IRB ADVISOR

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Special Report: Regulation and Rules — Are We Heading in the Right Direction?

IN THIS ISSUE

■ **Improving regulations will be challenging:** But some quick fixes and tweaking might get part of the job done . . . 64

■ **Institution's human subjects protection office closely monitors studies:** Taking human subjects protection seriously requires commitment from the top 66

■ **Studying social policy:** Oregon researchers studying a student drug-testing pilot program has its research suspended amid fears their study was biased 68

■ **Learn how to handle OHRP audit from the source:** OHRP official explains when these audits are initiated and what you need to know 70

■ **Inserted in this issue:**
— CE/CME evaluation form

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Is the problem overregulation or one of overinterpretation by IRBs?

New OHRP director brings up issue for discussion

(Editor's note: IRB Advisor *has asked IRB and human subjects protection experts from across the nation to discuss the state of human subjects protection regulations and how IRBs are interpreting federal requirements. In this issue, there is an article on the debate of whether IRBs overinterpret current regulations and an article on how current regulations could be changed to ease the documentation burden carried by IRBs. In future issues, there will be articles on how IRBs and institutions can improve the informed consent process by thinking outside the regulatory box and insisting that sponsors simplify their suggested informed consent documents; on certification and better training of investigators as a way to make the protocol approval process run more efficiently; and on shifting some IRB work to other committees.)*

From an IRB member's perspective, these are trying times. On the one hand, investigators complain that regulations for human subjects research and IRBs are too stringent, making it difficult for them to do their studies. Alternatively, human subjects advocates continually complain that IRBs and institutions are too lax in monitoring clinical studies.

Add to the mix the new privacy regulations and the recent focus on monitoring conflicts of interest — both of which have been shuffled off to IRBs in many cases — and it's a wonder that anyone volunteers to serve on an IRB.

The biggest question of all might be one that was raised recently by **Bernard Schwetz**, DVM, PhD, the new director of the Office for Human Research Protections (OHRP) in Rockville, MD.

Schwetz, in speaking to health care attorneys last fall and more recently

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to *IRB Advisor*, says that the problem may not be that research is overregulated, but that it is overinterpreted.

"Frequently, I'm at meetings where investigators say, 'If it weren't for the regulations, I could do research,'" he notes. "When you look beyond that statement and find out what they're talking about, very often they're talking about overinterpretation of the regulations."

Whether it's the IRB or institutional attorneys, overinterpretation frequently is driven by a fear of litigation, Schwetz says.

Some experts in the field of human subjects research say there is some merit in what Schwetz says, although there are many other factors to consider, such as the role of sponsors in creating more paperwork for investigators and IRBs and the greater media scrutiny paid to institutions that have compliance problems.

"Whether it's the high-profile shutdowns that took place in the late 1990s to 2001 or the increasing emphasis on compliance, I think IRBs are spending a lot of time shuffling paper without a clear relationship between that effort and the protection of human subjects," says **Robert M. Nelson**, MD, PhD, associate professor of anesthesia and pediatrics at the Children's Hospital of Philadelphia.

"The criticism of some of the shutdowns was that they were unrelated to subject protections and more related to whether institutions had dotted i's and crossed t's from a regulatory perspective," Nelson says. "The question is, 'What outcome do you want?' If that outcome is human subject protection, then should we begin to move toward an outcomes-based approach rather than just a compliance-based approach?"

At the very least, the research and human subjects protection industry need to have a lengthy discussion on this issue, he says.

"When Bernard Schwetz says IRBs are doing too much, then as far as I'm concerned, the next sentence should be, 'What should they be doing?'" Nelson adds.

The Secretary's Advisory Committee on Human Research Protection (SACHRP) for the Department of Health and Human Services (HHS) has been looking at the issue of overinterpretation of the regulations, finding problems in some cases, says **Ernest Prentice**, PhD, chair of SACHRP and associate vice chancellor for academic affairs of the University of Nebraska Medical Center in Omaha.

"We're actively evaluating 45 CFR 46, subpart D for children, and 46, subpart C for prisoners," Prentice says. "The problem with the regulations is that they have been inconsistently interpreted and sometimes misinterpreted by IRBs across the country."

This inconsistent approach has led some IRBs to approve research that should not have been

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Editorial Questions

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approved and to turn down research that should have been approved, Prentice says.

"The task force is taking a close look at the regulations to make sure they're adequate and appropriately interpreted. If they're not adequate they should be revised," Prentice says.

