IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

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Bad seed? Critics say drug study more marketing than medicine

Merck says research was legitimate science

Many in IRB circles have worried about the potential existence of "seeding" trials, which are defined as clinical trials that seek to market a product rather than answer a legitimate scientific question.

Now a recent paper in the *Annals of Internal Medicine* has brought the issue front and center, accusing a 1999 clinical trial of the painkiller Vioxx of being a marketing-driven seeding trial.[1] An accompanying editorial in the Annals describes the article as the "first to provide documentary evidence that proves the existence of seeding trials."[2]

The article references a study called ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness). The results of the study ran in the *Annals* in 2003. [3]

The ADVANTAGE study's stated purpose was to compare the GI tolerability of Vioxx to naproxen. It was carried out in 600 sites among more than 5,500 osteoarthritis patients and found Vioxx to be as effective as naproxen, with a superior GI tolerability.

But **Kevin Hill**, MD, MHS, a clinical fellow in psychiatry at McLean Hospital in Belmont, MA, says the real purpose of the ADVANTAGE study was to get the drug, which was in the midst of being launched, into the hands of prescribing physicians and to promote its use. Hill and his colleagues point to documents they found when working as paid consultants to plaintiffs who sued Vioxx's maker, Merck & Co. Inc., over cardiovascular problems associated with the drug.

Merck has strongly denied that ADVANTAGE was a seeding trial, saying it was intended to answer important scientific questions regarding Vioxx. It notes the authors' work for plaintiffs' attorneys and calls the seeding trials article "biased" and "inaccurate" in a letter posted on one of its websites. (http://www.merck.com/newsroom/vioxx/)

In any case, the controversy has certainly drawn the attention of IRBs. **Mark Schreiner**, MD, chairman of the Committee for the Protection of Human Subjects at the Children's Hospital of Philadelphia, says he dis-

tributed a copy of the Hill article to all three of his institution's IRBs.

"I thought that was very revealing," Schreiner says. "The importance of this was that everybody has believed that this was going on."

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• *Fax:* (800) 284-3291 • *E-mail:* stephen.vance@ahcmedia.com
• *Address:* 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: **Suzanne Koziatek** and **Melinda Young**.
Associate Publisher: **Coles McKagen**, (404) 262-5420 (coles.mckagen@ahcmedia.com).
Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Ami Sutaria.**

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Editorial Questions

Questions or comments?
Call **Gary Evans** at (706) 310-1727.

Analyzing document database

Hill says that he and his colleagues weren't thinking about seeding trials when they analyzed a database of about a million documents that had been submitted by Merck during the discovery process of the Vioxx lawsuit. Their job was to prepare an expert witness for his testimony in the case.

"An important piece of the case was whether Merck failed to warn patients about the dangers of Vioxx," Hill says. "As a result, there was a lot of specific inquiry into Merck's practices in relation to Vioxx – how they proved the medication was effective, how they decided to market it, that sort of thing.

"We came across documents that led us to believe that Merck had conducted seeding trials, in particular ADVANTAGE, which involved Vioxx."

First, Hill's team searched the database using keywords such as "seeding trial" and "marketing," then individually reviewed about 2,000 documents that turned up in that search. They eventually identified about 100 documents that were relevant to the issue, mostly Merck internal correspondence, marketing memos and presentations.

Among them was a form nominating Merck marketing employees for their work on ADVANTAGE, stating that an objective of the study was to "provide product trial among a key physician group to accelerate uptake of Vioxx." It stated that the study was "designed and executed in the spirit of Merck marketing principles."

The authors also cited a memo by the head of the research division at Merck Research Laboratories, who criticized the ADVANTAGE study, calling it a "marketing clinical stud(y)" and "intellectually redundant." They noted a memo by a marketing employee that referred to ADVANTAGE and wrote, "It may be a seeding study, but let's not call it that in our internal documents."

Hill's group also pointed to the relatively large number of doctors and small number of patients per/physician (six) targeted by the ADVANTAGE study.

