, law firm Monteau & Peebles told *The Arizona Republic* in March. "There were 23 different academic papers written."

The lawsuit also alleges that researchers misled the tribe about their intent to use the information in studies not related to the diabetes project.

They have evidence that there was never intent to strictly do diabetes research, Rosette said. For example, the tribal lawsuit contends that researchers collected handprints from some members in 1992, claiming that they would be used in diabetes research when they were actually used in a project to study inbreeding.

The additional use of the samples came to light, the attorney claims, when a tribal member read some of the published studies and realized it was her tribe they were talking about.

University officials have disputed that account, claiming that another researcher discovered the mishandling of the blood samples and reported it to university officials who initiated an investigation.

## *Lawsuit alleges IRB failures*

The lawsuit also alleges that ASU's institutional review board failed to stop the mishandling and transfer of the samples to other laboratories and research institutions. Information about tribal members was eventually published in 23 separate papers in 15 publications, Rosette said.

The tribe finds the studies of theories of population migration particularly offensive because their religion and culture is based on the belief that they originate from the Red Butte area of the Grand Canyon.

Without knowing the facts of the case, the allegations themselves raise interesting questions for IRBs examining protocols involving studies of whole populations, says **Dale Hammerschmidt**, MD, and associate professor of medicine at the University of Minnesota School of Medicine and director of Education in Research Ethics and Compliance at the school.

Discussions about protection of human subjects, and the federal regulations governing human research protections, have focused on the potential benefits and harms to the individual, and have been more cautions in their consideration of whole populations as units, he says.

"From a regulatory perspective, samples obtained for one purpose may be used for another purpose. If they are completely anonymized, the original sources won't even meet the federal regulatory definition of human subjects," Hammerschmidt tells *IRB Advisor*. "If they are not completely anonymized, but the code is quite secure, an IRB could, under certain defined circumstances, waive the consent requirement."

In order for the IRB to consider a waiver of informed consent for additional research using

the samples, the investigators should have to demonstrate that either the donated samples were anonymized (any identifying linkages to the donor were permanently removed), or, if the samples were not anonymized, that identifying information was protected by a secure code.

The IRB might then review another study protocol and stipulate under what circumstances a waiver of consent could be applied.

Federal regulations stipulate that investigators can seek a waiver of some or all of the informed consent requirements for the following reasons:

- The research or demonstration project is to be conducted by, or subject to the approval of, state or local government officials, and is designed to study, evaluate, or otherwise examine: i) public benefit or service programs; ii) procedures for obtaining benefits or services under those programs; iii) possible changes in or alternatives to those programs or procedures; or iv) possible changes in methods or levels of payment for benefits or services under those programs; and the research could not practicably be carried out without the waiver or alteration.
- The research involves no more than minimal risk to the subjects.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the waiver or alteration; and whenever appropriate, the subjects will be provided with additional pertinent information after participation.

"My question then would be whether the criteria for such a waiver were appropriately documented and applied," he says.

However, even if all of the regulatory requirements are met, it still can be argued that use of the samples for research that the Havasupai would find culturally problematic, and which still identified them as a group, constituted an inappropriate breach of their right to informed consent, he adds.

"Was there, in fact, an understanding that the samples would *not* be used for something else?" he wonders. "Was information sought or generated that could itself be problematic? For example, did they discover health risks or problems for which there would normally be an intervention?"

Even if the individual members could not be identified in the data or in publications, the group might be identified in a way that created breach of confidentiality or other informational risks, Hammerschmidt says. "In other words, is this a case where proper adherence to the regs was an insufficient protection?" ■

**SPOTLIGHT ON COMPLIANCE**

# Experimental devices need FDA approval

*Informed consent at heart of lawsuit*

By **J. Mark Waxman**, JD
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A report in the March 25 *Philadelphia Inquirer* regarding the use of experimental treatment on an infant in connection with a heart repair highlights a series of issues related to both the use of devices not approved by the FDA and, in turn, their use on minors, including infants.

According to the story, parents of a 3-year-old born with Down syndrome and a serious heart defect were offered a stent procedure, following two surgeries to correct an underdeveloped left heart pumping chamber, in lieu of a third surgery to reroute the blood flow. This stent procedure, less invasive than the generally accepted third surgery, was allegedly used on 20 children, but its study and use was apparently not considered part of a clinical trial.