Basically, SACHRP has concluded that subpart D, involving children, is adequate, but needs to be interpreted appropriately, Prentice says. "But that's not the case with subpart C, which was written in the 1970s, and, quite frankly, is out of date." **(See story on SACHRP and revising regulations, p. 64.)**

Others say that the blame for the problem rests with investigators, who often lack the necessary training in writing protocols for submission to IRBs.

Eliminating time wasters

Another example of how institutions overinterpret regulations involves the recording of IRB minutes, says **Erica Heath**, MBA, CIP, president of the Independent Review Consulting Inc. of San Anselmo, CA.

"The regulations say the minutes are a summary of controverted issues," she explains. "But with every warning letter or guidance, there is more to include."

IRBs have to include all issues discussed, reference the regulatory elements, people present during a vote, and show when each member came and went during meeting, Heath says.

"It's my opinion that the minutes protect the institution more than the subject," she says. "If you put that same amount of time into communicating with investigators about the issues and problems, that education would be a part of human subject protection."

On the other hand, having detailed IRB meeting minutes reduces an institution's risk of being found deficient, which leads to newspaper headlines and could result in a loss of reputation, she notes.

"When I look at complaints over the years, it's not that IRBs have overinterpreted the regulations, but that investigators have not provided enough information for the IRB to make a good decision," says **Dale Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota Medical School in Minneapolis.

"Having said that, I also think that institutions and IRBs have been running a little scared for the last several years, because of institutional shutdowns," Hammerschmidt says. "Ours was the first one. They just excluded the offending department from the assurance, so the headlines were smaller 10 years ago."

Fear of litigation a driving force

The prospect of a shutdown and newspaper headlines has made IRBs and institutions nervous about whether IRBs are stringent enough, he adds.

Perhaps it's not so much an issue of IRBs' overinterpreting regulations as it is a matter of institutions expecting more from their IRBs, says **Felix A. Khin-Maung-Gyi**, PharmD, MBA, CIP, chief executive officer of Chesapeake Research Review Inc. of Columbia, MD. He also is the senior policy fellow with the Center for Drugs and Public Policy at the University of Maryland in Baltimore.

"Not only are IRBs interpreting regulations in a way that may or may not be appropriate, the institutions are applying the interpretation of the regulations in a way that may or may not be appropriate as well," he says.

An example is adverse event reporting, which is a huge issue for many IRBs, Khin-Maung-Gyi notes.

"The interpretation of the regulations has led the research enterprise to behave in a way that has [made] the IRB the gatekeeper of all adverse event information," he reports. "So sponsors submit it to the investigators with the expectation that the investigator will report it to the IRB, but the regulations don't give guidance on what the IRB should do once it reports them."

Schwetz says an example of overinterpretation involves how some local IRBs are failing to take advantage of a central IRB's time and effort.

The National Cancer Institute, for instance, has created a central IRB model for use with oncology studies nationwide, he notes.

"These studies are reviewed by the NCI's central IRB, and an investigator at University X agrees to be part of this study," Schwetz explains. "The investigator takes the protocol to a local IRB and has the approval of the central IRB, and asks the local IRB, 'Are you going to review this locally or accept the authority of the central IRB where the review has already been done?'"

Often, when a local IRB is given this choice, it will choose to do a full review of the protocol rather than accepting the central IRB's decision or doing a simplified review of just the consent form, he says.

"The institution's attorney says, 'You have to review the protocol in detail,' so there's duplication

of effort and a concern over litigation," Schwetz explains.

"We see a lot of interpretation of the regulations that account for the workload that investigators and IRBs have to deal with," he says. "So there are quite a few sources of additional burden that in some cases have little or nothing to do with human subjects."

Institutions may decide to conduct full local IRB reviews in these cases because it's the job of the local IRB to reflect the interests of the community in protecting human subjects, says **Steven Peckman**, associate director for human subjects research at the Office for Protection of Research Subjects at the University of California-Los Angeles.

"I think there are a lot of issues here, but I don't know if any of it has to do with overinterpretation of regulations," he says. "It seems to me that lawyers are concerned about institutional responsibility, and if an investigator does research at an institution, does the institution have responsibility to oversee or review the work?"

Alternatively, if an institution decides to let the central IRB review the work and the local IRB only provides a review of part of the project, such as the informed consent document, does this make the institution responsible for all of the project if anything goes wrong, Peckman asks.

"Or do we wash our hands of all of it and make the central IRB responsible?" he says. "I don't think that has to do with overinterpretation so much as it has to do with lawyers doing their jobs." ■

Special Report: Regulation and Rules — Are We Heading in the Right Direction?