Hill and his colleagues say that the marketing aims of the ADVANTAGE study were not revealed to the FDA, to the physician-investigators who recruited patients for the study, to the institutional review boards that reviewed it and to the subjects who eventually enrolled in it.

Ironically, Hill says, the actual science behind the ADVANTAGE study was sound, although he

says it was not as large or well-designed as the better known VIGOR (Vioxx GI Outcomes Research) trial, which also compared Vioxx to naproxen and revealed an increased risk for heart attack associated with use of Vioxx. But he says a study that masks its true objective may cause people to enroll who might not have done so if they'd known all the facts.

"I think it's quite clear that if patients were told that this was a trial designed by marketing and it was primarily a marketing trial, they would have made other choices about participating," he says. "People elected to place themselves at risk where they probably wouldn't have if they had known the objectives of the trial."

He says the most important factor in determining whether ADVANTAGE was a seeding trial was whether there was clinical equipoise, or true scientific disagreement about the question the trial was designed to answer.

"I would say for ADVANTAGE, the answer would be no," Hill says. "Because at the time of ADVANTAGE, Merck had already run trials with Vioxx looking at this idea of GI tolerability and they were in the process of running other trials, namely VIGOR which is probably a superior study in terms of design."

Merck defends ADVANTAGE

Jonathan Edelman, MD, executive director of the Global Center for Scientific Affairs, Merck Research Laboratories, Whitehouse Station, NJ, has defended the ADVANTAGE study in a letter to the *Annals*.[4] He says that when the study first was conceived in 1998, the question as to whether Vioxx was superior to naproxen in GI tolerability was not yet settled, despite the fact that there had been a set of studies comparing Vioxx with various non-steroidal anti-inflammatory drugs (NSAIDS).

"The feedback that Merck got up to that point was that the information that was provided was insufficient for us to make a conclusion about the GI safety of this new mechanism of action for treating pain," he tells *IRB Advisor.* "There was good scientific reason to believe that the GI safety would be different from NSAIDS and it was necessary to demonstrate that through clinical research."

He says Merck conceived of two complementary trials, VIGOR and ADVANTAGE. VIGOR was devoted to GI hard outcomes such as peptic ulcers and bleeding.

"The ADVANTAGE study in concept was meant to answer the question: How does this new product Vioxx compare to the most commonly used NSAID in the commonly prescribed offices of primary care physicians?" Edelman says. "And that is all in complete contrast to the preceding studies and also to the VIGOR trial."

He notes that the Annals chose to publish the ADVANTAGE study because they saw value in the results that it produced.

Edelman says the study was designed and executed by the medical and scientific affairs department of Merck's U.S. Human Health Division, not its marketing department.

"It went through all the rigorous, routine reviews by Merck Research Laboratory committees," he says. "It was signed off on by the head of clinical research, by the head of biostatistics, by the head of regulatory affairs."

He says the nomination form cited in the seeding trials article merely praised marketing employees for "leveraging the research for marketing purposes."

"They chose to talk about it in marketing terms," Edelman says.

Similarly, he says the memo by Merck's research head was misinterpreted – he was referring to the cardiovascular results coming out of ADVANTAGE, not the question that prompted the study. Edelman says the memo calling ADVANTAGE a seeding trial was written by a public affairs employee who didn't understand the meaning of the term. "The fact that she wrote it is unfortunate but it doesn't make it so," he says.

Edelman noted that while the study originally targeted six patients per physician's office, the final numbers ended up being closer to 10 patients, which he says is a fairly typical number for a multi-site study.

And he says that while Merck clearly had commercial aims for Vioxx and ADVANTAGE did serve a marketing purpose, that didn't make it a seeding trial.

"The authors start out by saying that every bit of clinical research that's done to support an approved product is essentially a marketing study," Edelman says. "I think that's an unsophisticated and inflammatory way of talking about it.

"At the core of this issue is whether the primary reason for doing the trial is strictly commercial and there's no scientific benefit at all," he says. "In the case of the ADVANTAGE trial, there were legitimate, unanswered scientific questions that would influence the way potential prescribers would understand the data and make

decisions about a new product."

