IRB ADVISOR

*Your Practical Guide To Institutional Review Board Management*

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## IN THIS ISSUE



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# Human subject protection gets a boost with research advocates

*RSAs act as liaisons between researchers and IRBs*

The National Center for Research Resources (NCRR) of Bethesda, MD, established several years ago the role of research subject advocates (RSAs) for the purpose of providing an additional level of monitoring for research projects involving human subjects.

The NCRR laid out the groundwork for the RSA model, which enhances, but does not duplicate the IRB's role. Equally important, the NCRR made provisions for the National Institutes of Health (NIH) to fund RSA positions at institutions with General Clinical Research Centers (GCRCs).

Then the NCRR took a hands-off approach, which has allowed institutions and GCRCs to create priorities of their own for the more than 100 RSAs nationwide.

Given this flexibility, some RSAs and GCRCs have created very structured and thorough processes for monitoring human subject studies, especially with regard to informed consent and data safety monitoring plans.

"Some RSAs spend a lot of time in the clinic observing the informed consent process and interviewing participants to determine if they understand what it means to be in a GCRC research protocol and answering their questions," says **Susan Margitic**, MS, GCRC research subject advocate at Wake Forest University Medical Center in Winston-Salem, NC.

Margitic explains how she endeavors to complement the IRB's work in assuring that human subject research maintains high standards for safety and integrity. Here are some examples of the RSA's oversight activities:

**1. Assist principal investigators (PIs) with developing data safety monitoring plans.**

Margitic offers to meet early on with PIs to discuss their data safety monitoring plans (DSMPs).

"Every GCRC study has to have a DSMP, no matter what level of risk," she says. "I spend a lot of time looking at the DSMP in conjunction with reviewing the protocol and the consent form."

Margitic makes sure PIs understand what their DSMPs should include and how to determine a study's risks, which could fall into the categories of minimal risk, low risk, moderate risk, and high risk.

"There will be gray areas," she says. "For example, we have occasionally seen observational studies where there are no interventions, such as drugs, medical procedures, or devices, but which may involve tests done to measure study outcomes, and those tests could be risky."

An example would be an observational study involving a bronchoscopy being done as a research procedure in otherwise healthy asthma patients, she explains.

"Whenever you take relatively healthy volunteers and expose them to a risky research procedure or to an intervention of significant risk for which they are not going to benefit, most RSAs would say that's a high-risk study," Margitic says.

"Sometimes investigators need guidance concerning the level of safety monitoring that is needed," she adds. "The RSA can help them determine the physical, emotional, psychological, and other risks that may be involved in study participation."

Here are some of the questions that RSAs typically ask when working with investigators to develop a DSMP:

- What are the expected risks/adverse events (all of which should be included in the consent form)?
- How will risks/adverse events be minimized?
- How will subjects be treated if an adverse event occurs?
- Who is going to be monitoring the safety data for each individual subject?
- Who is going to be monitoring the accumulating safety and efficacy data across all subjects, and how often will this be done?
- Is there any conflict of interest for investigators or co-investigators?
- What specific lab alert values or clinical criteria will be formulated to determine when an intervention should be discontinued or changed?

"For example, if you are conducting a clinical trial in which you are giving a drug that causes renal problems, you want to monitor the blood for kidney function," Margitic explains. "And if the blood test indicates a certain level of renal toxicity, then it's essential to have plans in place to discontinue the drug or decrease the dose, depending on the specifics of the study, and these kinds of alert values must be pre-specified as part of the study DSMP."

- When adverse events are reported, what kind of scale will be used to describe how severe the adverse event is and what the presumed level of association is between the intervention and the event?

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## Editorial Questions

Questions or comments?
Call **Alison Allen** at (404) 262-5431.

• What is the adverse event reporting plan [i.e., to which offices or agencies will adverse events be reported, such as the IRB, the sponsor, the Food and Drug Administration (FDA), NIH]?

**2. Provide a thorough safety review of the proposed study protocol, DSMP, and adverse events.**

At Wake Forest University Medical Center, the RSA presents her safety review to the GCRC protocol review committee, which reviews all GCRC protocols and approves them before they are sent to the IRB for approval.

This two-step approval process was set up this way at the IRB's request, but it may be handled as simultaneous protocol submissions at other institutions, Margitic reports.

"I think that many RSAs review ongoing GCRC local adverse event reports that are sent to their IRBs," she says. "If a GCRC investigator reports an adverse event, I receive a copy of what was sent to the IRB."

Also, Margitic keeps her own longitudinal record of IRB-reported local adverse events, since some studies may not have a safety monitoring committee.

"This is an extra pair of eyes to look at safety," she explains. "We also review all data safety monitoring board reports and continuing annual renewal reports sent to the IRB for our studies."

The annual progress report includes details on how many people have been enrolled in the study; whether there have been any protocol deviations, study dropouts, subject complaints; discussion of unexpected complications or serious adverse events; and discussion of any new information that could affect the conduct of the study, Margitic says.

## Guidance in the informed consent process

**3. Offer hands-on informed consent guidance.**

"We want to make sure that our GCRC consent forms have all the mandatory elements," Margitic says. "For example, subjects need to understand that they are being asked to be part of a research study with a standardized research protocol, as opposed to receiving individualized medical care or treatment."

Other mandatory elements include:

• Purpose of the study.

• Description of study interventions and procedures.

• Alternatives to study participation.

• Risks and benefits.

• Steps taken to ensure confidentiality.

• Whether there is financial compensation.

• What treatment is available and who provides it if a research-related injury occurs.

• Name and number of the study's contact person who can answer questions or to whom an adverse event can be reported.

• Name of the office and phone number where subjects can report any concerns they have related to their being a research subject, such as if they feel their rights are being violated.

• Section that tells subjects that they have the right to refuse to participate in the study or to leave the study at any time and that this will not influence their care at the institution.

• Discussion of possible unforeseeable risks, (i.e., in an investigational or Phase I drug study).

• Advising subjects that they will be informed if there are any significant findings that may affect their participation, such as results from ongoing trials testing a similar intervention.

• Circumstances under which the subject's participation may be discontinued, such as if the physician believes it's in the best interest of the individual to not be in the study any longer.

• Whether there will be any cost to the subject for participating in the study.

• Consequences of early withdrawal from the study (i.e., a subject who drops out may have to gradually decrease the dose of study drug rather than discontinuing it suddenly).

• Number of subjects in a study.

• Explanation that if a drug or device is investigational and has not yet approved by the FDA then its safety and efficacy track record have not yet been proven.

• If the study involves a blind comparison arm, then subjects need to be informed that they may not know which treatment they are on until the end of the study, but that in an emergency situation, their treatment assignment could be revealed.

• If genetic or biological samples are involved, the informed consent form should include what will be done with samples, how confidentiality will be protected, and whether subjects can request to have their samples discarded at a later date.

In addition to guiding investigators when they design their informed consent forms, Margitic will observe how they or their staff handle the one-on-one informed consent process.

**4. Educate investigators and others working in research.**

Many RSAs also serve as educators, and Margitic is no exception. At Wake Forest, she

recently put together two half-day workshops called "Topics in Clinical Trials Research Studies," which covered 10 different topics.

The workshops cost $20 each, and they were open to the entire institution. About 75 people enrolled for each, she reports. "The turnout was gratifying."

The GCRC, the medical center's office of research, and the department of public health sciences sponsored the workshops. Margitic designed the program and found speakers, and made some presentations herself.

Topics included an overview of clinical trials, explaining good clinical practices, processing IRB documents, reporting adverse events, recruiting for studies, describing the informed consent process, encouraging adherence and retention of study participants, auditing by the FDA, and budgeting for clinical trials. ■

# Teleconferencing, web broaden member roster

*Meetings go on-line*

The four-year-old Goodwyn IRB of Cincinnati has a unique challenge when it's time for the board to meet and discuss protocols because the members are scientific and ethical experts who are spread out across North America.

However, this obstacle was quickly resolved through teleconferencing and Internet technologies.

Goodwyn IRB members receive all of their protocol packets and information through secure electronic channels, and they discuss these meeting dockets during telephone conference calls, says **Ellen Holt**, CIP, managing member and administrative vice chair.

"We didn't want to limit ourselves geographically," she explains. "We wanted to look for people who fit the requirements we had for the IRB rather than just look in a geographic area to see who was available, so we decided to do meetings through teleconferencing."

Once the decision was made to recruit board members from across the country, it was an easy decision to turn the IRB's work into a paperless process.

"It's hard enough to control what people leave on their desks when people are close by, but when people are far away, the best way to protect confidentiality is to avoid paper," Holt says.

The teleconferencing meetings have worked very well, partly because the IRB holds one weekend educational retreat each year, and all board members are required to attend, she says.

"That's an important part of what makes the whole thing work," Holt explains. "Being together face-to-face over a weekend is long enough for people to become reacquainted with review issues and to achieve and maintain camaraderie and trust."

IRB members often are on the telephone with each other throughout the rest of the year, but the annual retreat gives them an opportunity to build a team dynamic and learn each other's facial expressions and senses of humor, she says.

"It seems to be almost the same in our telephone conversations as it does in our face-to-face, but it wouldn't seem that way unless we had a chance to meet face to face," Holt notes.

Also, the programs presented at the annual retreats have been published by peer review journals, she says.

### *How and who?*

Holt, who had worked for 21 years in clinical research, administration, and regulatory affairs for pharmaceutical manufacturers and contract research organizations, founded the Goodwyn IRB in 1999 when she saw that there was an increasing need for private IRBs.

"The other impetus was the idea of participating in this arena and making a contribution to protecting human subjects," Holt says.

Here's how the IRB was formed and is run:

• **Recruiting members:** After creating an organizational plan that includes information on researchers' needs for IRB review, Holt made a two-page outline of the IRB's objectives, including one that called for a board with some experts in the area of pediatric research, she says.

Board members and alternates include people with backgrounds in regulatory science, bioethics, medical anthropology, statistics, genetics, clinical physicians, pediatrics, bioinformatics, and community representatives who also are parents, Holt says.

"We wanted a board comprising people experienced with dealing with complicated issues and who had experience in an in-depth way with the ethical issues posed by all kinds of research and also posed by transferring information electronically," she explains.

IRB members are paid an hourly fee that is somewhere between what they could earn as an hourly rate working in their field of expertise and a token payment, Holt says.

• **Using IRB consultants:** Some of the IRB's participants are members of a local IRB and have expertise in a field that sometimes is needed by the Goodwyn IRB. So they are asked to consult on certain subjects and participate in those meetings, Holt says.

By having consultants participate the board often is reassured about various concerns, and it opens up the discussion, she notes.

Sometimes IRB members find that their concerns about a particular protocol are alleviated when they hear from a consultant expert who has more knowledge of that particular patient population, Holt says.

• **Assigning tasks to board members:** "For each review, board members have specific tasks assigned to them," Holt says.

There are primary, secondary, and sometimes tertiary reviewers, she adds.

"For a core protocol, the primary reviewer is responsible for a total and thorough look at the entire protocol, and the reviewer reiterates that description to all board members at the meeting, highlighting some points of discussion," Holt says.

Primary reviewers discuss whether a study poses greater than minimal risk, privacy issues, interventions proposed, and benefits to subjects.

After the primary reviewer has completed a 10- to 15-minute talk, then the secondary reviewer speaks at the teleconference meeting. The secondary reviewer will bring up any description of the study or points that the first reviewer did not.

Finally, the third reviewer takes a turn discussing the protocol, and this is followed by the statistician's discussion of whether the study design is appropriate to achieve its objectives, Holt says.

"It doesn't really meet the ethical test to put people at risk if you're not going to achieve anything, so the statistician makes sure the study is appropriately powered and has a proper objective for the endpoint and analysis plan," she adds.

The core study review, including discussions about informed consent and other issues, may last two hours, Holt says.

• **Teleconferencing regular meetings:** The IRB meets via teleconference several times a week. "We thought we'd employ more videoconferencing, but we haven't found that to be necessary," she says.

"We have certain important requirements, and one is that it has to be transparent to everybody who is on the teleconference at the moment," Holt says.

Also, if someone leaves the teleconference for a moment then the board may lose quorum. The technology is set up to note when that happens.

The teleconference system introduces each board member entering the meeting and it announces to everyone who has just left. There's also a computer-generated display of all of the members present, Holt explains.

"The system doesn't determine who can talk," she says. "We manage that through rules of teleconference etiquette in which no one interrupts another person while they are giving points of discussion, and all points are noted and put on a cumulative list."

Teleconferencing etiquette also requires each speaker to say his or her name before talking, and the IRB chairman serves as a moderator.

After all the discussion points are collected, the IRB looks at them and decides which issues were resolved and which need further discussion, Holt says.

So far, there has been no electronic or other glitches with the teleconferencing system, she says.

"We have a backup teleconference system, and we all have our passwords for accessing codes for the teleconference meetings," Holt says.

• **Sending protocols electronically:** All protocol packages are sent electronically, and the entire process is handled on computer, she reports.

IRB members also receive other board information electronically, such as determining conflicts of interest, education, and the meeting minutes, Holt says.

"It's a managed electronic work flow that makes the meeting time more efficient, and produces the documentation that is required to make the official records," she explains.

One of the big advantages to working entirely electronically is that when an investigator or study coordinator calls to ask for a copy of an IRB letter or memo, it will take the IRB staff a few seconds to send them the copy, Holt says.

"One of the delightful things about our electronic documents is that you can't lose them," she says. "So they're always within our grasp, and we can always re-supply anyone who needs a document." ■

# Supply and demand: IRB fees now are the norm

*Covering expenses is the goal*

Is your IRB charging for reviews yet? If not, you are probably in the minority. A quick Internet Google search is all one needs to see that most institutional review boards now charge for reviews of sponsored research and that they require payment prior to reviews.

Click on some of the links that pop up, and you can even get a sense of how much the IRBs typically charge **(for a sampling of charges, see chart, p. 115)**. It doesn't seem to matter where the IRB is located or how big the school is: Most seem to charge about $1,500 for an initial review and $500 for continuing review services.

"IRBs have become a resource intensive operation for nearly every institution," explains **Steven M. Lascher**, DVM, MPH, director of research and clinical trials at Saint Vincent Catholic Medical Centers in New York City. "They require a great commitment from staff and committee members, so it makes sense that we charge."

That wasn't the case until the fall of 2001. "If we charged before then, we charged it through the principal investigators, and it was up to them to collect the money," he says. "That just didn't happen, though." Now it is suggested that investigators include IRB fees in their proposed budgets.

Only the 100 or so sponsored protocols each year are responsible for the fees, however. "We are an academic medical institution and have a large number of residents and fellows," Lascher says. "For most of them, part of the requirement is that they do some scholarly research. Usually, that's not funded, but it still has to be reviewed by our IRB. We don't charge them."

To avoid the appearance that the investigators are paying the IRB, billing and payment are handled by the office of research, which sends bills directly to study sponsors. Payment is sent to the corporate finance office, he explains. "That makes it clear that no one is paying for a result."

Although Lascher thinks his institution's fees — $1,500 for an initial review and $600 for continuing reviews — are about the norm, he isn't sure that the fees charged actually cover the cost of a review. "I know we aren't making money on this. The human subject protection program is still in-kind supported by the institution."

Fees started popping up at IRBs in the late 1990s. In many instances, they stayed static until very recently. At Southwestern Vermont Health Care in Bennington, the fee used to be $1,000 at the time of submission, explains **Caryn L. Fleming**, human protections administrator for the system. In 2000, it went up to $1,500, and now the fee is $2,000. The cost includes ongoing review, although an additional charge for that may be in the offing.

"If you want to have adequate human protections programs, you have to pay the staff to do it," she says. "We are providing a service to both the community and physicians in the community."

As with Saint Vincent's, the fees aren't intended to become a profit center. Fleming says the goal is to be budget-neutral for reviews. And not every research protocol has to pay. "We do waive fees on occasion," she says.

Fleming also is in the middle of discussions on whether grant-funded research should be exempt from fees in general, rather than each investigator having to apply for waivers. But that begs another issue, she says: If some of the grant-funded investigators are employees and you don't charge them, does that leave the IRB open to criticism or some potential legal issue?

Currently, those requesting to have fees waived submit a memo in lieu of payment that explains why they can't pay the IRB fees. "We consider each application on its merits, but we always accept them," she says.

Another topic of discussion is whether surplus fees should be refunded to investigators, says Fleming. "Let's say there are 100 protocols opened in a year, and the Alzheimer's researcher submits 20% of those. If our budget is $60,000, and our revenue is $200,000, should we give them back 20% of the surplus?

In the future, Fleming says she'll review the fees every couple of years. If the IRB committee of the board of directors approves an increase, then it will be forwarded to the full board for approval. "In the informal surveys I've done on the IRB Forum, I think we're the most expensive I've come across," she admits. "But we justify that because we have very little funding for our IRB."

### Abandoning local IRBs

IRB fees never cover the cost of the IRB function, says **Valerie Konopka**, MA, the director of research quality assurance at the Albany (NY)

## Selected IRB Fees for Sponsored Research

| Organization | Initial Review ($) | Continuing Review ($) | Effective Date |
|---|---|---|---|
| Medstar Research | 1,875 | 500 | 7/02 |
| UCLA | 1,500 | 350 | 7/02 |
| UC Irvine | 1,500 | 500 | 4/03 |
| University of South Dakota | 1,500 or 10% of direct cost funds, whichever is less | 300 or 2% of direct cost funds, whichever is less | 7/01 |
| Northwestern | 1,800 | 500 | 9/02 |
| University of Missouri | 1,500 | 750 | 7/03 |
| Oregon Health Sciences University | 2,000 | 1,200 | 5/03 |
| