IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

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Taking stock of financial disclosures: Most want to know, won't drop out

More express negative views of stock interests held by PIs

Knowing that an investigator has a financial interest in a clinical trial doesn't substantially affect people's willingness to participate, according to a study that surveyed 470 people about their reaction to informed consent documents that detailed such interests. At the same time, participants expressed stronger concerns about situations in which an investigator has an equity, or stock, interest in the product being tested — so much so that a few immediately said they would refuse to participate in such a study.

"There were a small number of people, 5%, who just said, 'Read no further, I wouldn't participate, because that equity relationship sounds a little bit greasy to me,'" says lead author **Kevin Weinfurt**, PhD, associate professor of psychiatry and behavioral sciences at Duke University School of Medicine.

The study, published in a recent issue of the *American Heart Journal*, is the latest in a series of studies that are part of a five-year, $3 million project known as the Conflict of Interest Notification Study (COINS).[1] The project's purpose is to provide guidance about how best to disclose financial conflicts of interest to potential research participants.

"Even though many professional groups and sets of guidelines call for the disclosure of financial interests in research, we really don't know who should do it, how to do it, when to do it, where to do it and what effects it's going to have on the research enterprise or on potential research participants," says **Jeremy Sugarman**, MD, MPH, MA, Harvey M. Meyerhoff Professor of Bioethics and Medicine at Johns Hopkins University, Baltimore, MD. Sugarman heads up the COINS project.

Model consent language

Previously, the COINS team has conducted focus groups with patients to discuss conflicts of interest and developed model language to describe various kinds of conflicts to patients. In a study

published earlier this year, that model language was used in a study of diabetes and asthma patients. The Internet-based study gave patients informed consent documents for hypothetical clinical trials, with different groups reading about different types of financial conflicts, Sugarman says.

One group read a document explaining that the investigator would receive a per-capita payment for enrolling patients to offset the costs of the study. Another group read a document stating that the investigator held stock in the company whose product was being studied. In each case, there was language saying that an IRB had reviewed the financial relationship and determined that it did not pose a risk to participants.

Sugarman says people assigned to receive the document about stock ownership were less likely to participate and less trusting in research in general than those who received the other documents. But he says questions were raised about the way the study was conducted.

"One of the critiques we had was 'You did this as an Internet study, but real research doesn't happen that way. Real research happens by way of someone talking to someone about the research,'" Sugarman says.

"So we repeated the study, but this time it was cardiology patients and we did it in a way that people actually might get enrolled in research," he says. "They got the informed consent document and reviewed it and then the research coordinator reviewed the essential points with them and asked if they thought they would participate in research."

Spontaneous responses

Again, the participants were more troubled by the equity or stock interest scenario. There were three times as many clearly negative comments in the equity group as in the per capita payments group. A total of 11 patients spontaneously said they would not participate in the study — 10 of them from the equity group.

"The thing that was really revealing to us in this study was for the first time, we were able to find out what people's spontaneous reactions were to this information during the consent process," Weinfurt says. "We tried our best to do a full consent process with these patients and record everything they said. We were able to say exactly how many people expressed negative reactions to the disclosures."

But overall, in both disclosure groups, patients were not substantially less likely to participate in the hypothetical study than a third group that received no financial disclosure at all. In fact, Weinfurt says, a far bigger influence on patients' willingness to participate in the study was the pre-existing level of trust

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that they had in research and researchers.

"We measured that before we even took them through the simulated consent process," he says. "That sort of basic trust they had — their trust in the specific investigator, the institution — was a very consistent predictor of their willingness to participate."

IRBs: Determine risks

What does this information mean for IRBs? Weinfurt says the results clearly showed that participants wanted to have the financial disclosure, even if it didn't dissuade them from enrolling.

"A lot of them say they want to know these things and they would feel angry if something happened and they found out later that this information was withheld from them," he says.

But Weinfurt says that disclosure to potential participants doesn't absolve the IRB from determining for itself the risks the conflicts pose. For one thing, conversations with participants have shown that even with the informed consent language, some patients still don't completely understand the complex financial relationships involved, he says.