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Kill it before it grows: IRBs and seeding trials

Hard to detect, but watch for red flags

IRBs striving to ensure they're not inadvertently approving a seeding trial have a tough job ahead of them.

Because of the nature of the trials, and the fact that they are likely to have plausible-sounding scientific rationales, they may be hard to ferret out, says **Kevin Hill**, MD, MHS, a clinical fellow in psychiatry at McLean Hospital in Belmont, MA. Hill and his colleagues published an article in the August issue of the *Annals of Internal Medicine* about a Vioxx study they identified as a seeding trial.[1] Merck & Co. Inc., the maker of Vioxx, has denied that the study was a seeding trial. **(See related story, cover)**

"Seeding trials have really evolved over time," Hill says. "Earlier papers about seeding trials talked about open-label trials with lots of sites. If that were the way seeding trials currently were configured, it would be a bit easier to identify them. But over time, the trials have evolved into fairly scientifically sound trials that you wouldn't be able to otherwise identify."

But there are signs that can make an IRB suspicious, if members are willing to ask questions and exercise some extra diligence.

Question the science

Hill says that simply asking the investigator, "Is this a seeding study?" is a good start, since it puts the burden on the investigator to be truthful. But it's possible that the investigator doesn't know the true origin of the trial.

One way IRBs can attack the problem is to concentrate on the scientific merit of the study under consideration, say Hill and **Mark Schreiner**, MD, chairman of the Committee for the Protection of Human Subjects at The Children's Hospital of Philadelphia, PA.

"The seeding trial often does not have a real scientific hypothesis," Schreiner says. "So the question is, does this study have a true scientific objective that can only be answered by a clinical trial?

"And then is the study adequately powered to address that objective? Are the comparators the right comparators? Is it necessary to use a placebo or should it be an active comparator? Is the dose that's being selected the correct dose? Is there an adequate search of the literature?"

Schreiner notes that most of the studies that might fall into the category of a seeding trial are Phase IV studies conducted after a drug has been approved. In those instances, IRBs can ask whether the trial is initiated by an investigator, or by the drug's sponsor.

An editorial in the *Annals* that accompanied the Hill article suggested other clues an IRB could consider suspicious: An open-label design, no control group or a short-term study of a chronic disease. "None of these clues is highly specific, but institutional review boards should start asking questions when a study has several of them," the editors wrote.[2]

Patient/physician ratios

A red flag can go up, Hill says, if the study has an unusually large number of individual physicians participating, or if the number of patients per/physician is unusually small. That might indicate that the purpose of the trial isn't to answer a question, but to put the drug in the hands of lots of doctors.

For that reason, Schreiner says, central IRBs may have more likelihood of being presented with a potential seeding trial.

David Forster, JD, MA, CIP, vice president in the Office of Compliance for Western IRB in Olympia, WA, says the question of whether a proposed study was a seeding trial has been asked occasionally over the years.

"You never had any true knowledge of whether it was or not," Forster says. "We often

disapproved studies for lack of scientific validity or an inappropriate risk-benefit ratio, but I do not remember when we've ever said we're disapproving this study because it's a seeding trial."

The criteria that IRBs follow in reviewing studies don't directly address this question, he says. "If you go through it and the risks are minimized, the risk-to-benefit ratio is acceptable, the knowledge is supposed to be scientific knowledge, not marketing knowledge. We have these checklists we use and there's really nothing in the regulations that addresses this issue."

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Pain enrollees cite complex reasons

Patients do own risk-benefit calculation

People participating in pain research report having complex combinations of reasons for enrolling — part altruism, part seeking new treatments, part simply having their pain understood and taken seriously.

But pain researcher **Ajay Wasan**, MD, MSc, says that complexity doesn't mean patients don't understand the limitations of research and it doesn't mean they aren't giving truly informed consent.

"Patients are doing a risk-benefit calculation," says Wasan, an assistant professor of anesthesiology and psychiatry at Brigham and Women's Hospital and Harvard Medical School, Boston, MA. "It may not be the exact way the IRB or ethicists write about as disinterested altruists, but they're clearly following a systematic evaluation process that's reasonable and that balances their own self-interest with the interests of the researcher in doing a study."

