IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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New Congress, regulators could take up human subjects protection

Clinical trials registry issue may see action this year

From a renewed push for a mandatory clinical trials registry to a new secretary of Health and Human Services, the political landscape promises to keep IRBs and others involved in protecting human research subjects busy.

Those who watch federal activity surrounding research say the clinical trials issue — buoyed by concerns that problems with some drugs weren't adequately disseminated to physicians and the public — is likely to be taken up seriously this year.

In October 2004, House and Senate versions of the Fair Access to Clinical Trials Act were introduced and sent to the committee in Congress. The bills would have required creation of a mandatory public electronic database (most likely building upon the existing www.clinicaltrials.gov web site) in which all privately and publicly funded clinical trials must be registered.

Rep. **Edward Markey** (D-MA), one of the co-sponsors of the House version of the bill, says he and Rep. Henry Waxman (D-CA) plan to reintroduce it during the 109th Congress.

Markey says he believes there is "significant momentum" this year to get the bill passed, spurred by reports of incidents in which important negative information about drugs was withheld from the public.

"Consumers are scared and outraged that drug companies have information about the risks of a drug that they don't share with them or their doctor," he says. "Congress is a stimulus response institution, and it responds when thousands of constituents call and write their members of Congress."

David Korn, MD, senior vice president for biomedical and health sciences at the Association of American Medical Colleges (AAMC), agrees that congressional action is likely this year, despite efforts by the pharmaceutical companies to voluntarily post their trials on publicly accessible company web sites.

"Unfortunately, there's been adverse publicity about suppressing clinical trial data and slanted reporting," he explains. "The companies

have lost a fair amount of credibility over all of this well-publicized activity. For credibility's sake, probably a public registry, meaning a federally funded and federally managed registry, is the only way out of this."

He hears there will be Republican co-sponsors to the bill this year, giving it needed political viability.

The difficulty will be in the details of exactly what would be posted on such a registry, and in what form.

Markey says his bill would require that all trials be posted except for those conducted solely to detect major toxicities in a drug or to investigate pharmacokinetics. Each trial registered would be assigned a unique identifying number, which would help keep duplicative studies from being republished in different journals.

IRBs would act as gatekeepers in this process, ensuring that trials don't go forward without being registered. Markey says he doesn't believe this would create a workload problem for IRBs, since their only task is to confirm that the trial has been registered.

The question remains what would happen with results of these trials. Markey's bill would require that results be posted "in the form of a structured abstract and in such manner as the Secretary [of HHS] may require. The results consist of information determined by the Secretary to be important to clinicians or researchers, in a form that ensures that the information is accurate and not likely to mislead or distort the results of the trial."

But results may not be of much use unless they are digested into some understandable form, says **Myron Genel**, MD, professor emeritus of pediatrics at Yale University. Genel is chairman of the Public Policy Council, which consists of representatives from the American Pediatric Society, the Society for Pediatric Research, and the Association of Medical School Pediatric department chairs.

Genel says the public, and even general practice physicians, would have difficulty understanding much of the data that could find their way to a registry.

"Good evidence for that is to look at some of the data that is already posted on [trial registry] sites that have been opened by some of the pharmaceutical companies," he says. "One site I looked at for one of the antidepressant drugs had 28 pages of data. For the cognoscenti, I suppose that's helpful, but it's not very helpful for ordinary physicians and certainly not for the public."

Genel says it's possible that working out the details of such a complicated issue could end up delaying action on a registry.

Also expected in Congress this year is the latest effort by Rep. Diana DeGette (D-CO) to pass a bill specifically aimed at improving protection for research participants.

The bill, which DeGette already has introduced

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twice before, would extend the protections of the Common Rule to all research participants, regardless of the source of funding for the research.

It would call for harmonization of HHS and FDA patient safety regulations, and give greater authority to OHRP to suspend research protocols regardless of funding source for reasons of noncompliance.

DeGette's bill also would expand the nonscientific and nonaffiliated memberships of IRBs to at least two members or 20% of the total members for each board. At least two members or 25% of the total IRB members would be required to have scientific expertise.

All IRBs would be required to register with the secretary of HHS, and the bill would provide for a system of voluntary accreditation, facilitated by the secretary's office.

