IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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IN THIS ISSUE

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Court treatment order raises serious ethical questions about research

Treatment INDs should be balanced decision

When a judge recently ordered a pharmaceutical company to provide an investigational drug to a teenage boy who had not met the enrollment criteria for a phase II trial, the IRB world took note.

The case raised ethical questions about the court's involvement in research, as well as about how the sponsor, investigators, and IRB handled subject recruitment.

Judge William J. Martini of the United States District Court in Newark ruled on Aug. 20, 2008, that 16-year-old Jacob Gunvalson of Gonvick, MN, should be allowed to receive an experimental drug called PTC124 even though the teenager does not meet the criteria for clinical trial eligibility, according to published reports.[1]

PTC124 is being studied by PTC Therapeutics of South Plainfield, NJ, a small pharmaceutical company that has been enrolling subjects in phase IIa trials to study the drug's potential as a therapeutic agent for patients with Duchenne muscular dystrophy.

PTC Therapeutics will appeal the court's decision, says **Stuart Peltz**, president and chief executive officer, in a statement issued Aug. 20, 2008.

"The issue here is that a judge can't order a pharmaceutical company to supply a drug to an individual without the FDA's approval, and because the drug is available only under an IND [investigational new drug], IRB approval is also required," says **Mark S. Schreiner**, MD, an associate professor of anesthesia in pediatrics at the University of Pennsylvania. A member of *IRB Advisor's* editorial advisory board, Schreiner is the chair of the committee for the protection of human subjects at The Children's Hospital of Philadelphia.

The court's order remains subject to FDA approval, just as all individual treatment INDs need to be approved by the FDA before the test article can be used outside of the clinical trial, says **LaDale K. George**, JD, a health care attorney with Foley & Lardner in Chicago, IL. George also is on *IRB Advisor's* editorial advisory board.

The FDA allows sponsors to apply for an individual treatment IND, which some people call "compassionate use" drugs.

"But these applications typically are made after a drug has some proven efficacy, [via] phase II or phase III trials," Schreiner says.

Whether an individual treatment IND is requested by a physician or a sponsor, it has to be approved by the FDA, George explains.

This case has moved the decision-making process from the sponsor and thrust it right on the FDA's doorstep, he notes.

One ethical problem with the court decision is that neither the patient nor the judge are equipped to assess the risks and benefits of an investigational drug, and yet these should be assessed before an individual is allowed to take the IND, experts say.

"I have a problem with a judge mandating clinical care," says **Merit E. Cudkowicz**, MD, an associate professor of neurology at Harvard Medical School and Massachusetts General Hospital in Charlestown, MA.

"This is a drug with no known efficacy, and it's early in development," Cudkowicz adds. "There is no knowledge of what dose to give, and it's not right for a non-medical person to mandate the treatment."

When a drug still is in phase II testing, as is PTC124, it is difficult to make a risk-benefit assessment, which is the whole point of conducting clinical trials, Schreiner says.

"There could be an individual treatment IND with a phase II drug, but it depends on the strength of evidence and rarity of condition and alternatives available," he adds.

"A lot of these treatment INDs happen in drugs in phase III trials and they're for life threatening conditions where the patients wouldn't qualify for the trial," Schreiner explains. "I believe we should not release agents until there is some more substantive evidence of efficacy from clinical trials."

IRBs face ethical quagmire

For IRBs, this situation is fraught with ethical conflicts.

For example, is it ethical to permit a sponsor to release an investigational drug to non-trial patients when it's still a major risk that the drug could cause the patient more harm than benefit?

"Ultimately, we could end up doing more harm to the individual and more harm to other patients if we were to permit uncontrolled access to unproven, potentially toxic medications," George says.

And if a judge does order a sponsor to make the drug available to patients who do not meet the study's criteria, how will these patient's experiences impact the overall study's recruitment and adverse event reporting?

"Randomization is the hallmark of clinical trials, and if you remove the randomization ele-

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ment from a clinical trial then you have no control group, and therefore no evidence is being produced," George says.

In addition, investigational drugs cannot be sold because they haven't received marketing approval from the FDA, so on what basis would these free drugs be denied to the many sick people who think they need them, he asks.

"So a pharmaceutical company would have to produce a product that's unproven and for which they have to give it away without compensation," George says. "That's the wrong outcome for everyone, and in the long term it's detrimental."