He says the findings of his study, which were published in a recent issue of the journal *Pain Medicine*, should reassure IRBs that subjects are not suffering from therapeutic misconceptions when they enroll in pain studies.[1]

The survey was administered to 52 back-pain patients after they had participated in a randomized controlled trial of intravenous morphine and placebo. Ethnographic researcher **Simone Taubenberger**, PhD, of Johns Hopkins University, conducted 15- to 30-minute interviews, asking subjects about their reasons for participation, their interactions with the investigator and their perceptions of the risks and benefits of participation in the study. Bioethicist **Walter M. Robinson**, MD, MPH, of Dalhousie University in Halifax, Nova Scotia, also contributed to the article.

Wasan says their goal was to see if patients in pain studies had unrealistic expectations of the research. Unreasonable expectations can be a problem both in pain treatment and in research, he says.

"It can actually make patients' pain and disability worse, and they cope less, because they have expectations that someone can just take all their pain away," he says. "It's the same thing in a pain study. If they have unreasonable or uninformed expectations about what's going to happen and why they want to do the study and they're disappointed, they're just going to drop out."

Subjects first cite altruism

Wasan says that when asked, many subjects at first gave the more socially accepted answer of altruism, but as the conversation progressed, they revealed other reasons of self-interest that gave a more nuanced view of pain research participation.

For example, one patient said at first that she wanted to participate in the study because the research could benefit her and other patients. Asked later in the conversation whether she thought the study might make any difference in her care, she said that her main reason for participating was that she currently was taking Celebrex and had heard that it stops working over time.

"So I had been hoping that I'd be getting on the (leading edge) of some research that I could pursue — that would result in solutions for me personally down the line," the woman told the researcher.

Overall, while 60% of patients reported they had participated to contribute to research, 50% of the same group said they participated in order to seek pain relief and 44% to try a different drug. Other reasons stated included monetary compensation (19%), to be taken seriously and listened to (17%), to find a new doctor (12%), to learn about

and access new treatments (10%), to get answers or a diagnosis (6%) and to seek a doctor despite being uninsured (2%).

Wasan says that in some cases, people who appeared to have understood the informed consent gave reasons for participating that at first glance wouldn't seem to make sense.

"If you ask them if they understand they're just going to get relief for a day or so, they'll say 'Yes, I understand that'," he says. "But then they'll say that even one day of relief is really important to them – it represents a big improvement in their chronic pain.

"They're still voicing an understanding of the study," Wasan says. "They're telling you everything that you would need for informed consent. Even if they have some self-interested reason which may not make any sense, it can still be informed consent. It's not necessarily a therapeutic misconception."

Ask about motivation

He says investigators may benefit from asking patients during the informed consent process why they want to enroll in a study, in order to make sure that they have an understanding of what it actually entails and to correct any misperceptions.

In fact, such a process can do a better job of giving informed consent than a long and cumbersome document can, Wasan says.

"By asking patients why do they want to do the study, and addressing if they have any unreasonable expectations, that is another way of obtaining informed consent that is truly more informed," Wasan says. "Because you're actually asking the question that the patient has a concern about, as opposed to theoretically addressing every possible issue in an extremely long document that's cumbersome and no one reads it anyway."

He says that the participants in his study also were asked about informed consent, and reported that they merely skimmed the document.

"People said what was more important were discussions with the principal investigator and trust in the institution," Wasan says. "Those factors gave them most of their information about the study as well as assessing the risk and benefits."

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New SACHRP chair looks to the future

Q&A focuses on harmonization & IC

Barbara Bierer, MD, professor of medicine at Harvard Medical School, and the senior vice president for research and the director of faculty development and diversity at Brigham and Women's Hospital in Boston, MA, is the new chair of the U.S. Health and Human Services (HHS) Secretary's Advisory Committee on Human Research Protections (SACHRP). *IRB Advisor* asked Bierer some questions about where she sees SACHRP directing its focus in the coming year in this question-and-answer session.