The article claims that some doctors were actually testing whether the third surgery could be omitted. It asserts, however, that "records were being compiled for a study," but no IRB approval was either sought or obtained.[1]

The parents asserted a variety of shortcomings. First, they said that although the manufacturer's patient consent form clearly stated that the device was not FDA approved and could have a variety of potential complications, the consent form was not provided to them prior to the use of the stent. Instead, they assert the consent form was sent approximately one year later, and they were asked to backdate it. Second, they were never told that the stent procedure was experimental. Finally, they alleged the stent might clog which would result in the third major surgery in any event.

These facts raise myriad concerns about the processes and checks and balances that were in place at the hospitals involved in these practices.

In particular: Why was this procedure not the subject of IRB review and oversight?[2]

### Medical devices and their categorization

A general definition of a medical device is "any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized." Clearly stents to reroute blood flow would be medical devices.[3]

Unless such a medical device is low risk or substantially equivalent [510(k) devices], it must undergo clinical testing and a pre-market approval process. An investigational device is a medical device that is the subject of a clinical study focusing on the effectiveness and safety of a device, and must meet the requirements established by the FDA for an Investigational Device Exemption (IDE).

From the IRB perspective, devices are categorized as either significant risk (SR) or nonsignificant risk (NSR). For SR devices, both an FDA approval resulting in an IDE and IRB study approval is required. For an NSR device, an IDE application is not required (although abbreviated requirements must still be met).[4]

Sponsors make the initial SR/NSR determination. If a sponsor concludes the device is an NSR device, it provides the basis for that decision to the IRB, including information related to the FDA's assessment of the risks of use if that assessment has been made. The IRB will review all the information available to it to make its own assessment. The SR/NSR assessment will be made taking into consideration the full context of the trial or study in which the device will be used. For example, a surgery necessary to implant a device would form a part of the SR/NSR determination.

If the IRB determines that the study is SR, then it would notify the sponsor and investigator of its decision. They study would then not be approved until an IDE was obtained.

### Policy statement on devices

Any hospital engaged in or allowing the use of new devices, those for which there is not an FDA approval in effect, should have in place a policy guiding their use. An appropriate policy would be along the following lines:

A. Any proposed use of an investigational device (ID) must be reviewed by the hospital for scientific [and financial] merit, as well as compliance with all applicable laws;

B. Any proposed use of an ID shall be reviewed for determination as to coverage prior to their introduction.

### References

1. In a subsequent article, it was claimed that the informed consent form had been lost, but was found.
2. The issues raised because infants were involved will be discussed in a later article. *See* also [Kennedy Krieger]
3. *See* generally 21 CFR Parts 312, 812.
4. 21 CFR § 812.2. ■

# Research on prisoners requires OHRP approval

*All IRBs should have a policy*

The regulations regarding the use of prisoners in research have not changed since 1978, but the research community's awareness and perception of these have changed. As a result it's a good idea for IRBs to update policies regarding such research.

Last year, the Office for Human Research Protections (OHRP) published revised prisoner research guidance, says **Karena Cooper**, MSW, JD, compliance oversight coordinator for the OHRP.

While most IRB members know that if investigators enroll prisoners as subjects of a study there are regulations that apply to this patient population, it is less well known that the regulations also apply to subjects already enrolled in a study who suddenly become incarcerated.

The simplest solution might be to have that particular subject drop out of the study. But in cases where this is not a feasible idea, then the IRB and investigator will have to follow all of the rules that apply to prisoners in research, Cooper says.

These rules apply to any study supported by the U.S. Department of Health and Human Services (HHS), not by the Department of Justice, she reports.

Cooper outlines some of the key issues that should be addressed in any policy written to cover the use of prisoners in research:

- **Are you really dealing with prisoners?** Each state has a different way of organizing the criminal justice system, and everyone defines prisoners differently, Cooper notes.

"Some institutions say anyone who has anything to do with the court, supervised by the

court, we'll call a prisoner," she says. "OHRP's definition of prisoner means any individual involuntarily confined or detained in a penal institution."

This issue can become tricky, particularly in cases where someone has been arrested and goes through the court process, but is offered an alternative to incarceration by the judge. The alternative may be that they have the option of enrolling in a study and going to a residential treatment centers, Cooper explains.

"That person may not be considered a prisoner at that point," he says.