"That's why in our recommended consent language, we have language saying 'This relationship has been reviewed by the conflict of interest committee and the institutional review board and judged to present little risk to you,'" he says.

"The important thing there is that the primary risk determination should be made by the institution and that our work has shown that subjects are not in the greatest position to make that risk determination."

Weinfurt says he's heard from IRB chairs that they're using the model consent language the COINS group recommends since it was published in a previous article. "We're very gratified by that," he says.

Sugarman says that as the COINS project draws to a close, his group is planning a policy workshop in Washington, DC, gathering IRBs and other stakeholders to help shape policy guidance on disclosing conflicts of interest.

Reference

1. Weinfurt KP, Hall MA, Friedman JY, et al. Effects of disclosing financial interests on participation in medical research: A randomized vignette trial. *Am Heart J* 2008; 156(4):689-97. ■

Separating public health from research a challenge

IRBs must walk a blurred line

The activities of state public health departments — including disease tracking, cancer registries and death statistics — can be a rich source of data for research.

But determining when the use of this data constitutes public health research that requires review by an IRB can be tricky, says **David Perlman**, PhD, former director of the Human Research Ethics Program for the New Jersey Department of Health & Senior Services.

Perlman, now an associate at the University of Pennsylvania Center for Bioethics in Philadelphia, also operates an independent ethics education company, Eclipse Ethics Education Enterprises or E4. He says public health department professionals often don't realize they need an IRB's review and waiver of informed consent for the research-related use of data they otherwise would have access to normally as part of their jobs.

Even for seasoned IRB members, the line between what is public health practice and what is public health research can be a bit fuzzy, he says. What starts as a normal public health activity may evolve into a research study.

"Even with all that experience and expertise, it was sometimes very difficult to make that determination," he says. "There was sometimes a very blurred line. You don't want to say, we'll punt on this one and go through the IRB review (if it is unnecessary) because you could actually stifle a really important public health project."

For example, Perlman says, someone collecting sensitive data from the HIV/AIDS division and using it to try to improve services being offered to that population may run across data that suggests another use for the information.

"They might say, 'This data seems to show that we ought to tell everyone in the country that the way we do it is beneficial,'" he says. "They actually then develop a hypothesis on the basis of just doing a program evaluation. Once they do that, and once they're thinking they might be able to generalize the results of their particular data to a population beyond that, that sort of blurs the line."

This issue doesn't only affect state health department IRBs, he says. Up to 15 states cur-

rently don't have specific IRBs within their state health departments, instead outsourcing IRB review to outside institutions.

Dealing with outside IRB

That's the situation Perlman found himself in when he took charge of the human research protection program for the New Jersey health department. There was no departmental IRB, and reviews were conducted by a nearby medical university IRB. This sometimes caused problems between that IRB and health department researchers, he says.

"Reports were coming up from the researchers that the IRB didn't understand what we were trying to do," he says. "They were sort of on the overprotection end of things and it was stifling a bunch of important projects we had at the public health department."

As a result, Perlman says, he worked to take control of which projects were sent to the outside IRB, and eventually helped establish a state health department IRB.

But then he was faced with the same dilemma: How would his office determine which projects were truly research that required IRB review and which were the regular functions of a public health agency? To help draw up a policy, he looked at guidance from the Council of State and Territorial Epidemiologists (CSTE), a national professional association of public health epidemiologists.

Perlman says the CSTE guidance stood out as having highly nuanced and well articulated advice about determining whether something is research. In the council's view:

An activity is a public health practice when it involves: applying proven methods to monitor a community's health status, investigate occurrences of disease, and to implement preventive measures based on existing understanding in public health sciences.

An activity is public health research when it involves: testing unproven treatments or strategies that are not known to be effective. In these cases, the collection and use of identifiable private health information requires either informed consent or a waiver of that consent.

'Just tell us'

In those latter cases, Perlman says, he often had to educate investigators that they needed to submit their projects to the IRB for review.

"People on the inside of the public health department aren't typically aware of when their projects cross the line," he says. "They'd say, 'Just tell us when we have to get this reviewed.' So we'd say 'Come to us with your project, we'll try to give you an initial determination, and when you get farther along, get back to us and we'll look at it again.'