IRB Advisor: We'd like to know what you hope to bring to SACHRP as the chair, some of the things you'd like to see the committee do.

Bierer: For my own tenure, I think there are certainly areas on which we as SACHRP will advise OHRP [Office of Human Research Protection] as questions arise.

Importantly I think that one of the most critical avenues that we can pursue as a committee is looking to harmonization of the privacy rule and common rule and also harmonizing FDA approaches to human subjects research protections and the common rule.

I say that knowing we're the committee advisory to the secretary with purview specifically being OHRP, and OHRP does not have the privacy rule or common rule under its umbrella. It's a little bit difficult to find the path to how we can have the department review areas of opportunity in order to make human subjects protection robust and synchronized. And we'd like it to be easier for investigators to know which rule applies when.

So if I could wish for any effort to be synthesized over the next few years that would be it. As I say, I know that this [objective] is not entirely in our purview. We certainly could make recommendations.

IRB Advisor: Could you be more specific about the privacy rule and harmonizing that with human subjects research?

Bierer: We can get you some specific issues. But the Institute of Medicine (IOM) is even considering this in a committee now. They're looking at the number of both definitions and approaches that are quite different with the privacy rule and common rule.

For instance what are the protections for data involving someone who has died? Those are interpreted differently. What are the approaches to future research, to limited data sets, to informing the patient or subjects? SACHRP will consider it, but I'm pretty sure we will not consider it in our next meeting because the IOM panel is completing its work, and we're going to look toward the IOM panel's recommendation before considering our own public commentary.

IRB Advisor: And the IOM's own recommendation will be about the privacy rule and the common rule?

Bierer: It's about the privacy rule, but there are specific recommendations apparently. I do not know whether they are about the intersection of the privacy rule and common rule. Until they can complete their work, they're not in a position to discuss this. They anticipate the work will be completed by the spring of 2009; we'll take that on then.

I do think one of the things I'd like to see addressed is how we make the informed consent document truly informative to human subjects. We have expectations for having the document use 8th grade language. The documents are becoming so long and arcane that people, participants have trouble understanding what is the research question, particularly in a therapeutic trial where the question being asked might be quite small on the background of a clinical approach that is actually the standard of care.

And I think we need to address how to make the documents or how to assess whether an informed consent is truly understood by participants. I think back on the days when I was doing pediatric oncology. I'm an adult oncologist and an adult hematology oncologist, but I spent some time doing pediatric oncology. And the informed consent documents for pediatric acute lymphoblastic leukemia (ALL) were 13-16 pages long. For pediatric ALL there is a standard of care and we do ask incremental questions on background of standard of care. But for parents and children old enough to give consent, it was difficult to understand the research question as they approached the next three months of their care for treatment of ALL.

IRB Advisor: Do you believe there are long legal paragraphs in the informed consent that should be taken out because they are there for legal issues and not for informing subjects?

Bierer: I personally think there is a role for an executive summary so that one could very clearly say, 'Here's the question being asked and you don't have to participate, but if you choose to participate this is the way we would approach this question.' So people could decide and, in a short document, understand what the question was. That said, I do think the human participants do have the right to the whole document to see all of it, including the whole boilerplate of legal reasons. They should be aware of it, and if they're interested in seeing it, they should have that available to them.

IRB Advisor: What role should SACHRP play in the human subjects research community? Why is it important to have a committee like this?

Bierer: I think it's critical to have a responsive committee that is there to address questions as they arise, to make recommendations when appropriate, and to be as an advisory body independent of the office itself. After all, we are the user group for people for whom the regulations are intended. The regulations may need further clarifications, since they were written some 30 years ago and now are applied in a very different world of research with different sensibilities. We need a forum where these can be discussed, analyzed, and thoroughly reviewed. ■

Two Questions for Marjorie Speers of AAHRPP

IRB accreditation rules explained

IRB Advisor: Dr. Marjorie Speers, would you please explain how AAHRPP accreditation requirements work with regard to institutions that are seeking accreditation and have plans to use foreign IRBs for a multi-site study that includes clinical trials located in other countries? Foreign countries hosting clinical trials often require a local board to review the study. So how does this work with accreditation requirements: do the U.S. institutions need to use a centralized and accredited IRB in the U.S. and/or require these foreign IRBs to be accredited?