One thing to keep in mind is that the federal regulations do not differentiate between jail and prison. People incarcerated in both places are considered prisoners, Cooper says.

• **Is there a prisoner representative on the board or available to the board?** "In order for the IRB to review a protocol that involves a prisoner subject, there needs to be a prison representative as a voting member on the roster," she says. "The IRB cannot review the protocol without a prisoner representative, and that's specific in the guidance."

Cooper says that she knows that many IRBs use public defenders as prisoner representatives, and others may use chaplains who work in prison settings.

Basically, the important thing is that the prisoner representative is someone who doesn't work for the jail and is someone who advocates for the prisoners, she notes.

"The prisoner representative has to be someone who is a member of the IRB and not a consultant," Cooper says.

For example, in the cases of IRBs who anticipate the rare research protocol involving one or more prisoners, a good strategy might be to have an IRB member who won't be on the meeting roster most of the time, but who is available for the times when the IRB is reviewing a protocol that involves prisoner subjects, she suggests.

"They have to be on the roster, but don't have to participate in other reviews and will only count toward the quorum when it's a subpart C protocol," Cooper says.

## *Study must qualify*

• **Does the study fit into one of four regulatory categories?** The four categories, which were written in 1978, do not always perfectly fit today's prison environment, so institutions and IRBs may spend a lot of time figuring out which category applies, Cooper explains.

The four categories are as follows:

**— Category 1:** This applies to the study of possible causes, effects, and processes of incarceration and of criminal behavior, Cooper notes.

"Studies have to have no more than minimal risk or inconvenience," she says. "There's a slightly different definition of minimal risk for prison research."

The baseline for rating health is the healthy, unincarcerated person, Cooper says.

**— Category 2:** This rarely used category applies to the study of prisons as institutional structures or of prisoners as incarcerated persons, and it involves no more than minimal risk, she explains.

"These are studies done in a prison setting," Cooper adds. "The regulations do not differentiate between juvenile and adult prisoners."

**— Category 3:** A wide-open category, there's no discussion of risk in this category, and it applies to research on conditions that particularly affect prisoners as a class, Cooper says.

For example, this category might be used for vaccine trials for hepatitis, which is more prevalent in prison settings, Cooper notes.

This category often applies to the study of infectious disease, she adds.

Category 3 is not popular with investigators because it includes a step of involving OHRP in the approval of the protocol. OHRP has to convene a panel of experts from across the country to observe the study and write an opinion about it. Then the secretary of HHS decides whether HHS will fund the study, Cooper explains.

"This all takes a long time — I've never seen it happen in a shorter time than six months," she says. "We've seen very few studies that have fallen under category 3."

**— Category 4:** This category also does not mention risk, and it involves the research on practice and innovation of processes that might have an impact and reasonable probability of improving the health and well-being of a subject, Cooper says.

This category also applies to studies that have an intervention, so most medical-type of studies fall into this category, she notes.

"The second part of category four is that the studies that require the assignment of prisoners to a control group that may not benefit the prisoners have to go to a second step of consultation by OHRP," explains says. "The control group could be a study group that gets standard care."

When the approval from HHS is required,

there will be a group of experts convened, including a bioethics expert, a medical expert, and others, Cooper says.

"If the study has a control group that is either a placebo arm or standard care, then it is a control group that has to have that extra OHRP consultation," Cooper explains.

One way that some investigators have avoided having to go through the process of having OHRP convene a panel of experts is by adding a little something extra to the control arm.

For example, if the control arm is getting standard care and treatment plus something extra, then it's not a control group that requires the next step in category four, Cooper says.

• **Has the protocol received certification under subpart C?** The regulations say that the institution has to certify to OHRP that they have followed subpart C, she notes.

"What that means is that the study conducted with health and human services have sent us a letter with the research proposal and specific details, along with a grant application," Cooper says. "And they certify they are following subpart C, and the study cannot begin until we receive it and sign off on it."

This certification requirement has been in the regulations for more than 25 years but it's more widely recognized now; it was formalized in 2000, Cooper says.

Institutions need to remember that if they review a study under subpart C, then they must notify OHRP before prisoners are enrolled and before they're given any treatment, she says.

Typically, OHRP will respond to the notification promptly and clear the study to begin, Cooper adds.

"It depends on how complete the information is that comes into OHRP," she says.

This requirement has confused some institutions and IRBs, which are responsible to send in the letter requesting certification.