Should IRB regulations be tweaked or revised?

Experts offer suggestions for best course

Human subjects research protection experts agree that IRBs are overburdened and that something should be done to improve the regulations and rules governing their work.

However, there is less agreement on how this could be accomplished. *IRB Advisor* asked IRB and research professionals to discuss how IRB regulations or the interpretation of them might be improved. Here's what they had to say:

• **Update prisoner research regulations.** The U.S. Department of Health and Human Services (HHS) has not updated the regulations regarding research involving prisoners since the late 1970s, says **Ernest Prentice**, PhD, associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha. Prentice also is the chair of the Secretary's Advisory Committee on Human Research Protection (SACHRP) for HHS.

"The penal system in the United States is distinctly different today than what it was in the 1970s," he explains. "We have a lot more incarcerated individuals; hepatitis C is endemic in the system, and a lot of prisoners are suffering from mental conditions and AIDS."

For these reasons, prison research also is different today, and members of SACHRP believe the regulations should be revised to reflect the current prison situation, Prentice says.

"We think research should be conducted in prisons to benefit prisoners," Prentice says. "The regulations are very restrictive, and you can't do the research that needs to be done, so the subcommittee is looking at short-term fixes."

While the Office for Human Research Protections (OHRP) has been trying to provide guidance for the existing prison research regulations, the recent guidance perpetuated one of the problems, says **Erica Heath**, MBA, CIP, president of Independent Review Consulting Inc. of San Anselmo, CA.

"Recent guidance says that subpart C includes situations where a human subject becomes a prisoner after the research has commenced," she explains. "Because of one person who had already made a free, informed, and voluntary decision, subpart C kicks in, and the full board — with the prison representative — has to reconsider the study."

The IRB also has to notify OHRP of the change in the roster, make and document seven additional findings, and certify this to OHRP, Heath adds.

"What would you do with that one subject who is now incarcerated — re-review or drop the subject?" she asks. "There are certainly new risk issues, but this level of distance from the basic requirements is over the top."

One short-term solution might be to encourage IRBs to interpret the regulations in a way that does not inhibit the IRB review and the conduct of ethically appropriate research involving prisoners, Prentice suggests.

The long-term fix would be to rewrite a part of 45 CFR 46, subpart C, he adds.

Minimal risk, minimal review

• **Change the way minimal risk research is handled.** The human subjects research community needs to start a debate about how minimal risk research is handled, questioning whether there is too much effort spent on those kinds of activities, suggests **Robert M. Nelson**, MD, PhD, associate professor of anesthesia and pediatrics at the Children's Hospital of Philadelphia.

Both IRBs and IRB staff spend considerable time on minimal risk research, he notes.

"For example, with chart reviews one could make an argument that the only risk of chart reviews is a loss of confidentiality — either through inappropriate data being extracted through the chart or an inappropriate storage of data in a way that breaches confidentiality," Nelson explains. "So why not move from a system where you have prior review of all applications to one where you do a spot audit of whether investigators are in compliance with all guidelines."

One could argue that random spot checks of minimum risk research would be more effective and efficient, he says.

"It's more effective because you'd see what they were doing, and if the audit program is random it'd have the same effect as having radar on certain roads — people drive a little slower," Nelson says. "Investigators would like it because they wouldn't have as much of a wait to get through the IRB approval process."

A chief drawback to this approach is that it would require regulatory change and that would take time, and it still would require someone to make an important decision about each minimal risk protocol, other experts say.

"Who makes the decisions on which protocols to review and which not to review?" asks **Felix A. Khin-Maung-Gyi**, PharmD, MBA, CIP, chief executive officer of Chesapeake Research Review Inc. in Columbia, MD. He also is the senior policy fellow with the Center for Drugs and Public Policy at the University of Maryland in Baltimore.

"We have a system where truly minimal risk studies under certain conditions can be expedited, and some can be exempt from IRB review," he says. "So there are two systems in place to expedite that."

Through the expedited review process, one member of the IRB is permitted to review and approve or modify the research, but to qualify a protocol must meet the criteria of minimum-risk research and fit into one of a number of specified categories, Prentice says.

"Could we expand and change the categories?" Prentice says. "Yes, it's been done once in 1998, so you could expand them to allow IRBs more latitude to use the expedited review process."

The other issue is that expedited reviews aren't used as often as the regulations allow because the concern over potential liability, he adds.

Perhaps IRBs should use expedited reviews more frequently, and the regulations should be changed to skip the continuing review of such research, since this also takes unnecessary time, Prentice says.

"When you add requirement after requirement, it's no wonder IRBs are totally overloaded with work and documentation," he says. "Is it all necessary, and does it contribute to human subject protections?"

While the idea of random spot checks has some merit, a chief problem is figuring out how to do triage for the level of scrutiny, notes **Dale Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota Medical School in Minneapolis.

Plus, the main reason IRBs spend a lot of time on minimal risk research now is because no one else has thought through the risks as well as necessary, he says.

"The investigator doing a transplant study will think a lot about risk, while someone doing a questionnaire study won't think for a minute about how the questions are compromising for certain people," Hammerschmidt explains. "The fact is that if an investigator does not perceive a study as risky, then he does not spend much time on the IRB application, and he delegates that to a junior person, and you have a lousy application."

If an IRB wants to conduct a spot check, it can do so already, in addition to its current workload, but it's another matter to substitute spot checks for IRB reviews, Heath says.

She also points out that many institutions — rather than IRBs — are instituting monitoring visits through quality assurance mechanisms, so the IRB remains the judge rather than both judge and police force.

Adding another category to the expedited review list could take care of many of these repetitive applications, Heath adds.

In the case of minimal risk, social-behavioral research, there might be some merit to the claim

that the common rule is overly restrictive, and SACHRP will be looking at regulations to evaluate these concerns, Prentice says.

Child research has its own issues

• **Work toward consistency in interpretation of subpart D.** 45 CFR 45, subpart D, regarding research involving children as subjects, has been inconsistently interpreted by IRBs and institutions, leading to inconsistent protection of children, Prentice notes.

An example of this is the Dryvax smallpox vaccine study in which three IRBs reviewed the protocol, arriving at different conclusions. Two IRBs approved the protocol, and one did not, which meant that the protocol was sent to HHS for review at the Secretary's level, a 407 review, he reports.

Ultimately, the federal government decided to pull the protocol and not conduct the research.

"I'm not suggesting that it was an unethical project, but I'm suggesting that IRBs inconsistently interpret these regulations, and we need more balanced protection across IRBs, and the only way we're going to do this is through guidance," Prentice says.

Federal guidance should address what minimal risk means, what it means to have a minor increase over minimal risk, and other questions, he says.

"So the charge is to look at those terms under subpart D and meaningfully clarify them, so that we can make sure we're protecting children consistently across the country," Prentice adds. ■

UPenn creates integrated clinical research program

The extra effort results in much better system

For the University of Pennsylvania School of Medicine in Philadelphia, there was no question that the only acceptable solution to the problems in human subjects research was to establish a comprehensive program that included all areas, including investigators, IRBs, and the institution's leadership.

While the university's human subject research program received intense scrutiny after Jesse Gelsinger died in 1999 during the course of a gene therapy trial, the research oversight deficiencies experienced by the University of Pennsylvania were no different from any other noncommercial research setting, says **Deborah Waltz**, MS, CIP, director of Research Compliance and Quality Improvement Office for Human Research at the university.

"I think the problem with some institutions is they don't look for problems, and if you don't have a feedback mechanism and don't sample what's going on, you're under a delusion that everything is fine," she says.

"What happened from the perspective of the research industry is that investigators in academic centers truly believed that the FDA laws and regulations did not apply to them," Waltz explains. "I came to this university after 20 years in the pharmaceutical industry and with experience in quality assurance and regulatory compliance."

Starting a comprehensive compliance and oversight program from scratch is very difficult, but it's been well worth the effort, she notes.

"The visibility that Penn has allowed us to have for speaking and talking about problems and solutions has helped make a difference in how research has been conducted across the country," Waltz says. "It's safer for the research participant, we have better data and more reliable results, and everybody wins."

Institution, researchers benefit

Waltz offers these details on how the university's compliance and quality improvement program is designed:

• **The focus primarily is on protecting human subjects.** While human subject protection is the chief goal, the program's role also includes protecting the institution and the investigator, and these additional responsibilities are in harmony with the primary focus, she says.

For example, when investigators make mistakes and otherwise show they lack the necessary understanding of human subjects protection, they are rehabilitated rather than punished through a denial of research privileges, Waltz notes.

"If we see that an investigator needs a better understanding of how to conduct compliant research, then we teach him," she explains. "We stop enrollment in his studies and show him how to do it properly. As he goes forward, we monitor closely, side-by-side, so that we ensure sustained compliance."

Compliance staff may attend informed consent sessions, providing instruction on how to improve

the process, Waltz says.

"We may continue on close oversight for two to three years," she adds. "Those investigators will be our best investigators going forward; whereas, at other institutions where they banned researchers for three to five years, what happens is the investigators eventually return and will do research with no better understanding of human subjects protection."

• **Recognize personal incentives to conducting higher quantities of research.** In the academic community, one of the major motivators for staff to produce volumes of research is the tenure track that rewards those who publish, Waltz says.

"Investigators graduate from medical school; and in the past, they had zero segments of their curriculum about clinical research," she explains. "So then they're told to go forth and publish, and there are no resources to teach them how to do this."

Their instructors and mentors also may lack adequate training in human subjects protection, and so the problem is compounded, Waltz says.

This is why investigators need proper training and monitoring, Waltz says.

"At first, investigators didn't exactly embrace the concept of having someone monitor their research, but now it gives them a comfort level that shows they're doing better."

• **Start a compliance and quality improvement program that begins with the top management.** "We say that you need strong top-down support from the highest levels of the institution because the first time you offend one of the renowned investigators, that person will head to the dean's office," Waltz says. "This will set the tone for the success of the program because if the dean tells the monitoring group to back off, then it undermines the whole program."

Waltz says she used to tell institutions to buckle up because once they start this program, the first visits will be bumpy.

• **Use monitors and stop relying solely on the IRB for all human subject protection.** Institutions often forget that the IRB is not enough protection against research abuses and problems.

"Pharmaceutical companies monitor every single study with people dedicated to going out and verifying what's happening," Waltz says.

Monitors check a variety of areas, including:

— Where is the money going?

— Are there really X number of patients enrolled as reported in the protocol?

— Are the data accurate?

— Is the study conducted according to the protocol?

"So one of the important notions to get across to investigators is how important it is to have strict protocol adherence," Waltz says.

"When I was in the pharmaceutical industry, I would come to academic centers across the country, and the investigator would tell us that, 'We don't really have to follow the protocol because we're academia,'" she recalls. "But this places the subject more at risk, because once you deviate from the known, you enter the unknown."

• **Pay close attention to investigational new drugs (INDs).** "The No. 1 mistake that people make in noncommercial settings is a failure to recognize that they need an IND for their research," Waltz says.

Investigators often confuse federal agencies and their responsibilities and may think that they've met federal regulations once their study has been approved for funding from the National Institutes of Health, when they may not be in compliance with the Food and Drug Administration (FDA) or the Office for Human Research Protections, she adds.

This contributes to what Waltz calls the phenomenon of IND avoidance, in which investigators may avoid applying for an IND because they fear they would have to follow good clinical practices if they do.

"Educating investigators about the need to follow good clinical practices regardless of IND status goes a long way to correcting that situation," she says.

"One problem is that many investigators in the country have never sat down and read the regulations, and many are not well versed in interpreting the law," Waltz explains.

This is why institutions, through a compliance or regulatory office, ought to centralize the responsibility for deciding whether an IND is needed, she suggests.

At the University of Pennsylvania, all investigators are required to present an IND number on a protocol that's submitted to the IRB, or they must present an exemption in the form of a letter from the compliance office stating that this protocol does not require an IND or an FDA letter of exemption, Waltz says.

"There are a number of physiological and metabolism studies that may not require an IND, but most other studies do," she says. "As soon as you start to use a drug outside of the approved labeling, you go into the unknown as far as the

FDA is concerned."

The institution has an IND tool, which must be completed by investigators and is used to decide whether an IND is needed, Waltz says.

"In filling out the IND form it drives the investigator to make his own conclusion that he needs an IND," she says. "It forces him to do something he otherwise would not have known how to do."

• **Require education and certification of investigators.** The University of Pennsylvania has an on-line certification program, and when investigators submit protocols they must include their certificate to show that they've completed the required training, Waltz says.

The certificates last three years before they must be renewed, and investigators are sent notices when it is time to renew their certification, she notes.

Developing the certification program was time-consuming and cost about $100,000 initially, reports Waltz.

"It takes a certain amount of ongoing resources to keep the certifications up to date and manage systems that track investigator certification and to let them know when it's about to expire," she adds. ■

Public outcry, confusion stops an Oregon study

Scrutiny of one study impacts the other

Investigators and officials with Oregon Health and Science University in Portland have learned a difficult lesson about research evaluating controversial social policies.