This court case has been a hot topic because it puts drug companies in an awkward position, says **Stephanie J. Zafonte**, MSN, RN, CCRP, CQA, RAC, director of operations at George Washington University, biostatistic center, in Rockville, MD.

"If you allow compassionate uses of an IND, you don't know what the implications will be," Zafonte says. "What if something happens to this boy after he takes the drug?"

The judge's decision could put the boy in risk and even result in the company stopping drug development because of an adverse event that occurs to a patient who should not have been included in the study, Zafonte adds.

"This could impede drug development that could, in fact, help hundreds or thousands of others," she adds. "So how do you choose this single person versus society?"

Reference

1. Grynbaum MM. Judge orders drug maker to provide experimental treatment to terminally ill teenager. *NY Times*. Aug. 21, 2008. ■

Did company go too far in subject recruitment?

Overnight stays blur boundaries, experts say

Subject recruitment is one of the more ethically troubling issues raised by the recent case in which a judge ordered that a teenager receive an investigational drug from PTC Therapeutics of South Plainfield, NJ.

The family of the 16-year-old muscular dystrophy patient, **Jacob Gunvalson** of Gonvick, MN, told Judge William J. Martini of the United States District Court in Newark, NJ, that they had a special relationship with PTC Therapeutics. Gunvalson's mother said that company officials had assured her early on that her son could take part in the PTC124 phase IIa trial.[1]

One reason why she felt this way was because a PTC Therapeutics' official had invited the Gunvalson family to stay in their home overnight, a practice that apparently wasn't unusual during the recruitment process. The judge appeared to sympathize with the Gunvalsons' claim that they had a relationship with PTC Therapeutics that went above and beyond the typical sponsor-subject relationship.[1]

PTC Therapeutics CEO Stuart Peltz acknowledges in an Aug. 20 media statement that company staff formed a close relationship with the Gunvalsons, as they did with other potential clinical trial participants.

"We believe the court may not have appreciated that PTC is a small, start-up company doing pioneering work to develop treatments for rare forms of muscular dystrophy and similar diseases," Peltz says.

"In contrast to big pharmaceutical concerns, it is quite natural for our team to form close relationships with patients and other members of the rare disease community," he adds. "In fact, on the very night Mrs. Gunvalson and her son were staying at the home of a PTC employee, another patient's parent was staying with her as well."

Peltz says the company has received awards from patient advocacy groups for these efforts.

Raise the red flags

This practice is very problematic from an ethical perspective, experts say.

"An IRB wouldn't have approved having patients stay at sponsor's homes," says **Stephanie J. Zafonte**, MSN, RN, CCRP, CQA, RAC, director of operations at George Washington University, biostatistic center, in Rockville, MD. Zafonte previously was the senior extramural regulatory analyst with the office of clinical research at the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in Bethesda, MD.

"That's completely unethical, and the company should be held accountable for choices, whether they're forced to give the drug to the boy or not," Zafonte says. This could be seen as coercive during a recruitment process, he adds.

"It's an interesting recruitment process to

invite someone into the home of the sponsor," says **LaDale K. George**, JD, a health care attorney with Foley & Lardner in Chicago, IL.

"I'd like to understand the rationale for intimate relationships with a patient because it appears to present a situation that could be interpreted, as in this case, as somewhat coercive and promising more than exclusion/inclusion criteria would entail," George says.

Mark S. Schreiner, MD, an associate professor of anesthesia in pediatrics at the University of Pennsylvania, says, "I think the sponsor should not have a personal relationship with subjects. At our hospital we had a similar experience with a company developing a drug for a rare condition. Someone high up in the company had two children with the condition. They wanted the children to receive the drug."

The children would have been the only subjects in the study. This case never even got so far as the IRB because the research institution felt that it was a conflict of interest and there wouldn't have been equitable selection, so the request wasn't approved, he adds.

The ethical way for clinical trials to recruit subjects is to have the process be objective and impersonal, the experts say.

"If you're a patient and you're seeking to obtain access to the clinical trial, there is a mechanism for doing that," George says. "You can identify where the investigator is located and then attempt to go through the investigator to gain access to the trial, or you can contact the company and the sponsor's process is to direct you to the investigator."

Any contact between the sponsor and the patient beyond the formal process could lead to misinterpretation of motive on the part of the sponsor or patient, he adds.