DeGette's press secretary, **Josh Freed**, says DeGette currently is looking for a Republican co-sponsor to reintroduce the bill in the 109th Congress; its former co-sponsor, Rep. Jim Greenwood (R-PA), retired last year.

Freed says the bill hasn't faced particular opposition in its previous attempts.

"It's a complex issue — on the one hand, the critical need to protect patients vs. what some may see as protecting the independence of research institutions," he says. "It's going to be tricky maneuvering it through Congress, and oftentimes issues involving medical research and regulation may take a bit longer."

Marjorie Speers, PhD, executive director of the Association for Accreditation of Human Research Protection Programs (AAHRPP), says IRBs should keep an eye on the progress of DeGette's bill, particularly if new problems erupt at individual research institutions.

"Congress has a lot of things on its mind right now, but as long as issues arise with respect to human research, then Congress could act at any time," she says.

Another issue that may receive attention from Congress this year is a 2004 report by the Institute of Medicine, "Ethical Conduct of Clinical Research Involving Children," that outlined ways to improve pediatric research. The report's recommendations include increasing the number of pediatric specialists serving on IRBs that approve pediatric research, and having the government offer better guidance to researchers and IRBs regarding the more restrictive rules that apply to child research subjects.

Genel says that while the release of the report in March 2004 may have been overshadowed by the debate over a clinical trials registry, senators from both sides of the aisle have expressed interest in its findings.

"I think it's generally bipartisan," he says. "I don't think this is a partisan issue."

Genel adds that he expects to see the introduction of legislation this year that would address some of the IOM's recommendations.

He says the upcoming reauthorization of the Children's Health Act could provide a vehicle to enact some of the IOM's recommendations. Genel says the Public Policy Council had recommended including demonstration grants that could show best practices involving children and research.

Leavitt statements 'encouraging'

In the area of federal regulation, Korn and Genel say they are encouraged by the early statements made by Mike Leavitt, who was sworn in in January as the new secretary of Health and Human Services. Testifying at his confirmation hearing before the Senate, Leavitt called the HHS a "trustee of our nation's most treasured brands,"

New OHRP proposed rules to affect IRBs

Here are some items identified by OHRP as the subject of possible regulatory action this year:

— **An advance notice on proposed rulemaking regarding new protections for adults with impaired decision-making capacity.** OHRP, FDA, and HHS are seeking comment on whether it's necessary to develop additional safeguards to protect these adults in research. Dates for the comment period for this notice will be announced soon.

— **A notice of proposed rulemaking on IRB registration requirements, slated for final action in April.** The proposal would require that IRBs register with the HHS, providing information about membership, accreditation status, approximate numbers of active protocols and staffing. FDA simultaneously published a proposed rule regarding FDA IRB registration requirements.

— **A notice of proposed rulemaking on human subjects protection training for institutional officials, IRB chairs, board members and staff, investigators, and others involved in human subjects research.** Dates for action have yet to be determined. ■

Most Americans believe clinical research is safe

Two-thirds of Americans believe that clinical research is safe for people who participate in them, according to a survey by the Center for Information and Study on Clinical Research Participation (CISCRP) and Opinion Dynamics Corp. (ODC).

But most respondents said they would have more confidence about clinical research if results were published on a public web site or registry.

The nationwide survey asked 1,000 adults about their attitudes about the research process. The survey was conducted in December after national media reports of problems with medications such as COX2 inhibitors and antidepressants.

When asked, "In general, how safe do you think clinical trials or studies are for people who participate?" 17% said studies were "very safe," while 49% said "somewhat safe." Ten percent chose "not very safe," 5% "not safe at all," and 18% were not sure.

A second question asked, "The federal government is requesting that all organizations conducting clinical research trials or studies report the results on a public web site. Would this increase your trust in information received from clinical research professionals?"

A total of 57% said such a reporting program would increase their trust "a lot" or "somewhat," while a total of 35% said "not very much" or "not at all." Eight percent were unsure.

Most of those surveyed — 87% — had never been asked to participate in a clinical study themselves.

The Center for Information and Study on Clinical Research Participation is an independent nonprofit organization started in 2003 to educate the public and policy-makers about clinical research participation. ODC does market research, polling, and consulting for health care and other industries.

This survey is the first in a planned series of polls CISCRP and ODC are undertaking to increase understanding of the public's views about clinical research.