"We tried to be as helpful as possible in doing that, and for the most part we were successful, because most people had the protection of subjects in mind."

Once a project is determined to be research, the IRB then must decide whether to grant a waiver of informed consent for the use of identifiable health information. Often the most difficult part of the decision, Perlman says, is determining whether the research could practicably be carried out without a waiver, one of the criteria the IRB must consider under the federal regulations.

"What does that mean? Does it mean it has to be one small shade away from being impossible?" Perlman says. "In the end, we sort of know impracticability when we see it."

For example, asking a researcher to get consent from 200,000 people in a database he wants to use could be described as impracticable, he says.

"However, there was a project we had that involved the census, and the researchers argued it was impracticable to get informed consent," Perlman says. "And we argued, 'No it's not.' The census worker is going to be right in front of the people who are going to be the research subjects. Why not just ask them?

"We got the sense that in a lot of public health projects, people just didn't want to do it. They thought they'd slide it in under the category of impracticability."

Perlman says IRBs that work with a school of public health should be sure that they understand the distinction between public health research and public health activities. He says an IRB should be ready to seek assistance from organizations such as the CTSE, the Centers for Disease Control or the American Public Health Association.

"I guess the best thing to do is to be humble," he says. "IRBs should be humble and say we don't have the expertise to do this, we're going to call in a consultant. Or we're going to try to educate ourselves so that we can make this determination." ■

Tool measures capacity of Alzheimer's patients to give consent for research

Survey results tracked opinions from experts

A recent study of an instrument for assessing decisional capacity in patients with Alzheimer's disease shows that it's a reliable tool for determining whether those patients are competent to give their own consent for research.

The study, published recently in the *American Journal of Geriatric Psychiatry*, showed that scores patients received on a subsection of the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) tracked well with experts' opinions as to whether that patient was able to give consent.[1]

Jason Karlawish, MD, associate professor of medicine and associate director of the Penn Memory Center at the University of Pennsylvania in Philadelphia, says these results may help IRBs be more comfortable with the use of tools such as this one to help gauge decisional capacity.

Karlawish says IRBs need to consider tools such as the MacCAT-CR whenever a population under study has a reasonable probability of clinically significant cognitive impairment.

"Then it's worth thinking about what process or procedure you will have in place to assess capacity," he says. "We show one method, but by no means is that the method or the only method. That should be a function of the nature of the study's risks and benefits and complexity.

"But I think the field has reached the point where it's simply inappropriate to say that you cannot assess decisional capacity, which is a phrase that used to fly around out there."

Tool used in trial

Previous studies of the MacCAT-CR had shown it to be a reliable tool when used with patients who had mild to moderate Alzheimer's disease. This time, Karlawish and his colleagues studied its use in an actual clinical trial.

Karlawish's group studied 59 subjects who were participating in a clinical trial of simvastatin, a cholesterol-lowering drug being studied in the treatment of mild to moderate Alzheimer's disease. Each subject was accompanied by a study partner, an adult relative or friend who the subject trusted and who could serve as a knowledgeable aide to the subject.

The MacCAT-CR was administered to both the subjects and the study partners. The instrument itself is a semi-structured interview that is adapted to fit the specific information from the trial.

"This is not an instrument that has pre-specified questions with answers," Karlawish says. "It lets you plug relevant information from your clinical trial into structured questions with standardized scoring criteria."

The patient and study partner would have a written summary of the clinical trial, organized according to the sections outlined in the informed consent. After each section was read aloud, the interviewer would ask if there were questions, answer them, and then administer the questions from the MacCAT-CR pertaining to that section. Those results were tabulated.

Afterward, an audiotape of the interview was shown to three consulting psychiatrists who, without seeing the score or knowing the severity of the subject's illness, judged for themselves whether they thought the subject had sufficient capacity to give consent on his own.

Using a consensus of at least two out of three judges, 39 patients (53%) were found capable of giving their own consent. Comparing those results to the scores from the MacCAT-CR, the investigators found the scores — particularly the understanding subscore — highly predictive of the expert's opinion.

"In our paper, we're not even pushing the value of the other scales (included in the MacCAT-CR). We're saying if you just use the understanding subscale of the MacCAT, you get some decent information to structure your assessment of whether someone has adequate decisional capacity," he says.

No set cut-point

Karlawish says he was pleasantly surprised to see a reasonable proportion of patients were able to give their own informed consent.

"Even for those patients who were not capable, you were probably getting some information from them about their preferences and desires to be in research," he says.

He doesn't believe that it's necessary, or even desirable, to have one set cut-point for the MacCAT-CR — a score below which a subject is always incapable of giving consent. That cut-point could fluctuate from study to study,

depending upon the risks involved. He notes previous studies have shown that experts' judgments of competency are dependent upon the risks of the research.

The cut-point also could vary based on the comfort level of the IRB, he says.

"There's no question that you can take the same protocol and give it to a variety of IRBs and you get back very different assessments of the research risks and benefits," he says. "It only logically follows that you get very different judgments about what are appropriate subject protections."

Reference

1. Karlawish J, Kim SY, Knopman D, et al. Interpreting the clinical significance of capacity scores for informed consent in Alzheimer disease clinical trials. *Am J Geriatr Psychiatry* 2008 Jul;16(7):568-74. ■

Strategies for handling poorly-written protocols

A jumble of jargon, tech terms, acronyms

Put any group of IRB administrators into the same room and soon you'll hear a discussion about how they have to deal with so many poorly-written protocols.

"I have about five years of IRB experience, and this is a common theme: poorly-written protocols," says **Michelle Gibel**, IRB administrator at Rutgers, The State University of New Jersey, office of research and sponsored programs in New Brunswick, NJ.

And it's not just the protocols. IRB professionals also deal with incomprehensible informed consent forms. Investigators and their staff are accustomed to using jargon, technical terms, and acronyms, which are useful in their every day clinical activities, but are not necessarily understandable to non-medically-trained individuals, says **Steward A. Laidlaw**, PhD, an associate vice president for compliance at the Los Angeles Biomedical Research Institute at the Harbor-UCLA Medical Center (LA BioMed) in Torrance, CA.

"From my perspective, and this is a personal opinion, informed consent forms should provide information in a short, simple fashion and in such a way that people get an idea of what they're being asked to take part in," Laidlaw explains. "You don't have to explain every potential risk, no matter how unlikely it may be."

Gibel has kept track of protocol problems and finds that many informed consent (IC) forms are written in language that does not meet the criteria of being readable at a sixth to eighth grade level.

"Basically, the readability is the key because you can have great information, but if it's not written in a language or in a way that the average person you're targeting will understand, then it's worthless," Gibel says. "It's important that you write in 'you' language, lower the reading level, and provide contact information so that if people have questions about the study or study procedures then the full contact information is included."

For studies that are conducted by a student, the student's advisor's contact information also should be included, Gibel adds. And by contact information, Gibel means they should include telephone numbers and email addresses, as well as names and full addresses. So how do you inform and educate investigators and clinical trial staff about how to improve the writing in their informed consent forms and protocol submissions?

LA BioMed has an informed consent template that IRB staff can use to make certain the forms contain all that is needed, and IRB staff analysts work to make the IC forms more readable, Laidlaw says. **(See related story, p. 140.)**

University IRBs receive protocols from both experienced faculty researchers and neophyte student researchers, and often the students will submit work that suggests they could have used a bit more mentoring, Gibel notes. "Sometimes people will recycle their old material and try to fit it into their current application," she adds. "Perhaps we're not always clear enough in terms of what we expect for a protocol."

The IRB at Rutgers has tackled this problem by starting a pilot program called the IRB Advisor in which senior IRB members will coach applicants in terms of how to successfully submit a protocol to the IRB. **(See related story, p. 139.)**

"It's available to faculty, staff, and students," Gibel says. "Here at Rutgers we have people in the staff role who may not teach, but they do conduct research," Gibel says. "It could be the person in the library who wants to study the usership of library services, so our target audience for the IRB Advisor program is anyone who does research."

IRB professionals are reaching out to the university's research community to announce the new program and to provide advice on their protocol submissions. "You can have as much great information as you like on the Web site, but it will only reach a handful of people who seek out the information," Gibel says. "So we utilized a list service to announce the program."

Also the IRB has hired an advisor to travel to different campuses to teach investigators what is needed in a complete submission. "One thing mirrors another," Gibel says. "If you have an application that's poorly written, then the subsequent material may not be well written either."

The IRB office also has other educational outreach. "Another administrator and I will go out and talk with faculty, students, and staff about how to navigate the IRB process," Gibel says.

All investigators at Rutgers have to take a human subjects certification program, which can be taken on-line with different modules.

"There are case study examples of things that potentially could go wrong," Gibel says. "It also has education about specific requirements in New Jersey and at Rutgers."

This material is available on-line at all times, and it's an alternative to a classroom session that shows participants a film about human subjects protection. Anyone who already has been certified may request the film and show it to other investigators, Gibel says.

The important thing is to enhance any human subjects protection education with specific information about how to write clear protocols and informed consent forms. The Rutgers IRB and compliance staff will contact faculty who submit a poorly-written protocol to discuss the specifics of the missing information, Gibel says.

"We give examples, and we ask them for specific language, providing them with any guidance we can offer," she says. "If it's a student who turned in the protocol then we'll normally reach out to the student's faculty advisor and first discuss it with that person."

After meeting with the faculty advisor, the IRB staff will ensure that the advisor and student are both clear of how to improve the protocol submission, Gibel says. Then the IRB staff will follow-up with an email.

"We always follow-up by email as part of the discussion," Gibel says. "We're sensitive to how they've sacrificed time to conduct research and we respect their ideas and will give guidance and assistance where needed to make a smooth transition to something that's acceptable for IRB review."

Gibel offers these tips for investigators on how to improve their protocol submissions:

• **Make sure you answer all application questions clearly:** "We tend to see a lot of questions where they write, 'Not applicable,' or they leave a lot of blank areas, suggesting they didn't complete this very carefully," Gibel says.

• **Go into details:** "It doesn't have to be arduous detail or have long paragraphs," Gibel says. "But let it be a well-written paragraph that defines all basic questions."

For example, if the question involves subjects, then the answer should be more specific than saying simply "students," she explains.

"If they are using Rutgers students, the form allows for them to say all students at Rutgers or students in a given course or given department at Rutgers," Gibel says. "We want them to explain this as best as possible."

• **Describe methodology as it pertains to subjects:** "We see with protocols that investigators haven't specified the methodology but give a lot of background and their literature review," Gibel says. "We'll look at specifics of a protocol's methodology — not for critique purposes — but to understand how the subject is going to do what is written in the protocol."

For instance, if a study is looking at anxiety, then the IRB would like to see details on these items:

- What is the risk level for participation?
- Who are the subjects?
- How is this population chosen?
- What procedures are employed?
- How will problems be handled?
- What are the identified risks?
- What are the identified benefits?
- What is the trial's duration?
- "We want investigators to take time to illustrate that they understand their protocol," Gibel says. ■

Advisor pilot program an immediate success

Reduction in returned protocols

The new IRB Advisor pilot program at Rutgers, The State University of New Jersey

in New Brunswick, NJ, resulted in a reduction in protocol submissions that had to be returned to investigators, according to the IRB director.

"So far, we've seen a drastic improvement," says Michelle Gibel, IRB administrator at Rutgers. "We've seen some dramatic increases in better-written protocols submitted to the IRB. It's a positive trend."

Here's how the program works:

• **Experienced IRB reviewers provide information:** "We have one of our seasoned IRB reviewers and faculty members — who is also a researcher and has been through the process successfully herself — provide information to researchers," Gibel says.

The IRB reviewer speaks at 45-minute educational sessions held monthly. "We've had 20 to 30 people show up for each session," Gibel says. "She has a PowerPoint presentation and goes over the whole aspect of human subjects research from soup to nuts."

For a start, the educator asks researchers to think about how research is defined and how human subjects are defined. "It's broken down in laymen terms," Gibel says. "Everyone comes from a different background, and [the IRB reviewer] takes it from a very pragmatic way of explaining research."

There is a 15-minute question and answer period at the end of each session.

• **The reviewer is available through email and office:** "The IRB reviewer is available to whoever in the community might have additional questions," Gibel says. "She holds office hours before deadline submission." The office hours are held just before the 12th day of each month for about a week before the IRB submission deadline.

"So if people show up to seminars they can email and correspond with the reviewer if they have any specific questions or are addressing specific issues in their IRB application," Gibel says.

The response to her educational sessions and follow-up availability has been phenomenal, Gibel says. "She provides a great deal of information to the audience, and then she has an opportunity to meet with different individuals involved in research about potential IRB submissions," she adds. As the program evolves, increasing numbers of researchers are requesting information via email or telephone, and the education sessions have grown in popularity, Gibel notes. ■

IRB improves consent forms with help from analysts

Avoiding the 'MEGO' syndrome

It's just about a given that informed consent documents making their way to the IRB for approval will need to be revised for comprehension and readability. Investigators and sponsors tend to include long sentences and paragraphs and technical jargon that leads the MEGO syndrome — "my eyes glaze over," says **Stewart A. Laidlaw**, PhD, an associate vice president for compliance at the Los Angeles Biomedical Research Institute at the Harbor-UCLA Medical Center (LA BioMed) in Torrance, CA.

So IRBs often have to be the ones to simplify the forms, while maintaining the key information. The LA BioMed IRBs have staff analysts who review informed consent documents for readability, style, and substance, Laidlaw says.

"They make sure that nothing that should be left in there is left out, and they make sure it's easily understandable," he adds. "So we have IRB analysts move around paragraphs for clarity and replace technical terms with accepted simplified terms or simplified discussion of it if the technical terms can't be replaced."

The staff analysts also will read the consent forms from the perspective of intelligent, non-scientists, Laidlaw says. While this isn't the IRB staff's only work, they do spend about 25-30% of their time rewriting consent forms, he notes.

"They have the benefit of their many years of experience in reading hundreds of consent forms, and they make acceptable re-organization of words, turning the document into a coherent discussion," he explains.

An investigator can write an informed consent form where everything in it is correct, but it makes no sense because the words are not comprehensible to a nonscientist, Laidlaw says. The narrative might lack order, for instance.

"They may decide after they write the description that they forgot to mention something else, so they slip it into the last paragraph, when, instead, it should be in the beginning of the narrative," Laidlaw says. "Investigators and their staff are busy people."

Investigators who have worked with the IRB in the past know what the IRB wants in an IC form and often will present their documents in that format, so that only tweaking is necessary,

Laidlaw says.

"But some investigators have their own perspective of the appropriate way of conveying information, and while it may be perfectly valid, it doesn't conform to the IRB's expectations," he adds. "So there may be some resistance to changing it."

For this reason, the IRB staff analysts work with investigators whenever possible, Laidlaw says.

The staff analysts also work from a template, which is available to investigators through an Intranet Web site. **(See sample from informed content template, below.)**

"They use the template and then make sure the IC form's formatting is right and the narrative is right," he explains.

The revised IC form is sent to Laidlaw for his review and signature before it is returned to the investigator.

Once the investigator reviews the changes, the IC document is sent to the IRB reviewer who often might make changes, Laidlaw says.

"The reviewer can make substantive changes, such as saying this risk should be here, and it's not," he explains.

Although the staff analysts' work can add to the time spent on IRB protocol submissions, the IRB has an average five-week turnaround time, Laidlaw says.

"From the receipt of the project in our office to the release of an approval letter is about five calendar weeks, 36 days," he adds. ■

Seven key features of UCLA consent form

The Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Los Angeles, CA, has a three-page template that IRB staff analysts use when reviewing informed consent documents for style simplicity and inclusion of all necessary elements.

Here is an excerpt from the template:

1. Purpose of the research.
2. If you take part in this research, the following will be done:
3. The following treatments and procedures are experimental:
4. You may reasonably expect the following risks and discomforts (including the likely results if the experimental treatment does not work):
5. You may reasonably expect the following benefits:
   • To yourself:
   • To humanity:

   These benefits may not happen and unexpected side effects may also develop.
6. If you choose not to take part in this research, the following alternative procedures might help you:
7. The results of this research may be published to inform other physicians and scientists. Your laboratory tests, photographs, videotapes and x-rays, if any, may be published. Your name or your records will not be given out without your consent, unless required by law. Your records may also be reviewed and/or photocopied by the Food and Drug Administration, the Institutional Review Board (IRB) or its staff and the sponsor of this study. ■

Quality assurance in trials protects human subjects

Ensures they receive treatment specified in protocol

Quality assurance programs for clinical trials do more than improve the data coming out of studies and the validity of the results.

They also can improve the protection of human subjects by ensuring that the intervention an IRB approves is the one that subjects actually receive, says **Thomas J. FitzGerald**, M.D., a radiation oncologist and director of the Quality Assurance Review Center (QARC) in Providence, R.I.

QARC is a research program of the University of Massachusetts Medical School that provides services for National Cancer Institute-supported clinical trials involving radiation therapy. QARC coordinates everything from credentialing sites to ensure they are equipped to carry out trials, to managing data and providing feedback to physicians during the course of trials so that study interventions are carried out as planned.

The center helps NCI clinical trials cooperative groups put together multisite protocols that meet the needs of NCI and the FDA, as well as dealing with IRBs' varied requirements, Fitzgerald says.

"One of the things an IRB looks for is consistency and uniformity in a clinical trial and that the trial is written in a standard template that will permit trial execution and trial closure," Fitzgerald says.

Navigating IRB process

Fitzgerald says that while he occasionally talks

directly with IRBs that have questions about a protocol, he usually works with investigators to help negotiate the IRB process at their own institutions.

When an IRB raises an issue with a protocol, QARC can help the investigator figure out a way to address it while maintaining uniformity with the trial as a whole.

"We can say, 'That's a good point, but here's how others have addressed that point,'" Fitzgerald says. "So sometimes we can bring that language back to them and they can think about that and say, 'Well, yeah, you've addressed that point. I see what you're saying.'

"I think so much of it is the ability to keep an open mind and understanding there are many ways of achieving the correct objective."

As the trial moves forward, QARC maintains a database that is connected to institutions around the world conducting the study.

"Let's say you're in Australia and a patient is entered on a particular cooperative group trial," Fitzgerald says. "QARC is notified at the same time. And we will update the Children's Oncology Group; we'll send a note to the investigator in Australia that day that this is the data that's expected for this particular trial at this particular time. If it doesn't arrive, our (clinical research associates) are working with the Crass on site to get the information and data to QARC."

Fitzgerald says 50% of the time data is sent to QARC, it's incomplete. The center continues to go back to researchers and collect the necessary data to ensure it meets the guidelines outlined in the protocol.

Review protects subjects

The center also conducts real-time review of the data, comparing it to trial guidelines and suggesting changes when necessary. Fitzgerald says that review can keep a well-designed trial from running off the tracks. For example, he says QARC worked on an international trial for head and neck cancer that included radiation therapy. "On that trial, which was approximately 900 patients, we were responsible for doing a review of the images and radiation therapy treatment objects within the first three days of patient treatment," Fitzgerald says. "I asked for changes in the treatment plan on 211 patients, because I felt the tumor wasn't being fully covered with the intended radiation field."

In every case where the investigator made changes at QARC's recommendation, the patient had a long-term survival equal to the nearly 700 patients whose radiation was compliant the first time.

"Of those patients where the adjustments were not made, there was a 20% decrease in patient survival," Fitzgerald says. "Quality assurance on clinical trials is important and it does affect the potential outcome of a trial, as well as outcome for individual patients.

"The oversight function actually improved protection of human subjects as well as creating uniformity for the patient which could then further validate the results of the trial." ■

Amend protocols to participants' needs

Add flexibility to inclusion/exclusion criteria

Clinical trial professionals and investigators should reconsider the inclusion/exclusion criteria and other factors to meet the needs of their study participants, an expert suggests.

"Some of the criteria we like to think can be used generally, and that's our goal, but in reality it might be difficult for sites to enroll under those criteria," says **Erin J. Iturriaga**, RN, CCRC, a nurse consultant and project officer for the National Institutes of Health (NIH) in Bethesda, MD.

For example, a clinical trial enrolling people who use methamphetamines might exclude enrollment of people who are infected with HIV because of potential drug interactions with the study drug and the antiretroviral treatment received by this population, Iturriaga explains.

"But while some of the medications HIV-infected people are on might be exclusionary, the HIV treatment field is changing so rapidly that it might not be necessary to exclude all of the people receiving medications used to treat HIV/AIDS," Iturriaga says.

"If you did a study two years ago, and this was the exclusion criteria then, the science might have changed so rapidly that you will now need to look at the exclusion criteria and change it," she adds. "Maybe two years ago when a new HIV medication came on the market we didn't know much about it, but now we have a much larger safety profile."

Therefore, the trial should be designed with

enough flexibility to permit enrollment of HIV-infected participants who are being treated with antiretrovirals that would not compound health problems or cause drug interactions in the study.

The reason CT sites and researchers will want to be more flexible and think of inclusion/exclusion criteria more on an individual basis is because in some studies it will be very difficult to enroll enough subjects if the inclusion/exclusion criteria are very strict.

The NIH encourages investigators to collaborate when deciding inclusion/exclusion criteria and to take into consideration their own potential study population and its needs, Iturriaga says.

"We try to collaborate with investigators to have a better understanding of what the standard of care is out there in the community," she says. "It might be very different on the East Coast versus the West Coast."

Such information about variations in the standard of care might be as important as historical information about similar clinical trial experiences a few years earlier, Iturriaga notes.

Sometimes science moves more quickly than do clinical trials.

This is why CT sites also need to be aware that a promising study drug might be seen as worse than standard of care a couple of years into a study, Iturriaga says.

When investigators begin studying methamphetamine addiction in a trial, there maybe no standard of care therapy available, she explains.

"But during the trial, the standard treatment could be improved, and this could kill your trial if the new treatment is a really good drug," Iturriaga says.

Clinical trial professionals need to assess the latest treatment trends, science, and other information in their fields of study, and they should make adjustments to their ongoing trials as new information comes to light, she adds.

At the very least, when a new treatment comes on the market while a clinical trial of a competing treatment is underway, the informed consent form should be updated, Iturriaga says.

"You need to inform subjects of the new treatments that are available," she says. "That may change the mind of a study participant of whether or not they want to continue in the study because of the new information that's available."

Another thing for investigators and CT sites to keep in mind is that they need to anticipate subject retention problems before they write the informed consent and begin enrolling participants, Iturriaga says.

"You may have subjects who are impaired due to drug use, or they could be incarcerated, so how do you deal with that?" she says. "A lot of them are vulnerable populations; they live in substandard housing or have no access to transportation, and these are all hurdles you need to overcome to keep them in your trial."

CT sites need to think about how research coordinators will obtain informed consent if a potential participant arrives intoxicated or high

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

- Conducting research in the aftermath of disaster: New suggestions
- Increasing participation of pregnant women in research
- QA program focuses on improving human subjects research
- Consent process should be interactive
- Learn from past IC process mistakes

CE/CME *questions*

21. Which of these did the COINS project show was the best predictor that a person would decline to participate in a research study?
    A. The disclosure to potential participants of the study investigator's financial conflict of interest.
    B. A potential participant's pre-existing level of trust in research and researchers.
    C. A potential participant's income level.
    D. None of the above

22. True or false: If a public health employee has access to personally identifiable health information as part of his job, he is free to use that data for research as well without seeking IRB review or a waiver of consent.

23. Which of the following is a good strategy for improving protocol submissions to the IRB?
    A. Answer all application questions clearly
    B. Go into details
    C. Describe methodology as it pertains to subjects
    D. All of the above

24. Which of the following is a common problem with informed consent documents?
    A. They are written at a 6th-grade reading level instead of the preferred 4th-grade reading level
    B. They are wordy and use technical jargon
    C. They use too many headlines, bullet points, and boldface to draw attention to certain lines
    D. All of the above

Answers: 21. B; 22. False, 23. D; 24. B.

from some illegal substance. They need to have contingency plans for when subjects become homeless or are incarcerated, Iturriaga says.

"There are many different types of sensitive therapeutic areas, so whatever study you're conducting, you should look at the hurdles for recruitment and retention," she advises. "Think about it up front when you're writing the protocol rather than waiting six months down the road and then being stuck." ■

IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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