A 1999 National Institutes of Health-sponsored project to evaluate the results of a drug-testing program in Oregon public high schools was ultimately suspended after the federal Office for Human Research Protections (OHRP) decided that the goals of the research protocol appeared to have become intertwined with the drug-testing policy it was intended to study.

Critics claim that the design of the Student Athletic Testing Using Random Notification (SATURN) study coerced student athletes to participate in school-sponsored random drug testing and failed to provide appropriate informed consent procedures and confidentiality protections.

Researchers and university officials contend that their study protocol simply consisted of surveying students who independently agreed to participate in the drug-testing program and that critics both inside Oregon and nationwide have confused elements of the SATURN study with the testing program it was designed to evaluate.

According to a report published in the winter 2004 edition of the *American Journal of Bioethics (AJOB)*,[1] SATURN encouraged schools to adopt random drug-testing policies of students participating in extracurricular activities. In some schools, consent for random drug testing was a condition of the students' being allowed to participate in extracurricular athletics. Positive drug tests resulted in the notification of school administration, the student's parents, and the loss of athletic participation privileges.

The informed consent documents signed by participants in the SATURN study do not adequately inform participants of the risk of loss of confidentiality if they test positive for drug use and do not adequately explain the randomization methods used to place schools in the experimental and control groups of the study, argues **Adil Shamoo**, PhD, a professor at the University of Maryland School of Medicine, editor-in-chief of the publication *Accountability in Research*, and the co-author of the report in the bioethics journal.

The study also coerced participation because it allowed the school administration to decide whether to participate — by implementing a testing program — and then allowed the disclosure of drug testing results, which could result in disciplinary action.

The IRB at Oregon Health and Science University failed in its mission to appropriately oversee and monitor the study protocol, Shamoo states.

"I believe that research involving mandatory public health initiatives [like the drug-testing program] can be conducted, and one can design a study of the effects of a mandatory public health requirement that is totally de-linked from the mandatory requirement itself," he tells *IRB Advisor*.

Doing so is one of the key challenges of research into compulsory public health interventions, Shamoo notes. The subjects of the health interventions are inherently vulnerable populations, and efforts to conduct research studies on the populations that are concurrent with the intervention are difficult.

"This [the suspension of the SATURN study] has important implications in terms of mandatory public health requirements linked to a research protocol," he adds.

Researchers must be extremely careful that the

research is clearly de-linked from the public health intervention and that participants are aware of the distinction. In the Oregon case, Shamoo contends, participants were unable to distinguish between participation in the testing program and participation in the research protocol.

Critics confused the facts

The SATURN project did adequately separate its intervention from the drug-testing initiative, and Shamoo's article misstates several key facts, argues **Gary Chiodo**, DMD, director of the Office of Research Integrity at Oregon Health and Science University. Chiodo, with two of the researchers who worked on SATURN, published a response to the *AJOB* article in the same issue of the publication.[2]

Relying largely on inaccurate accounts in the news media, the article by Shamoo and Moreno comingles elements of the drug-testing program with features of the study design, Chiodo charges. The protocol, in addition to being approved by the local IRB, also was vetted by a scientific review panel at the National Institutes of Health, he says.

First, Chiodo says, schools independently decided whether to implement a policy of random testing of student athletes. The schools also independently — without input from researchers — decided whether students would be prohibited from participating in athletics if they refused to participate in the program.

SATURN's purpose was to study the impact of the drug testing interventions — whether their use influenced student attitudes and reports of student drug use.

The research intervention consisted solely of the administration of written surveys to students who had already agreed to participate in the program, Chiodo says. The study was divided into two groups: an experimental group consisting of students at schools with random drug testing in place, and a control group of students at schools that did not use random drug testing.

In order for a school to be considered a research site and its student athletes eligible for recruitment, the school had to have already decided to implement a policy of random testing of student athletes. Schools randomized to the control group agreed to defer implementation of the program until after the SATURN surveys were completed. As a condition of participation, all schools agreed to defer implementation of the program if the site was randomized to the control group.

"The student populations for experimental and control schools had to be comparable for a legitimate randomization," Chiodo explains. "Students in schools that had not decided to implement drug testing could have an entirely different belief or mindset regarding drug and alcohol use than their peers in drug-testing schools."

In addition, none of the schools included in the SATURN study used punitive policies — policies that prescribed punitive measures if a student tested positive for drug use. Researchers excluded the schools with punitive policies in favor of only schools that had developed policies mandated counseling and referral for students testing positive.

"Punitive policies were those that prescribed a punishment for a positive test," Chiodo says. "This could include being suspended from athletic participation or other school activity, detention, involvement of law enforcement, or similar measures. Nonpunitive policies were those that prescribed an educational or counseling intervention. These students were not excluded from extracurricular activities."

Consent form made distinction

So, no student athletes in the SATURN study schools, neither those in the experimental nor those in the control schools, were at risk of having the results of their drug tests disclosed to their parents, authorities, or being excluded from athletic participation. Punitive policies were in place at some of the schools implementing random drug testing, but not at schools included in SATURN, he points out.

The consent forms used by SATURN researchers also clearly identified the research project as separate and distinct from the consent process to participate in the drug-testing program, Chiodo says. And researchers have evidence that the students and the parents of students (who received the consent forms) understood the difference.

"Because the schools' intervention [random drug testing of athletes] is very distinct from the study intervention [completion of questionnaires] the chance for confusing the two was already reduced," he explains. "However, high schools students may not always perceive this distinction. The distinction was emphasized and the chance for confusing the two diminished by the informed consent process and documents and by involving the parents in the consent process. The SATURN informed consent documents addressed both parents and the students and made it clear that the schools' policies and procedures were separate from the study's

interventions and goals. In addition, live meetings with parents, informational letters, and [frequently asked questions] sheets were used throughout the project to help reduce any confusion about school vs. study objectives and procedures. All of these emphasized that students did not have to participate in the study; and if they declined to do so, they would not lose any rights, privileges, or benefits to which they were otherwise entitled. Students received multiple messages to this effect."

Data support researchers

Data obtained during the study indicate that the students clearly grasped the difference. During the period of the SATURN study, student athletic participation increased in those schools that were participating in the study and, 30% of the athletes in the drug-testing experimental schools chose to participate in sports but declined to participate in the study.

People in Oregon and beyond who objected to the drug-testing programs then confused the study protocol with the programs, which were the subject of the research itself.

"Oregon citizens and individuals from around the world confused the SATURN project with the drug testing intervention it was designed to study," Chiodo says. "The study did not require drug testing of any student. It appears that those who objected to the study objected to any policy of drug testing students. This is a civil liberties issue and far afield from the specific aims of the study. The study held out the prospect of proving with scientific accuracy the ultimate outcome of random drug testing of high school students. Drug testing may be beneficial, have no effect, or, in fact, be harmful. SATURN was designed to prove which of these outcomes result from this intervention. If it is harmful or neutral, society would be much better off devoting the resources spent on drug testing to other interventions, such as education, after-school programs, peer mentoring, and other methods."

Although OHRP did suspend the study, researchers have anonymized the data they did collect and intend to publish the results they have, he adds.

Studies that delve into sensitive social issues will always be targets for those impassioned about the issue, even if they misunderstand the study, he contends. Investigators, institutions, and IRBs must be prepared for this.

"Such studies are critically important and must go forward," Chiodo concludes. "President Bush recently announced in a State of the Union address that he was recommending $23 million be spent on drug testing in schools. If such testing is ineffective or counterproductive, the funds will have been wasted and an opportunity to provide a more meaningful intervention will have been lost. The current system of scientific review group scrutiny followed by strict IRB review, holding the study to the highest ethical standards, did, in fact, work for the SATURN study. The study design was sound, the ethical bar was set high, the investigator team was responsive and acted with integrity, and the subjects were clear on what enrollment in the study meant."

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No need to panic when OHRP comes a calling

OHRP compliance official explains process

It's a rare occurrence, but each year some institutions are subjected to a for-cause audit by the Office for Human Research Protections (OHRP).

Such audits often turn up documentation problems and review process problems with the IRB, but occasionally they also highlight very serious problems relating to the clinical trials management, such as failure to provide adequate informed consent or failure to seek an IRB review, according to OHRP officials.[1]

Complaints come from subjects, internal whistleblowers, investigators, research coordinators, advocacy groups, media reports, and other sources, says **Kristina Borror**, PhD, director of the Division of Compliance Oversight.

"Sometimes there's evidence of problems in the scientific press," Borror says. "We might see a medical journal article about a clinical trial that doesn't mention informed consent or IRB review, and we may look into something like that."

Once OHRP receives a complaint, staff determine whether OHRP has jurisdiction and then

evaluates the complaint by sending an initial inquiry letter to the institution to say what the allegations are and to send the institution a copy of the complaint, she notes.