For more information, visit the organization's web site, which can be accessed at either www.ciscrp.org or www.smartparticipant.org. ■

particularly the FDA, the National Institutes of Health, and the Centers for Disease Control and Prevention.

"I can only go by his public pronouncements, which are very encouraging," Genel says. "There are issues relating to the operation of FDA that he says he will address. They're going to have to be addressed. One of these is the issue of clinical trials registries, but another is post-approval surveillance."

The OHRP has a number of regulatory actions planned in the coming year **(see box, p. 27)**. Speers says IRBs should watch the actions of the Secretary's Advi-sory Committee on Human Research Protection, which may suggest guidance or revisions to the Common Rule (45 CFR 46, Subpart A).

But IRBs can do more than simply be silent observers of the political debate, Genel says.

He says the research community can do a better job of communicating with legislators about issues of human subjects protection. By staying in contact, particularly with staff members, IRBs can help them navigate the nuances of research policy-making.

Genel suggests that IRBs work with professional organizations such as the AAMC. They also should keep in touch with their own representatives, even inviting them to an IRB meeting to help give them a better understanding of the review process.

Speers says that as more human subjects protection programs seek voluntary accreditation, it could assure Congress and regulators that the research community is behaving responsibly, potentially staving off new federal action.

"There will always be problems with individual protocols or individual investigators, but what accreditation should help is to prevent the systemic problems we were seeing a few years ago," she says. "I think accreditation will not only influence perhaps what Congress does, but I think it will perhaps influence what the regulators do and that there will be less need for more regulation or a more stringent interpretation of regulation if the institutions are conducting research according to high ethical standards." ■

NIH's new ethics rules create controversy

It could have an impact on staffing

New ethics guidelines rolled out by the National Institutes of Health (NIH), aimed at repairing a damaged public image, angered employees and could create internal problems for the organization.

"I think that anybody who had any kind of clear ethical foresight could easily have foreseen the effect of this," says **Rushworth Kidder**, founder and president of the Institute for Global Ethics in Camden, ME. "My worry is that the effect will be to decimate the ranks of the NIH at the very highest level."

Namely, concerns quickly arose that the new rules could adversely affect employee retention and recruitment.

Over the past year, the NIH has worked to address perceived conflict of interest issues that stem from the outside consulting activities of its employees who have reaped financial benefits from the pharmaceutical and biotechnology industries. During testimony before a congressional committee last summer, NIH director **Elias Zerhouni** said, "Drastic changes are needed."

As a result, the new regulation focuses on outside consulting with pharmaceutical and biotechnology companies, financial holdings, and awards for all of the public health agency's employees.

"This regulation is critical to restoring the integrity of the NIH and the public trust," Zerhouni said in a memo distributed to all NIH employees, "and I fully support it."

The guidelines prohibit staffers from engaging in certain outside employment with pharmaceutical and biotechnology companies, supported research institutions, health care providers and insurers, and related trade, professional or similar associations. Stock holdings in biotechnology and pharmaceutical companies are not allowed for employees who are required to file public and confidential financial disclosure reports, and are restricted for other staff.

That latter provision, in particular, drew the ire of NIH employees during a staff-only meeting held in February at headquarters in Bethesda, MD. According to an account in *The Washington Post*, a number of staff members voiced their displeasure over the new equity divestment rules. Kidder says such irritation showed that the newly drafted policy overstepped its intent.

"I don't see how I, as a taxpayer, am benefited by insisting that secretaries at the NIH can't own stock in certain companies," Kidder says. "I don't think that's taking us where we want to go. It needs more finesse, more nuance, and needs to be more clearly targeted."

Further addressing the stock divestiture issue, he noted that current market conditions might not be optimal. Officials at the NIH did not respond to attempts to seek comment, but in Zerhouni's memo, he said staff will have several months to sell the prohibited holdings, "during which time you may seek an exceptional circumstances exception to this provision or apply for a special tax document that will allow for the deferral of any capital gains tax owed as a result of the sale of the stock."

The regulation was developed in concert with the Department of Health and Human Services and the Office of Government Ethics, a federal agency devoted to executive branchwide ethics standards. HHS, the agency under which the NIH falls, intends to further evaluate provisions regarding outside activities and financial holdings within the next year and could revise them.

But Kidder again questions such a tactic.

"I think the notion of putting [the ethics guidelines] in a trial form is actually a failure of due diligence on their part, a failure to think hard about the consequences," he says. "You could say, 'We had to try it and see.' Well, we don't run NASA that way, saying, 'Let's just see whether this thing blows up while it's in space, and if it does, we'll go back to the drawing board.'"

But he does not question the NIH's motive behind drafting the new policy. Along those lines, Kidder does not doubt Zerhouni's assertion on the importance of trust, as Zerhouni himself told the congressional committee last summer.

"Our public health mission is too important to have it undermined by any real or perceived conflicts of interest," Zerhouni said. "It is imperative that Congress and the American people trust that the decisions made by our scientists are motivated solely by public health priorities and scientific opportunities, not personal financial concerns."

Also at that committee meeting, Zerhouni said the consulting practices were rooted in a 1995 change of prior ethics rules and policies that resulted, in part, out of the NIH's desire to better its recruitment and retention.

Zerhouni added in his memo: "I strongly believe that this regulation and all of its provisions are necessary and will strengthen the programs and

operations of the NIH. It will also help us regain the public's trust that has eroded because of the actions of a few."

Going forward, its scientists will continue to be able to conduct academic activities such as teaching at universities, writing textbooks, performing scientific journal reviews, participating in scientific meetings, and providing general lectures to physicians and scientists at continuing professional education and similar events. They also are permitted to practice medicine as appropriate.

But Kidder, whose 15-year-old organization counsels and trains other organizations on creating ethical cultures, says that might not be enough. He wondered why no one inside the NIH tried to stop the final draft of the guidelines before consulting the policy's potential ramifications on internal morale.

"My only sadness is that they rammed it through, apparently," he says. "They rushed in without the sufficient consideration of the thoughtful tradition of ethics, and things that they really should have foreseen."

Perhaps, Kidder adds, Zerhouni and others at the top might rethink their decision and rework the policy in the coming weeks. ■

EPA postpones child pesticide study

Agency seeks external review

The U.S. Environmental Protection Agency (EPA) has decided to delay the start of a controversial effort to study the effect of pesticides on children after some agency officials raised concerns about its recruitment procedures.

The Children's Environmental Exposure Research Study (CHEERS) was planned as a cooperative effort between the EPA and the chemical industry trade group the American Chemistry Council (ACC). As originally conceived, the two-year study would follow 60 children in Duval County, FL, ages 3 years and younger, to determine how children come into contact with pesticides and chemicals in the home.

According to an ACC press release announcing the study last October, families would be asked to keep records of their pesticide and household product use, with researchers following up to monitor the children. The study is designed to measure the concentrations of the chemicals in the children's homes and determine how the children are exposed to chemicals that are present in the consumer products used.

However, an Oct. 30, 2004, report in *The Washington Post* made public several internal e-mails between EPA staff members expressing concern that the study's recruitment procedures would entice low-income families to put their children at risk to participate.[1]

In exchange for participating in the study, the *Post* reported, families who used pesticides in the home would receive $970, some children's clothing, and a camcorder that the parents could keep.

In internal e-mails obtained by the newspaper, EPA officials not affiliated with the project questioned why the agency would encourage some parents to continue to use pesticides in the home when such chemicals have been linked to lung and neurological problems.

EPA officials responded that the study would involve adequate education for the parents about the risks of pesticide exposure and that they would be informed if their children's urine samples showed abnormally high levels of pesticides.

Families could remain in the study even if they stop using pesticides, the agency said, as long as they were using them before the project started.

However, the study also took fire from outside sources, many of whom questioned the federal agency's acceptance of a $2 million grant from the ACC to help fund the research, the key role the trade group would have in designing the study, and concerns that the ACCE might be able to influence public dissemination of the research results.

"Instead of assigning a qualified team of independent scientists to gather this information using government funds, your agency has instead accepted industry funding and guidance from the makers of the very chemicals in question," wrote **Kenneth A. Cook**, president of the nonprofit advocacy organization Environmental Working Group.[2]

The Organic Consumers Association pointed out that the EPA and the ACC have data showing that many of the chemicals to be studied in CHEERS are harmful, but that those studies are of incremental exposures over time. The short duration of the CHEERS project will not reliably detect the effects of exposures, it claims.[3]

The agency does not intend the study to provide concrete data on the effects of exposure — since long-term exposure has been demonstrated to be harmful — but that the agency and chemical industry want to understand the mechanism of

exposure in order to develop safer methods of pesticide manufacture and use, says **William McFarland**, PhD, the EPA's acting deputy assistant administrator for science in its Office of Research and Development.

"CHEERS is designed to fill critical data gaps in our understanding of children's exposure to pesticides and other chemicals commonly used in the home," he stated in a Nov. 8 memo to employees that has been posted on the EPA web site. "Recent news articles have mischaracterized the study, and EPA is actively working to assure all interested parties that the study is designed to meet rigorous ethical and scientific standards."

To that end, the agency is sending the study protocol for another external, independent review, this time by an expert panel made up of members of the federal Science Advisory Board, the Science Advisory Panel, and the Children's Health Protection Advisory Committee. It is anticipated that this review will be completed, and that a report will be forwarded to the EPA administrator, in the spring of 2005. Based on this review, the agency may refine the study design, McFarland reports.

The study design for CHEERS already has been externally reviewed for scientific merit and ethical protections by four separate IRBs, he noted. The IRBs and the dates they approved the study are: Battelle Memorial Institute (August 2004), University of North Carolina (September 2004), Florida Department of Health (pending approval), and University of Florida (May 2004).

More information about the CHEERS trial is available on the web at www.epa.gov/cheers.

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Group questions value of vulnerability designation

Concept has lost meaning over time

Although IRBs are often charged with giving special consideration to research involving subjects deemed to be particularly vulnerable to exploitation, there is no standard definition of what this term means, and no guidance governing what additional protective measures it should prompt.

Moreover, argues a group of research ethicists, so many people and groups of people are now considered to be vulnerable that the concept itself has lost meaning and needs to be re-examined.

"When we talk about vulnerability now, we tend to focus exclusively on the capacity to give informed consent," says **Carol Leavine**, director of the Families and Health Care Project at the United Health Fund of New York and a member of the national Consortium to Examine Research Ethics. The consortium recently published a report detailing the limits on the concept of vulnerable populations. "But then, many IRBs don't take that a step further and ask themselves, in what ways does the research protocol pose special risks to this group of people, or to anyone, and are these risks acceptable? They tend to focus on making sure that there is informed consent, and then deciding if that exists, then it's OK."

Since the now commonly accepted codes of research ethics were developed in the mid and late 1970s, the research enterprise has changed dramatically, the group points out. Where the Belmont Report focused on protecting certain specifically defined populations, such as children, the mentally ill, or persons confined to institutions, many more groups of people are now considered to be at least potentially vulnerable. For example, the concept of vulnerability has grown to include whole societies of Third World countries in which the United States and other industrialized countries want to conduct studies.

Almost everyone, at some point, due to some facet of their life or work, could be considered a member of a vulnerable group, Leavine says.

Aside from subjects in need of the special protections clearly defined in the law — children, prisoners, etc. — categorizing a subject as vulnerable can have a stigmatizing and limiting effect.

"Not all members of potentially vulnerable populations will be vulnerable in the same way," Leavine says. "One person's ability to understand the risks and benefit of a particular protocol and willingness to consent may be very different than his neighbor's, though they both may be considered members of a vulnerable population."

In some cases, focusing on the population as

vulnerable masks larger problems with the research protocol and with society.

"For example, there is a lot of concern that poor people might be unduly coerced to participate in medical research as a means of getting access to basic medical care," she notes. "While this is certainly valid, we should address the problem of people not being able to afford health care, rather than just considering it one of a number of factors that might make this person a bad candidate for research."

Some people may be at higher risk for harm from certain aspects of a particular protocol, even though they may not objectively be considered a member of a vulnerable population, she adds. People with a rare genetic disease might be more vulnerable to risk and coercion in a study of an experimental therapy, for example.

The group advocates an approach that focuses more on the risks posed by individual protocols, evaluating these to determine whether they place specific groups, or all potential subjects, at increased risk for harm — and determine ways in which investigators should minimize the risk and seek appropriate informed consent.

Certain studies, they say, should be categorized as requiring special scrutiny by IRBs.

A study would require special scrutiny if one of the three criteria are met:

- the research involves initial experiences of translating scientific advances into humans, especially when the intervention is novel and/or irreversible;
- there is known or credible risk of significant harm and there is no potential of an offsetting direct medical benefit;
- the protocol raises ethical questions about research design or implementation to which there is no consensus.

Special scrutiny is a mechanism that aims to provide appropriate protections to all research participants, not just those officially deemed vulnerable, Leavine says.

"Some have interpreted our argument to mean that we want to abandon the concept of vulnerability completely and not consider special protections for certain groups of people," Leavine says. "That is not the case at all. We certainly respect the need for certain protections — those for children, as we mention, and there should be clearer regulations governing research among the mentally ill and those with diminished mental capacity. But we also want to urge IRBs to also consider the ways that people are individually vulnerable. What characteristics of each protocol might make certain people more vulnerable."

Reference

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Autonomy key to audit team effectiveness

Early intervention can reduce long-term impact

An effective compliance oversight process can nip noncompliance problems in the bud — acting quickly to handle small problems before they get bigger, even preventing future noncompliance from occurring.

But getting to the heart of allegations fairly and efficiently takes a strong audit team, with the expertise to handle varying types of investigations and the independence to examine anyone, even the IRB it serves.

George Gasparis, CIP, executive director of the human subjects protection program at Columbia University says that regardless of whether an audit team is officially part of an institution's IRB staff, it should have the autonomy to directly address senior institutional officials, if necessary, to have its concerns heard.

"Regardless of where the audit team is in the institution, if that audit team compliance officer doesn't report directly to the highest institutional officials and reports to somebody else, then there needs to be a dual reporting line to the higher institutional official," he says.

At Columbia, Gasparis is assistant vice president and senior assistant dean for research ethics, which gives him responsibility for developing the university's human subjects protection program. He oversees Columbia's four IRBs as well as the university's compliance oversight team for human research, which generally has three to four members.

Although both functions are under his authority, Gasparis says the compliance oversight team does maintain a certain separation from the IRBs. It is designed so that at least one member is completely independent of the boards, in part because whenever the team does a full-blown audit for

possible noncompliance, IRB records are part of the investigation.

"To have someone audit themselves creates a potential conflict," he says. "We may have some people from the IRB to assist in the audit, but we want to have individuals who are outside of the IRB as well."

Audits examine records globally

At any one time, the compliance oversight team handles 20-25 investigations, ranging from small inquiries into minor issues to full-scale audits. Allegations of noncompliance can come from a number of sources — from the IRBs, research staff or other employees, subjects, from institutional officials or from Gasparis himself.

After a brief inquiry, the team determines whether an investigation or audit is warranted. If an audit is appropriate, then a more intensive review of documents is conducted, Gasparis says.

"We'll conduct interviews and review relevant documentation for investigations," he says. "For audits, we will review more information, including the regulatory documentation, research records, and source documentation. When appropriate, we will review a significant percentage of the research records or broaden the audit to more than one study. Audits also will include a review of the IRB records.

"We'll look at it as globally as we can to see all noncompliance that may have occurred and whether there is more noncompliance than the allegation is initially reporting."

The compliance oversight team will come up with its findings, and with recommendations to fix the problem and prevent its recurrence. Those recommendations are forwarded to the IRB, which can accept them in full or modify them.

If the team doesn't agree with the IRB's decision, the program's standard operating procedure (SOP) allows it to take up the matter with a senior institutional official — the dual reporting line that Gasparis says is important to give the team its autonomy.

"In a situation like that, the institutional official most likely would call for a separate investigation that is independent of the IRB to make a determination," he says. "Fortunately, something like that hasn't happened yet since I have been here, but our SOP is designed to deal with it."

An institution that wants to strengthen its compliance oversight process should be sure it has an SOP that spells out exactly how noncompliance allegations are handled, Gasparis says.

It should be clear how an inquiry proceeds to a full investigation — who decides, and on what that decision is based. As the findings come in, there should be a clear-cut process for handling them objectively.

Gasparis says it's important that the SOP allows for due process, giving the investigator an opportunity to respond to any findings of noncompliance from the team.

"The findings should go to whoever is accused of noncompliance, for them to comment on the audit's findings before they're released to a federal regulatory office," he says. "You may ruin someone's reputation, and if you didn't have it correct or you misrepresented the facts, you could incur some liability."

Affording investigators due process isn't just a legal issue, Gasparis says.

"It's important not just for preserving reputations, but also for getting it right," he says. "You need to have due process, and due process isn't always in everyone's SOPs."

Gasparis says institutional officials, legal counsel, and appropriate representatives of the IRB, including the chairs and the director, should review a proposed SOP.

Another vital step in creating a strong compliance oversight team is carefully choosing who will serve on it, he notes.

Ideally, members should have both experience with IRBs and strong research experience.

"I think it's important that the audit team manager, or at least one or two auditors, were actually involved in clinical research," he says. "To audit a clinical research study, one should be familiar with how they keep their records — what records should be kept, what regulatory files should look like, what clinical research data looks like, how adverse event information is usually collected, how to go through source documentation.

"Somebody who is sent out to a research team to look through their records and isn't familiar with that research methodology is going to be a little handicapped at being able to conduct a solid audit," Gasparis says.

He says a successful auditor must be able to write well, and present findings in a clear and objective manner, not going beyond the documentation to draw conclusions.

Finding these candidates can be difficult.

"The ideal candidate to me for what we want to do here is somebody who has research experience as well as IRB experience. That's a really

hard candidate to find, because it's hard to find people with good IRB experience," Gasparis says.

While auditing is inherently an adversarial activity, Gasparis says it's important that the process be as collegial as possible, to maintain a good relationship between faculty and the IRB.

"Many believe that an IRB works best when it works with the researchers to protect human subjects," he says. "If you work in a collegial manner with investigators, you're probably going to have a better human subjects protection program."

As the program at Columbia continues to grow and develop, Gasparis plans to introduce a quality improvement program, inviting researchers to volunteer to have their work examined to look for ways they can improve protection of study participants.

Such a voluntary program can help enhance an IRB's relationship with investigators, while finding and correcting smaller problems before they become more serious.

"Most researchers really want to do it the right way," Gasparis explains. "When noncompliance occurs, it's usually a result of lack of resources, lack of attention to detail, or lack of follow-up. Something gets missed, wasn't followed up on and with a high volume of work, people move on to do other things and it slips through the cracks. And then suddenly, one is out of compliance." ■

Reporting adverse events on e-form saves time

Pilot program already garnering praise

A pilot program of a web-based system for reporting adverse events in clinical trials already has shown itself to be a timesaver for study staff at the Dana Farber/Harvard Cancer Center.

The program allows investigators to submit adverse events on a web-based form and IRB staff to view up-to-the minute information on submissions with the click of a mouse button, says **Deborah Barnard**, MS, CIP, assistant director of quality assurance and education at Partners Human Research Committee.

Barnard helped develop the e-form in use at the cancer center, which is a collaboration among the Dana Farber Cancer Institute, Harvard Medical School, Harvard School of Public Health, Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Children's Hospital Boston, and Massachusetts General Hospital (Partners Health Care is made up of Brigham and Women's Hospital and Massachusetts General).

For an organization such as Dana Farber — five Boston-area hospitals participating together in a "virtual" cancer center — the time saved taking adverse event submissions to the IRB has been a real boon, Barnard says.

"We do know that since we've been able to implement just these very modest e-submission tools, we estimated we're saving people five to eight hours a week, in just walking back and forth time," she says. "Not to mention all the stuff that was just getting lost.

"That's a lot of time out of someone's week, when you know they're already overscheduled."

Real-time information available

The e-submission form looks like the center's paper form for reporting adverse events. Currently, it's only in use for adverse events from clinical trials, but Barnard says it later could be used to report other unanticipated problems in studies.

An investigator can key in a five-number ID code and call up basic information about the study in real time — the study title, the name of the investigator, its current status, etc.

He or she then goes through the e-form, answering all of the questions. Many of the questions are required; when the investigator reviews the form, the program will highlight any omissions, as well as raising a red flag if information submitted conflicts with existing policies, Barnard explains.

Once the investigator submits the e-form, an e-mail is generated to confirm the submission. The investigator also can print a copy for his or her paper records.

Back in the IRB office, the staffer who is responsible for handling adverse events reports is notified by e-mail that a report has been submitted, Barnard says. The program also links to the IRB's database and updates the numbers of adverse events for the study.

"She would print off a paper copy for the IRB, because the IRB still reviews the hard copy," she says. "Then she'll go into the database and mark that [the report] is pending, and it would start through the process, with it ultimately getting scheduled for full review or just ending up with an expedited review."

The IRB still is developing a tool to use to analyze the data submitted through the e-forms. "But the

basics are such already that we can say, 'It seems like we've been seeing this particular event in this drug a lot.'" Barnard says, making it a useful tool to spot trends early.

Because of the automatic updating of the database, the IRB always has access to the most current data on adverse events.

"When pulled up, it's up-to-date as of that moment," she says. "It's all live, real data."

Barnard credits much of the success of the project to two key factors:

— **Seeking lots of input.** At the beginning, the developers of the e-form sought opinions from those who would be using the information — the IRB committee that reviews adverse events.

"We wanted to find out what was really important to them, both in terms of what they received on the form and what information they would like to have access to, literally at a moment's notice and how they would make use of that information," Barnard says. "That was our first step."

The developers later went back to the committee as well as to IRB chairs and study staff, to show them the prototype and elicit feedback."

"They could have a look and tell us what they thought — actually use it and say, 'That doesn't work, or this doesn't make sense,'" Barnard says. "We were able to create help texts, and make adjustments immediately, based on actual user feedback."

Among the changes: Adding more required fields because of feedback from study staff. Because they dealt with different sponsors and other outside groups, they had a better idea of some of the information those groups were looking for, she reports.

"It's important to really think those steps out and be open to both criticism and people's desire to help," she says.

— **Finding the right technical help.** Barnard says the developers hired a programmer who was familiar with the architecture of the existing database, having served as a consultant when it was created in-house.

He was also, she says, a good listener — able to understand their goals, and the necessity of making the form user-friendly for investigators and study teams as well as IRB staff and the IRB chairs.

"It's really an interesting combination of somebody who has those amazing technical skills but that real people skill to listen and understand and appreciate what you're doing," she says. "He ended up spending months and months with us and learning more and more about every aspect of this one particular piece, which was a very complicated process."

Finding that combination of technical skills and user sensitivity can be difficult, Barnard says. Often technical staff want to change the process of how an organization works to fit the technology.

"This project had actually been discussed three years before, and the reason it never went forward was because the computer guys decided how it was going to be done, and all the IRB staff said, 'You're crazy, that's not how we work,'" she says. "It literally didn't go anywhere until we were able to get the funds and engage this programmer."

The e-form pilot project at Dana Farber launched last June; developers still are tweaking it to get it ready to make it the required submission form for all adverse events. But so far, Barnard adds, response has been positive, primarily because of the time it saves.

"We did focus groups all along the way and we got some really good feedback," she says. "It saves so much time from printing and hand-carrying or printing and having to rely on our interoffice mail, which isn't that great."

There have been a few kinks along the way. During development of the e-form, the National Cancer Institute updated its Common Terminology Criteria for Adverse Events. The e-form was based on the old version; Barnard says that changing to include the new version is one factor holding up making the e-form a required submission form.

For IRBs interested in tackling a similar project, Barnard has this advice: Don't give up.

"It's really disheartening when it takes longer than you think," she says. "I think we're all were feeling kind of embarrassed that we weren't able to make our own deadlines. But stuff happens that you don't anticipate, and that's really beyond your control. Just keep plugging ahead, because you want it to be a quality product.

"We really believe it's going to enhance every aspect of our program," Barnard says. ■

COMING IN FUTURE MONTHS

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CE/CME objectives

For more information on this program, contact customer service at (800) 688-2421; e-mail: ahc.customerservice@thomson.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 to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

9. Which recommendation was part of the Institute of Medicine's 2004 report, "Ethical Conduct of Clinical Research Involving Children"?
A. A mandatory clinical trials registry for all new drugs.
B. Increasing the number of pediatric specialists on IRBs who handle pediatric research.
C. Registration of IRBs with the Department of Health and Human Services
D. None of the above

10. The Belmont Report designated which of the following populations as "vulnerable"?
A. Children
B. The mentally ill
C. People confined to institutions
D. All of the above

11. What percentage of Americans believe clinical research to be "very safe" or "somewhat safe" for human participants, according to a survey conducted by the Center for Information and Study on Clinical Research Participation?
A. 45%
B. 22%
C. 67%
D. 90%

12. An effective compliance oversight team needs to have the ability to directly address senior institutional officials, if necessary, to have its concerns heard.
A. True
B. False

Answers: 9-B; 10-D; 11-C; 12-A.