"This is where the subjects, as it appears to be the case here, believe they were entitled to some level of preference beyond what inclusion/exclusion criteria is mandated," George says. "And it appears to give the illusion of recruitment efforts beyond what an IRB has the responsibility for approving."

When the sponsor provided housing to the patient, it deviated from standard practice.

"Usually you arrange housing through the clinical trial site," Schreiner says. "The investigator is the one who has the relationship with the subject, not the sponsor."

There are some rare diseases in which parents and interest groups work with sponsoring companies directly, and these relationships might have some blurred lines, Schreiner notes.

"But I think that impacts the ability of the subjects to make a risk-benefit decision," he adds. "The prospective participants may be unduly influenced into taking part in a risky trial for altruistic reasons."

Blurred relationship lines can lead to research participants failing to understand that the investigational drug might not work at all and that the participant might not even receive the actual drug, but could be on the placebo arm.

"These families are in desperate situations," says **Merit E. Cudkowicz**, MD, an associate professor of neurology at Harvard Medical School and Massachusetts General Hospital in Charlestown, MA.

"These are horrible illnesses, and especially if it's your son whose sick you want to do everything you can."

Sponsors and investigators who do not follow ethical standards when interacting with potential research participants run the risk of bad outcomes, such as what has happened with the PTC124 court case.

"It appears that the behavior of the sponsor was misleading to the patient and their family," George says. "And if more appropriate boundaries were maintained then the family's impression of what they were being offered by the therapeutics company likely would have been very different."

Reference

1. Grynbaum MM. Judge orders drug maker to provide experimental treatment to terminally ill teenager. *NY Times.* Aug. 21, 2008. ■

Follow the money: IRB office boosts collections

Taking ownership has dramatic impact

IRB fees that are not billed or collected may cost an IRB office the staffing and resources it needs to maintain efficiency and quality in reviewing human subjects research. So it's a good idea for research institutions to take a second look at the IRB fee collection process and improve the policies and procedures wherever necessary.

At least one institution has a process that's worth taking a look at: The IRB office at Saint

Louis (MO) University developed a very successful IRB fee collection process, doubling its number of collected invoices and raising its collection rate from 83% to 96% from 2006 to 2007.

This improvement occurred during a period in which the IRB reviewed 11% fewer protocols that qualified for billing than it had previously, says **Melissa G. Fink**, MA, behavioral and social sciences IRB manager at Saint Louis University in the department of research compliance/IRB office.

"We were just better about getting invoices out," Fink adds.

The IRB office and research institution decided to review the IRB fee collection process after Fink and others noticed some problems with generating invoices and collecting payment.

"The old system had a business manager who was part of the grants and contracts staff send invoices to sponsors," Fink explains. "Because the IRB fee went into the contract, that business manager generated the invoices because the person had contact information for the sponsor."

However, the business manager didn't have the best data from the IRB side with regard to when IRB reviews were completed, so it was a challenge to have fees billed consistently, she adds.

So one of the first changes was to give the IRB staff the fee-billing task.

"The first step was for our staff to take control of the actual invoicing to make sure bills were going out the door," Fink says. "Along with that, we enhanced our home-grown database system to include an invoicing component so that when we're entering information about new protocols we can flag it as a protocol that can be billed."

The invoices then are sent from the same database.

As a result the IRB billed 281,500 IRB fee invoices in 2007, compared with 112,000 in 2006. And the number of billed invoices that were collected was 271,500 in 2007, compared with 92,500 in 2006, Fink says.

Here's how the process works:

1. Negotiate fees.

"The fees remained constant throughout that period," Fink notes. "The IRB charges $2,000 to the sponsor or clinical research organization (CRO) for any initial review, and then we charge $500 for any continuing annual review or substantial modification to the protocol that requires board review."

Most sponsors will incorporate IRB fees into their research contracts, or it's negotiated by the research institution, says **Anne Imlay**, a secretary in the Saint Louis University IRB office.

Imlay was assigned the IRB fee collection process because she is the person who does the data entry for any protocol or protocol action and can see in the database when something is billable, Fink explains.

2. Include new protocols in field for fee billing.

"We compile a list of billables to protocols or to changed annual reviews, and that list goes to me," Imlay says. "We generate invoices from that list, and our board meets twice a month so twice a month the bills are sent out."