"People in some cases reviewed the protocols appropriately, and they probably had a prisoner representative locally on the board, but before 2000, they probably didn't know they had to write a letter and send in the research proposal to OHRP," Cooper says.

"Now more people know about it, but we still find people reviewing it appropriately, but who haven't sent a letter to OHRP," Cooper adds. "It's the IRB's responsibility — most investigators are unaware of subpart C and they don't have the training in it."

The letter at the very minimum must certify that the IRB has made seven findings in the 305A regulations, and that they've chosen a category into which the protocol fits, Cooper says.

"That's the minimal letter, and that's OK, but it's not helpful because we have to call them up and say, "What's the grant award number?' and 'What agency is funding this?' and we have to ask them all kinds of other questions," Cooper says. ■

# Common compliance problems: IRB issues

*OHRP study points to IRB failures*

Add up the number of citations of noncompliance related to IRB issues that the Office of Human Research Protections (OHRP) at the Department of Health and Human Services in Rockville, MD, handed out between October 1998 and June 2002 and the numbers are pretty staggering. Of the 1,120 citations given to 155 institutions, 1,014 of them say something about IRB noncompliance and deficiencies.

Those figures were reported last fall in a review published in *IRB: Ethics and Human Research.*[1] The review was done partly in response to a request from the Institute of Medicine.

During the time frame studied, 269 compliance oversight letters were sent to those 155 institutions. Only 13 of the institutions received no citations of noncompliance. Among the citations that were issued:

• 27% related to problems with IRB approved informed consent documents and processes.

• 25% related to the IRB initial review process.

• 10% related to problems with continuing reviews, with half in this category failing to conduct continuing reviews at least every year.

• 8% found problems with written IRB policies and procedures, and nearly as many found issue with IRB records.

Of the 155 institutions that got the citations, more than half of them had deficiencies in the initial review processes by the IRB, and 55% had issues with written IRB policies and procedures. Just over half the institutions cited had problems with informed consent processes and documents. Continuing review was a problem in 45% of the institutions, and 37% had issues with IRB records. A quarter of the institutions had problems with

IRB review of protocol changes. At the very bottom of the list, 5% had overburdened IRBs.

### *Not written down? Didn't happen*

Despite the numbers, things are probably getting a little better, says **Kristina Borror**, PhD, director of the Division of Compliance Oversight at the OHRP. "In 2002, there were more total findings issued than in 2001, but 2003 looked lower." That said, there were 37 letters issued in the context of a single case. "The previous highest one month total we issued was in April 2002, when 30 letters relating to two cases were sent."

Besides, she adds, "I'm pretty sure that there are problems at every institution," she says. "There are always ways in which we can do better."

That so many of the problems related to having good written IRB procedures, and that so much of the total number of citations related to IRB issues just shows areas where improvements can and should be made, probably for every single research institution, she says.

"I think one of the real messages here is that you have to document things. If you don't document it, you can't show you did it," says Borror. Furthermore, if you do document things, "you are less likely to forget to do things."

Borror says the most common problem in written procedures that she has seen is that institutions must have written procedures for determining which projects require review more than once a year, and which need verification that no material changes have occurred. "People don't know what that means," she says."

Another issue is that some institutions will have written procedures that cite regulations rather than explaining how they will apply those regulations. They simply iterate what the law says, Borror explains, rather than explain what the institution does to comply with the rules.

There is help, though. On the OHRP web site, there are some model procedures, as well as guidance on preparing written procedures. All of the examples, she says, are taken from institutions that have done a great job at fulfilling those requirements.

The documents and guidance can be found at http://ohrp.osophs.dhhs.gov/g-topics.htm.

Borror says she has some suggestions for staying in compliance. First and foremost, pay attention to the informed consent process. In the 330 citations related to informed consent reported in the study, the problems ran the gamut from problems of description — everything from explaining risks and discomforts to benefits, alternatives, and even the purpose of the study — to the forms being too complex for easy understanding. Twenty-six of the citations related to a complete failure to obtain informed consent.

"It's not just about making sure that the document has all the right elements, but that the person you are recruiting understands the research, understands it is voluntary, and understands what participating means for them," Borror says. "You have to be absolutely sure that there is no undue influence from the coordinator or researcher."