Speers: This is a complicated question and the answer depends on the type of research organization seeking accreditation. If the organization seeking accreditation is a university, for example, AAHRPP expects the university to meet all the accreditation standards for its human research protection program but does not hold the university to ensure that its collaborating partners meet

Ask2-4U

Editor's note: *IRB Advisor* is introducing in this issue a new feature called "Ask2-4U." Each month, we'll ask an IRB expert or leader to answer two questions that might clarify some regulatory, ethical, or other type of concern that IRB directors, chairs, and members might have. So in this first issue, *IRB Advisor* has asked **Marjorie Speers**, Ph.D., president and chief executive officer of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), to explain some of the nuances in accreditation requirements for research institutions and the IRBs used by these organizations.

the standards. The exception is when the university uses an external IRB to review its research. In this case, AAHRPP expects the university to ensure that the external IRB meets the accreditation standards. The simplest way for this to occur is for the university to use AAHRPP-accredited external IRBs. Another way is for the university to put procedures in place to ensure the external IRB meets the standards.

Let's say, that the research organization seeking accreditation is a CRO. In this case, the CRO must meet all the accreditation standards. For those standards pertaining to the IRB, the CRO needs to ensure that the primary IRB for each study (generally the one the sponsor or the CRO selects for the multi-site study) meets the accreditation standards. This ensures that the study is reviewed appropriately and meets the higher standards set by accreditation. The CRO can use AAHRPP-accredited central IRBs or must have procedures in place to ensure that the standards are met. If the CRO were conducting a study outside the U.S. and engaging a foreign commercial IRB, the foreign commercial IRB would need to meet the accreditation standards or be AAHRPP-accredited.

Another way to think about this complex research enterprise and accreditation is AAHRPP looks at each institution as an individual entity that has a human research protection program. A human research protection program can be comprised of components internal to the institution and also external. When there are external components, such as a central IRB, the external components must meet the accreditation standards in order for the institution to achieve accreditation.

IRB Advisor: What kind of flexibility is there in the requirement that accredited research institutions use only accredited IRBs?

Speers: The IRB component is an essential part of the human research protection program. It is the entity that determines whether a study is ethically sound. From AAHRPP's perspective, an organization cannot have a high-quality human research protection program without using IRBs that meet the accreditation standards. AAHRPP expects research institutions to use accredited IRBs. And now, there are options: Nine independent IRBs are accredited by AAHRPP. If a research institution does not wish to commit to using an accredited IRB then it must have a process in place to evaluate and ensure that the IRB meets the accreditation standards. Those research institutions that are currently accredited and use an external IRB have chosen to use AAHRPP-accredited IRBs. It's the smart thing to do. ■

High 'Hope": Private institute overcomes IRB obstacles

Accreditation process took about two years

Accreditation for an academic research institution is a time-consuming and difficult process for the research office and the institution's IRB office. But for a small, private research organization, the task is Herculean.

Since the private research site doesn't have its own IRBs, it has to rely on private and regional IRBs. And since the research site may use only accredited IRBs when it submits its application for accreditation, the accreditation process becomes a maze of trying to match research contracts that come with their own recommended IRBs to different IRBs that are accredited.

These were the obstacles that Hope Research Institute of Phoenix, AZ, overcame to become the first private research site accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC.

"We use only AAHRPP-accredited IRBs," says **Patricia Adams,** managing partner with Hope Research Institute.

When Hope Research Institute first sought accreditation, there were far fewer accredited

regional IRBs, Adams notes.

"The first step was finding enough IRBs that were approved by AAHRPP for us to attain accreditation," Adams says.

"At first there were only a few IRBs that were approved, so it was an almost impossible obstacle for us to overcome," she explains. "Sponsors typically suggest that sites use a central IRB."