The IRB bills only for protocols that go to the full board, a determination that is made by the IRB coordinator, Fink says.

3. Check invoicing status regularly.

"I make it a habit when I get a submission to automatically check the invoicing status," Imlay says. "If it's a fair amount of time since our last correspondence with the sponsor then I'll send another invoice to remind them that it's outstanding."

Imlay makes a point of doing this at the end of each month.

"Some sponsors will pay after one invoice, but most sponsors have a 45 day turnaround, so I try to make a point at the end of each month to look at a list of everything I've done and follow up one more time on anything that's outstanding," Imlay adds.

4. Address ongoing challenges.

"There still are challenges we have that are internal in nature," Fink says. "I think that some sponsors and CROs that prefer to send payment for things related to contracts to one site at an institution, and often that is the research department here at the institution."

So when Imlay calls the sponsor, the sponsor might indicate that a check has already been sent and that it went to the department that is doing the research, Fink explains.

"Then she has to track down the research office person and let them know about the check," she adds. ■

Avoid mission creep, blurred boundaries for IRB

Worry less about liability

An IRB expert makes the case that an IRB can improve its quality by working smartly with

data safety monitoring boards (DSMBs), rather than sliding into their jurisdiction.

"There's been a tremendous amount of mission creep between both boards," says **Stephanie J. Zafonte**, MSN, RN, CCRP, CQA, RAC, director of operations at George Washington University, biostatistic center, in Rockville, MD.

"IRBs are concerned that they need to see every event that happens if it might impact a study," Zafonte says. "However, when they're looking at events individually they don't get the context of what it means for the overall study."

Zafonte produced a poster abstract that was submitted to national human subjects research conferences last year. It was about how DSMB plans can alleviate IRB burden. She also has worked as senior extramural regulatory analyst for the office of clinical research at the National Heart, Lung and Blood Institute of the National Institutes of Health in Bethesda, MD.

DSMBs also have experienced the mission creep of being expected to review feasibility and performance metrics that really start to push the boundaries of what they should be reviewing, she adds.

"So you have the overlapping gray area of everybody wanting to see more information data," Zafonte says.

Every protocol has a data safety monitoring plan, so what the industry should do is strengthen those plans and delineate the responsibilities of the DSMB and the IRB, she suggests.

"Then we build trust between the groups and cut down on mission creep," Zafonte adds. "The IRBs have a mission of looking at the big picture, and they don't have time to look at every serious adverse event (SAE) that comes along for a protocol."

The DSMB has the context of looking at trends in a study's SAEs, so the IRB would be smart to listen to what the DSMB has to say about unexpected events rather than making their own decision based on limited data, she says.

"Everybody thinks they're liable, and so they need to look at every aspect of the trial," Zafonte says. "So we're becoming counterproductive, and the approval processes become so overburdened, and IRBs are overworked."

What should be happening is the DSMB should be assigned the role of looking at unanticipated events, and the research organization should develop a plan of what should be reported, she adds.

"We need to stop with the mentality of 'If I don't know what to do then I'll report it,'" Zafonte says.

"We have the mentality that over-reporting is better than under-reporting, and what has happened is that it's almost impossible for IRBs to distinguish the important events among all the noise they're getting," Zafonte says.

IRBs should say they don't need to see every SAE that comes along, but that they want to see the DSMB's assessment of the impact of those events, Zafonte says.

Put the burden on the DSMB instead of the IRB.

Likewise, the DSMB should accept from the start that the protocol is scientifically strong and was adequately reviewed by the IRB from a human subjects protection perspective, Zafonte says.

And the research organization should focus on strong data safety monitoring plans, strengthening the process whenever possible, she adds.

"I recently did a review of several hundred protocols coming through the review cycle at NIH," she says. "I found it very upsetting that those DSMB plans were very short or brief or nonexistent."

Having a strong data safety monitoring plan helps to make the system stronger and less burdened, Zafonte says. ■

Tribal IRBs shape research in native populations

IRBs can point out potential harm to communities

Across the country, Native American communities have begun setting up their own research processes — in some cases, their own separate IRBs — to review research proposals involving these unique populations.

The processes differ from place to place, but have the same goal: Ensuring that research proposals don't cause harm to either individuals or the community as a whole, and that they return maximum benefit to the tribes and communities they study.