Every year, there are study subjects who report that they felt coerced, she continues. "It can be very subtle. Highly educated people can think that since they are being asked to participate, it must be a good thing for them. They have to do this because *they* think it's the right thing to do, not because the researcher does."

It isn't just small practices with little research experience that have problems with informed consent, either. In a compliance letter issued Feb. 26, University of California San Francisco researchers were brought to task for having informed consent documents that incorrectly stated the research would not lead to a change in routine care for the patients agreeing to be part of the protocol.

Compliance letters are always available at the

OHRP web site and make for informative and instructive reading, particularly as they include the corrective actions taken by the institution and approved by the OHRP.

Second, Borror admonishes all investigators and their staffs to follow the rules. Believe it or not, "there are cowboys out there who do research without IRB review, without true informed consent. They don't think of it as research, but as innovation or a change in techniques. But if they are collecting data on outcomes, then it is research."

Surveys and retrospective chart reviews also count. If you aren't interacting with subject or providing an intervention, that doesn't mean it's not research, she says.

Borror hopes to keep collecting the letters of citation so that investigators and institutions can get a good sense of what some of the most common lapses are. In the meantime, she suggestss looking monthly at the determination letters (see the web site at http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.htm) for guidance.

### *Reference*

1. Borror K, Carome M, McNeilly P, et al. A review of OHRP compliance oversight letters. *IRB: Ethics & Human Research* 2003; 25(5):1-4. ■

NEWS BRIEF

# Bernard Schwetz to head OHRP

Department of Health and Human Services (HHS) Secretary Tommy G. Thompson announced the appointment of Bernard A. Schwetz, DVM, PhD, as the director of the Office for Human Research Protections (OHRP). Schwetz had served as acting director since February 2003.

OHRP leads the department's efforts to ensure the protection of human subjects in research. The office monitors programs at more than 10,000 HHS-funded universities, hospitals, and other medical and behavioral research institutions in the United States and abroad.

As director, Schwetz said he will work to maximize the availability of the OHRP staff — and their extensive knowledge — to the research community. This will include an increased presence of OHRP personnel at institutions for activities such as quality improvement within the institution's human subject protection program. Responding to requests from the research community, he aims to work to provide more OHRP guidance on the interpretation of the HHS regulations.

In bringing a focus to some of the broader aspects of human research protections, Schwetz will develop a public communications program to help assure that subjects in clinical trials have access to and knowledge about their rights as participants. He also will provide information to help educate the general public about opportunities for involvement in research.

Prior to joining OHRP, Schwetz served as the senior advisor for science at the Food and Drug Administration (FDA) and a Distinguished Scientist at the University of Maryland at College Park. He was the acting principal deputy commissioner of the FDA from January 2001 to February 2002, and before that the agency's acting deputy commissioner and senior advisor for science. He also chaired FDA's IRB for the protection of human subjects. ■



## COMING IN FUTURE MONTHS

- Are IRBs creating too much work for investigators?
- Improving informed consent document
- IRB accreditation
- Minimum necessary rule

# CE/CME objectives

*For more information on this program, contact customer service at (800) 688-2421; e-mail: customerservice@ahcpub.com.*

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

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **describe** the regulatory qualifications regarding human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research;
- **apply** the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- **explain** the potential for conflict of financial interests involving human subject research;
- **discuss** reporting adverse events during research. ■

# 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 in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

17. Which of the following is a situation that might trigger an institutional COI?
A. A private company that licenses technology from a research institution may reward the institution with stock and/or cash payment.
B. A senior person who is not involved with the actual research at all, but who is a manager to the people who are involved in the clinical research, holds equity.
C. Managers or senior people who sign off on some aspect of research have a consulting arrangement with a research sponsor.
D. All of the above

18. Under Health and Human Services regulations dealing with research conducted with prisoners, which of the following definition would not qualify as a prisoner?
A. Anyone who is in jail or prison at the time the study commences.
B. Someone who is arrested and then given community service.
C. Anyone who is arrested and put in jail or prison after having already enrolled in a study.
D. All of the above

19. From a regulatory perspective, if samples are completely anonymized, the original sources don't meet the federal regulatory definition of human subjects, and there would be no need to obtain consent for additional or future studies.
A. True
B. False

20. The most common compliance problems include:
A. Informed consent documents and processes
B. IRB initial review process
C. Written IRB policies and procedures
D. All of the above

**Answers: 17-D; 18-B; 19-A; 20-D.**