"We will request them to investigate it and to respond to specific allegations, and we request IRB records, including the protocol, grant application, the IRB minutes of meetings where it was discussed, the continuing review, adverse events reports, and any publications that came out of the research," Borror explains. "We also request information about their system, IRB policies and procedures, forms used and required information about how they educate both IRB members and investigators in human subjects protection."

Systemic problems targeted

Once OHRP receives a response, compliance staff check this for answers to the specific allegations and also for problems with how the system functions.

"The things we consider when deciding whether or not to do a for-cause site visit is whether there is evidence of systemic problems," Borror explains. "The complaint may be about a specific clinical trial, but we may have seen evidence that the system is broken."

Other events that could prompt a full audit are the death of a subject, which may have been caused by problems in the system, she notes.

OHRP compliance officers also may be concerned if they are having difficulty getting to the bottom of what's going on at a particular institution, so this would prompt an on-site visit, Borror adds.

"If a complaint is about a particular protocol, we request interviews with the investigator or their research coordinator," she says. "We don't call them inspections — we call them evaluations, and it's done either all on paper or sometimes we'll do telephone evaluations."

Typically after receiving correspondence from an institution, investigators, or IRBs, OHRP compliance officials will find a few problems that require corrective action. The institution is then asked to take corrective action, and if it does this to the satisfaction of OHRP, then the issue is concluded. But there are times when the actions haven't been carried out and these would trigger a site visit, Borror reports.

If OHRP officials decide to conduct an on-site audit, then the staff give the institution four to six weeks notice whenever possible, she notes.

"We don't go in unannounced," Borror adds. "We give them a chance to get records together."

OHRP compliance staff will ask the IRB to pull records of 50-75 additional protocols, particularly those related to high-risk and vulnerable populations, she says.

Expedited reviews and protocols that resulted in interesting discussions at the IRB meetings also will reviewed, Borror says.

"When we have a for-cause site visit, we will often interview the different researchers separately so we can make sure no one is feeling coerced into answering questions depending on who is present," she explains.

OHRP compliance staff also will interview clinical trials staff and, sometimes, research coordinators to make certain that everyone understands what they are responsible for doing and what the protocol is all about, Borror says.

The goal is to see if the allegations are substantiated or not, she adds.

"We ask them about their responsibilities, what they are responsible for, and what their relationship is with the IRB and PI [principal investigator] and ask about specific instances where maybe there's a case of a particular subject who complained and the subject is known," Borror says. "We ask about the interaction with that subject, and we ask what they say and how they interact with the subject and investigators."

The main purpose for these types of questions is to figure out how the trial is being run and how the research is being conducted, she explains.

Since OHRP officials already have requested all of the written materials they will need to conduct the audit, the clinical trials manager and investigator do not have to bring anything with them to the in-person interviews, Borror notes.

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However, sometimes clinical trials staff will bring additional information to these interviews, she says.

They may include specific details about the protocol, material that helps to clarify certain points, such as a table that shows exactly what subjects are doing and when with regard to dosages, etc.

"Or they may bring the results of an audit that they performed or somebody from the outside performed and they want to see results, or maybe some sort of organizational chart that shows different people in organizational reporting lines of reporting," Borror says.

OHRP officials also will ask clinical trials staff about how informed consent is handled, she notes.

Borror offers this advice to clinical trials managers and investigators who want to be prepared in the event of a for-cause audit: "Just make sure records are in good shape and easily accessed and easy to read." ■

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.

The semester ends with this issue. 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.

21. According to SACHRP, what is a chief problem with the current prisoner research regulations?
A. Too often prisoners feel coerced to participate in research studies.
B. The regulations are too lax and need to be made stricter.
C. The regulations are too stringent and need some adjustments to make it easier for investigators to begin studies using prison populations.
D. None of the above

22. Institutions that form a human subjects protection program that extends the work of IRBs should create a role of monitor who will check studies for:
A. Where is the money going?
B. Are there really "X" number of patients enrolled as reported in the protocol?
C. Are the data accurate?
D. All of the above

23. Researchers of the Oregon study designed to determine the effectiveness of mandatory drug testing of student athletes assert that their informed consent documents addressed both parents and the students and made it clear that the schools' policies and procedures were separate from the study's interventions and goals.
A. True
B. False

24. If OHRP decides to conduct a for-cause audit, institutions typically will be asked to provide records of ___ additional protocols?
A. 5-10
B. 25-40
C. 50-75
D. Records for all active trials

Answers: 21-C; 22-D; 23-A; 24-C.