Unless the central IRB was accredited, Hope needed to request an exception to using an accredited institution, Adams adds.

"Some sponsors turned us down," she notes. "Hope had a challenge to balance our business' financial needs against the desire to become accredited."

Over a two-year period, this changed as increasing numbers of independent IRBs became accredited through AAHRPP.

"As we moved in the direction of using accredited IRBs, the IRBs moved in the direction of becoming accredited," Adams says. "It was remarkable that the process was going on in a parallel motion."

However, there were some growing pains.

At times sponsors would offer the research site a contract and tell the site that a particular IRB will be serving as a central IRB on the project. If the IRB was not AAHRPP-accredited, then Hope Research's partners would have to say they couldn't use that IRB, and they'd suggest alternative IRBs, all of which were accredited, Adams says.

"Then the sponsor would say, 'Yes, you can use one of those other ones,' or 'No, you can't use any except this IRB,'" she recalls.

Some sponsors were flexible; others were not.

"Some sponsors have understood and have come to us with protocols, saying, 'We're supporting this IRB, but you can use any you want,'" Adams says.

"One of our challenges has been if we're approached for an in-hospital study, and the doctors want us to do that study in a hospital that has its own IRB," she explains. "And if that IRB is not AAHRPP-accredited, but the study is important to us to do, then I have to encourage our investigators to use a regional IRB that is accredited."

Aligning the organization with accredited IRBs was the biggest hurdle, but there were other challenges, as well.

Small research institutions typically have one person who has to work on the accreditation package, and Adams was the point person for writing policies and procedures.

"One challenge was learning how to use Adobe so that our application was acceptable to AAHRPP," Adams says.

Her first application was formatted strangely, and she asked AAHRPP for help in formatting it according to the accreditation organization's requirements.

"The uniqueness of Hope's site was a chance for AAHRPP to learn, as well," Adams says. "The challenges of 'fitting a square peg in a round hole' helped AAHRPP fine-tune its directions and application process."

Another challenge was making certain all 15-plus investigators who work with the research site were trained according to the written policies, she says.

Prior to seeking accreditation, the research organization had been following the right policies and practices, but these weren't put in writing, Adams says.

"I realized that we were practicing what we weren't preaching," she says. "Because we were a small business we didn't have written policies a larger institution is founded upon."

Once the policies were put into writing as the organization sought accreditation, it was time to train investigators and staff about those policies.

"They're encouraged to do things our way, which is consistent with good clinical practices and AAHRPP standards," Adams says. "And they're used to being private practitioners and small business people who run things their own way."

Investigators also have to take Web-based training, such as the National Institutes of Health (NIH) training course or the CITI online training course.

"More and more, IRBs are looking at investigators and saying, 'We want you to have clinical research-specific training, especially if you're a new investigator,'" Adams says. "There are a number of different options for training, and I provide them to the investigators."

Investigators who will be working on clinical trials that are funded in part by federal money will have to be trained as part of the Federal Wide Assurance, she adds.

Adams keeps investigators up-to-date on new safety reports and regulatory news.

"If the news is related to a study we have, then I print out a hardcopy of the information

and make sure investigators sign it," Adams notes.

Since AAHRPP requires all investigators to be aware of how to report adverse events, safety issues, and other pertinent information, Adams has created a one-sheet list of regulatory agencies and important information, including contacts to call. She updates that list each year, and it's kept in the investigator records. **(See regulatory list, right.)**

This type of list could be personalized with the names, phone numbers, and emails of people at the regulatory agencies with whom the research institution has worked in the past.

"We laminate it for them and stick it on a bulletin board or anywhere else it can be seen," Adams says. ■

Real time: Web-based data system for CTs

Recruitment was on time; results were quick

A new web-based data management system serving clinical research has improved data collection and accuracy through an ongoing data collection and analysis process.[1] In a study of Amyotrophic Lateral Sclerosis (ALS) patients, the new approach helped produce on-time recruitment, quick results and analysis, and low error rates and missing data, says **Richard Buchsbaum**, senior data manager at the statistical analysis center, biostatistics department of Mailman School of Public Health, Columbia University of New York, NY.