In many cases, IRBs or other review processes were formed as a result of past research that the communities saw as harmful. **William Freeman**, MD, MPH, CIP, human protections administrator at Northwest Indian College in Bellingham, WA, says some tribes burned by previous experiences with researchers set up new review processes to

gain control over how their members and their community are used in research.

"When tribes establish their own IRBs, it transforms the situation so they feel confident that their issues of protecting maximizing benefits to communities will be met in this process," Freeman says.

'The committee that said no'

That advocacy for the community can make an IRB or review committee extremely choosy about the projects it allows — at least until it has educated researchers about its expectations, says **Mary Frances Oneha**, APRN, PhD, director of quality and performance at the Waianae Coast Comprehensive Health Center, Waianae, HI.

"We were actually known as 'the committee that said no' for the longest time," she says. "Because many of the proposals that came to us did not take into consideration the process or challenges that community health centers currently face or what has gone on in this community in the past."

But both Oneha and Freeman say tribal and community IRBs have been able to establish cooperative relationships with outside researchers and IRBs, bringing a new perspective to the protection of research subjects and the communities to which they belong.

Freeman, who previously chaired the national Indian Health Service (IHS) IRB, says the current federal regulations pertaining to research have a major omission — the protection of communities, rather than simply individuals.

He says research done badly or good research disseminated without care can do real harm to communities. For example, in the 1970s, researchers went to Barrow, AK, to study the effects of alcoholism. The resulting study, whose results were reported in Eastern U.S. newspapers, caused problems for Barrow's attempts to sell development bonds on Wall Street and left many community members feeling stigmatized.

In 2004, the Havasupai tribe in Arizona sued Arizona State University, alleging that researchers who had come to their tribe to do genetic research on diabetes also did schizophrenia and migration research on the tribe without permission. "I have been told that experience has really riled the Havasupai tribe — if anybody wants to do research now on the Havasupai people, you can just forget it for a while," Freeman says.

In addition, groundbreaking CDC research on the 1993 hantavirus that affected the Four Corners region of the Southwest exposed the Navajo people living in that area to unwanted invasions of their privacy, Freeman says.

Over the objections of Navajo health officials and Freeman at the IHS, researchers published papers that explicitly named Navajo chapters that were affected by the disease. Freeman says he had suggested using anonymous place names (Community A, Community B, etc.) or geographic information systems (GIS) codes, to no avail.

While characterizing the CDC's work as an incredible scientific achievement, he says many Navajo people felt harmed by the disclosure of the Navajo place names. As a result, the Navajo Nation established its own IRB.

Tribal IRBs, review committees

The controls that tribes place on research vary, Freeman says. Tribal governments in general may prohibit researchers from entering the reservations, which in effect stops the research. Some tribes have IRBs in addition to a tribal government, and the two often work in tandem.

In some instances, tribes coordinate with a nearby tribal college or university IRB. Freeman's own IRB at Northwest Indian College is in the process of coordinating with the Lummi Nation to possibly develop a combined IRB.

For researchers who wish to study the Native Hawaiian population served by the Waianae Coast Comprehensive Health Center, Oneha says the health center's IRB is only part of the review process. While she notes that the health center IRB does not control all research within the community, it does control any research involving the health center.

Proposals submitted to the center first must go through a review committee that asks many of the hard questions about protecting the community and returning results to people later: What is the community involvement? What collaborative arrangements have been made? How will the data be used? What is the dissemination process?

By the time the study reaches the IRB, that process is not much different than it would be at any other institutional review board, she says.

When a proposal is rejected through this process, it's often because researchers haven't thought through the demands it places on the health center's resources, or it involves a medical condition that isn't a priority for the community, Oneha says.

Freeman says that when tribal IRBs and out-

side IRBs review the same study, both can bring added value to the process.

He cites one example, in which a study of organ donation was improved by issues raised by both the tribal review and the university IRB.

"Every tribal IRB I know of appreciates any other IRB that's involved," Freeman says. "It's not seen as an either/or — it's seen as an addition. Many tribal IRBs want to see the university IRB approval first, before they even look at it. University IRBs where there's a fair amount of research being done with tribes are increasingly recognizing the authority of tribal IRBs and [acknowledging] that they have perceptions, understandings and concerns that their own IRB and researchers may not have." ■

IRBs should consider effect on community

Regulations 'a floor, not a ceiling'

While tribal and community IRBs can bring a unique perspective to the study of a specific population, all IRBs should consider community concerns in their reviews, says **William Freeman**, MD, MPH, CIP, human protections administrator at Northwest Indian College in Bellingham, WA.

"I don't think it's unique to tribes," Freeman says. "This applies to lots of groups — be it the breast cancer community, schizophrenia community, autism community, a rare genetic disease community, an ethnic community and so on.

"In any research there may be harms to that community that could be minimized with the proper review process — harms that even well-intentioned, experienced and knowledgeable researchers in that community may not understand." He notes that while federal regulations do not explicitly require consideration of potential community harms and benefits, they don't preclude it, either.

"It's always been said: The regulations are a floor, not a ceiling," Freeman says.

Gaining community perspective can mean suggesting or even requiring the researcher to present the study plan to a community organization, and report the results to the IRB. "'What did you learn? What did they suggest you change? Can you change it?' That's one way to do it," he says.

The Waianae Coast Comprehensive Health Center in Waianae, HI, has created an advisory board to deal with community-based participatory research that researchers conduct through the center, says **Mary Frances Oneha**, APRN, PhD, director of quality and performance for the center.

"We were getting a few requests where they each wanted to have their own community board, and we thought we would just exhaust community residents having a board for every proposal," Oneha says. "So we just decided to develop a community advisory board that researchers can tap into."

The IRB can seek to have representatives of the community being studied as members of the IRB. But Freeman says even that doesn't diminish the need for outside help from community organizations.

Avoiding stigma

Controversies over tribal research have pointed out the problems that can occur when communities are identified as having a stigmatizing medical problem. But those type of issues can occur in other communities as well, Freeman says.

For example, publishing HIV/AIDS prevalence rates in a particular geographic location or within a specific named community can be stigmatizing to everyone in that community, infected or not.

Tribes concerned about being identified have often been given the chance to review an article before it's published, so that it can then decide whether to be named, Freeman says.

Another key point in reviewing a study for community concerns is maximizing the benefit to the community after the study is completed, he says. That could include the tribe being the first to get results, before they're published.

"Researchers need to let the tribe know what the results are and how the research results can to help the tribe, so that the tribe can do something to improve — a health program, whatever it is," Freeman says. "In my experience, this is what almost all tribes want to know; they want to improve their life directly from this research."

Oneha says her health center is in the process of revamping its policies regarding the return of research findings to the community. In the past, she says, it was difficult to enforce.

"Now, not only must the scholarly work come to our review committee (before publication), but also the researcher must produce some type of media that would be useful for the lay public to use regarding their findings," she says. "That

could be in the form of a brochure, a flier, a curriculum, a policy brief. We have ideas if researchers were interested in figuring out what would work in the community." ■

Human subjects violations cited in report on AR facility

Investigators: IRB failed to follow-up problems

A Veterans Health Administration hospital in Arkansas is currently being monitored by the VA after an investigation found human subjects protection violations on a number of protocols.

A report from the VA's Office of Inspector General (OIG) was released in August alleging problems with research protections at the Central Arkansas Veterans Healthcare System (CAVHCS) in Little Rock. Violations identified included lack of documentation, informed consent issues and inadequate IRB follow-up when problems were identified.

As a result of the investigation, the undersecretary for health at the VA, **Michael Kussman**, ordered continued monitoring by the Veterans Health Administration until remedial actions have been taken at the facility. "Upon complete implementation (of the remedial actions), I will make a final decision on continuing human research at this facility," Kussman said in a statement.

At the University of Arkansas for Medical Sciences in Little Rock, whose IRB was until recently the affiliate IRB for CAVHCS, university officials say they're working to improve auditing, training and communication, programs that were under way even before the investigation. But they dispute many findings in the report, calling them sensationalized and misleading.

"It's very frustrating to try and deal with a report like that when they're not giving the whole story and you spend a lot of time trying to clarify things," says **Bob Bishop**, UAMS vice chancellor for institutional compliance. "We're not saying that everything was perfect, but recognizing that there are going to be errors and you're trying to identify them accurately."

Addressing allegations

They note that much of the detail in the report came from the UAMS IRB's own audits, and that their attempts to delve further and make changes were halted when federal officials ordered studies to be closed.

Among the specific violations cited in the OIG report:

Documents, including informed consent and subject eligibility documents, appeared to be missing from study files in a number of studies. **Jennifer Sharp**, a UAMS research compliance officer, says the documents in question originally were in the study files. She believes they probably were misfiled as files were moved from agency to agency during the investigation.

"We know that all the consent forms were present at least at one point in time when we looked at one of the studies," Sharp says. "The investigators' files were first looked at by the FDA, then the VA OIG took those records and so the PI has never been given an opportunity to assist in reorganizing these documents and locating some of these things."

The report states that deaths of 105 veterans involved in four studies were not reported to the IRB in continuing review forms. Although the OIG report states that it is unlikely any of the deaths were related to the patients' participation in studies, VHA policy still requires that they be reported.

"Even though you may think a death had nothing to do with a research study, all deaths are supposed to be reported," says Dana Moore, PhD, the OIG's deputy assistant inspector general for healthcare inspection. "Maybe people involved in a study started having car accidents at some alarming rate. Maybe there is something going on."

Bishop and Sharp, however, say that in all but one of the studies, the investigator's involvement with the patient was brief, in some cases lasting only a day. Since there was no long-term follow-up in the protocol, there was no opportunity for the investigator even to know that the patient had died.

The OIG report stated that during a study of coronary artery bypass surgery, a subject receiving a required follow-up angiogram in 2006 had complications requiring air evacuation to an outside hospital. The IRB approved an addition to the informed consent explaining this risk. Subsequent audits showed that not all patients involved in the study had been given the new consent document. The OIG report charged that the IRB failed to identify and report continuing non-compliance in that case.

Bishop says subsequent audits showed that patients were only given the new consent form when they came in for their one-year follow-up

angiogram.

"The reality was that almost everyone who was supposed to get a follow-up angiogram was accounted for," he says. "Either they left the study, they had the procedure or they had a different procedure or didn't come back for some reason."

Not an isolated issue

Since the investigation started, the CAVHCS has created its own IRB, with seven members of the previous UAMS IRB moving to it. There have been leadership changes at the CAVHSC as well and the OIG reports that the new leadership has made significant changes in response to concerns raised in the report.

The VHA itself issued a directive in March detailing a facility's obligation to conduct protocol audits.

At UAMS, Bishop says the university is revamping its compliance system, enabling it to better audit the IRB's operations. The university also is seeking an additional auditor and Sharp says they're looking at the education program to see where there might be improvements.

Moore says the VA's OIG has investigated alleged human subjects protection violations at a number of veteran's hospitals over the past few years, with some investigations involving IRB problems.

"We don't think Little Rock was an isolated issue," she says.

Bishop says many VA facilities are moving toward establishing their own IRBs. For those university affiliates who remain, he advises prompt attention to the results of audits.

"I think based on our experience, probably the IRB needs to be a little more active," he says. "In some actions that normally they might want to look at a little longer, I think they need to look at acting more quickly." ■

Work with PBRNs to tailor HSP training

One-size-fits-all training can be burdensome

Because practice-based research networks (PBRNs) conduct research across a web of physicians' offices, making sure the necessary staff are trained in human subjects protection can be a daunting task.

IRBs can help facilitate practice-based research by working with PBRN researchers ahead of time, determining the minimum amount of training required for studies and who should receive that training, says **Rowena Dolor**, MD, MHS, assistant professor of medicine at Duke University and herself a PBRN researcher.

One key, she says, is understanding the unique nature of practice-based research, and the training challenges it creates for community physicians who participate.

"As an academic researcher, if my institution tells me I have to do this training in order to get IRB approval, I'll protect an afternoon to do that," Dolor says. "But if you're a community physician and research is a secondary interest, asking somebody to sit in front of a computer or attend a lecture all afternoon is a little bit harder."

She says training for such practices should include the important human subjects protection information needed to conduct the minimal risk studies generally conducted in physicians' practices. But she says it should not overload physicians and their staff with information they don't need.

Achieving that balance can take some negotiating between the PBRN researcher and his or her IRB — as is evidenced by the discussion on a PBRN listserv sponsored by the Agency for Health Care Research and Quality.

The listserv is a place for PBRN researchers to exchange ideas, says Dolor, who wrote about the listserv's human subjects protection training discussion in a recent article.[1]

"For all practice-based research network directors and coordinators, this was a topic that resonated with us," she says. "I've been doing these types of studies for the past 10 years and in attending the PBRN meetings, there is always a discussion about IRBs, especially with human subjects protection training."

The listserv discussion began with an inquiry from a North Dakota PBRN researcher who was worried that the IRB's required training might make it difficult to recruit physicians for a study. The ensuing discussion highlighted many of the challenges of training a far-flung group of people and issues that IRBs should keep in mind when looking at practice-based research, Dolor says.

Tailoring training

Who should be trained? Dolor says that when she began doing practice-based research, the train-

ing requirements were not particularly difficult to fulfill. Usually only the academic faculty member leading the community project did the training.

"Then sometime in the 1990s, IRBs began requiring human subjects protection training of people in the community site if they were actually collecting primary research data," she says. "For anything beyond the standard of care, whether it was consenting patients or actually filling out a data form that contains primary research data, (IRBs) felt that people should go through training."

Dolor says it's possible to design studies to minimize the number of people who need to be trained in a practice. A research coordinator can go to the site and do the research related activities, such as recruitment, consenting and filling out data forms.

"If the clinician is really just aware that the project is going on at the practice site, and is minimally involved in the research project, then they don't need to go through training," she says.

But she notes that arrangement is not always possible. For large networks, it may not be feasible to send coordinators to every site. In that case, some of the practice staff and physicians will have to be trained.

How much training is needed? Once it's been established that community site training is necessary, Dolor says IRBs and researchers should figure out together the minimum training necessary to protect research participants without overburdening practice staff.

Because much of the research done by PBRNs is minimal risk — chart reviews, surveys, quality improvement-type projects — Dolor says it may not be necessary for community physicians and practice staff to undergo training that addresses higher risk research. But that means negotiating with the IRB, which may have one-size-fits-all training requirements. If IRBs are willing to focus on a core number of required courses, it can help facilitate practice-based research, she says. Since many institutions began requiring training through the Collaborative Institutional Training Initiative (CITI), it's become easier to craft standardized training requirements, Dolor says.

"Each institution decides which modules they want people to go through," she says. "The VA requires a set of modules on human subjects protection and good clinical practice — the number varies for new or experienced investigators/coordinators. The American Academy of Family Physicians had talked to their IRB and had gotten permission for four modules that they thought were the most common types of research conducted out in the community.

"That's why a discussion with IRB leaders about how they can tailor the training to the needs of the community physician is highly suggested," she says.

Reference

1. Dolor RJ, Smith PC, Neale AV, et al. Institutional review board training for community practices: advice from the Agency for Health Care Research and Quality Practice-Based Research Network listserv. *J Am Board Fam Med* 2008 Jul-Aug;21(4):345-52. ■

CNE/CME Objectives

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

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

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

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

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

COMING IN FUTURE MONTHS

- ■ SACHRP weighs in on heavy topics
- ■ Improve your office's atmosphere
- ■ An IRB office can work in tandem with QI efforts
- ■ Departmental IRBs for social/behavioral research? One proposal
- ■ Reporting deaths in research - When? How? To whom?

CNE/CME *questions*

13. Which of the following is a good strategy for improving IRB fee collection rates?
    A. Move IRB fee invoicing to the IRB office where protocol approvals can be more easily tracked
    B. Enforce having IRB fees paid before the protocol is reviewed
    C. Send out IRB fee invoices automatically through computer software and have reminders emailed on a bi-weekly basis
    D. None of the above

14. How could the research industry improve the work that IRBs and data safety monitoring boards (DSMBs) do?
    A. The industry could strength data safety monitoring plans for protocols and delineate the responsibilities of the DSMB and the IRB
    B. The industry could build trust between DSMBs and IRBs and cut down on mission creep
    C. The DSMB could take charge of assessing serious adverse events (SAEs), and the IRB could review DSMB reports on SAE trends
    D. All of the above

15. IRBs are allowed to go beyond the federal regulations to consider how a study might cause harms or create benefits for the community in which it is to be conducted.
    A. True
    B. False

16. Which of these is a way that an IRB can help facilitate human subjects protection training in practice-based research?
    A. Reducing the number of modules that PBRN staff are required to take, depending upon their involvement in the study and the details of the research.
    B. Allowing for flexibility in the method of training.
    C. Both A and B
    D. Neither A nor B

Answers 13. A; 14. D; 15. A; 16. C.