The process resulted in less than 0.7% errors on submitted forms, and data were available within 48 hours of when an event occurred. Also, an analysis data set was produced nine days after the final patient visit. After years of working on a 24-hour basis in posting financial information and numbers, Buchsbaum found it astonishing to move to a field where people were expected to wait for months or years before analyzing data. "It's much easier to approach something in real time," he says.

Reference

1. Buchsbaum R, Kaufmann P, Barsdorf AI, et al. Web-based data management for a phase II clinical trial in ALS. *Amyotroph Lateral Scler*. 2008;9:1-16. ■

Regulatory Contact Information

Hope Research Institute of Phoenix, AZ, hands investigators a brief page of information about human subjects research regulations, regulatory agencies, and their contacts. Here's a sample of this tool:

• Patricia Adams, Managing Partner – HOPE Research Institute, LLC. Direct: 602.288-4681; Cell: 602.350-1192. Email: patricia.adams@hriaz.com

• Please refer to the "Code of Federal Regulations" and "ICH Guidelines" manuals that HOPE provided for questions concerning:

Regulatory Guidance

• Title 21 Code of Federal Regulations
• Part 50: Protection-Human Subjects
• Part 54: Financial Disclosure
• Part 56: Institutional Review Boards
• Part 312: IND
• Title 45 Code of Federal Regulations
• Part 46: HHS Protection of Human Subjects

Good Clinical Practice

• ICH Guidelines Good Clinical Practice
• The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research

• Human Research Protections Program

HOPE Research Institute, LLC shall work to ensure the protection of human subject participants by defining a Human Research Protections Program in the policies defined by:

• HOPE Research Institute's SOP's;
• The Study Protections Policy Guide;
• The Contracts and Budgets Policy and Procedures Guide.

These documents are readily available to you at any time. Please ask your study coordinator and/or Patricia Adams to bring them to your attention.

• FDA: U.S. Food and Drug Administration
19900 MacArthur Blvd. Suite 300
Irvine, CA 92612-2445
(949) 798-7600

Websites:

• Food and Drug Administration (FDA) - http://www.fda.gov/
• Agency for Health Care and Research - http://www.ahcpr.gov
• Regulatory Affairs Professional Society - http://www.raps.org
• Association for Clinical Research (ACRP) - http://www.acrpnet.org

CE/CME Objectives

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

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

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

■ Post-approval monitoring proves effective for one IRB

■ Here's how to handle poorly-written protocol submissions

■ Should IRBs require interim monitoring reports from sponsors

■ Continuing consent – keeping subjects informed over the life of a study

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PS Form **3526**, September 1999 *(Reverse)*

CE/CME *questions*

17. What might be a red flag that a proposed clinical trial is in fact a seeding trial?
    A. The trial is post-marketing
    B. A large number of sites are participating with few subjects targeted at each site
    C. The study appears under-powered to meet its primary objectives
    D. All of the above

18. True or False: The complex reasons pain patients cite for participating in pain research indicates that they have therapeutic misconceptions about these studies.

19. Which of the following is true of standards created by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)?
    A. If an organization seeking accreditation is a university, AAHRPP expects the university to meet all the accreditation standards for its human research protection program but does not hold the university to ensure that its collaborating partners meet the standards
    B. If a university uses an external IRB to review its research, AAHRPP expects the university to ensure that the external IRB meets the accreditation standards
    C. Universities could put procedures in place to ensure the external IRB meets the standards
    D. All of the above

20. According to the new chair of the U.S. Health and Human Services (HHS) Secretary's Advisory Committee on Human Research Protections (SACHRP) which of the following is a problem with informed consent that should be addressed by the committee?
    A. IC documents have too many legal paragraphs that make it difficult to filter through to the pertinent risks and benefits issues
    B. IC documents are long, arcane, and people have trouble understanding what is the research question, particularly in therapeutic trials
    C. The IC process often is too short and isn't presented at the average person's grade-level of understanding
    D. All of the above

Answers 17. D; 18. False; 19. D; 20. B.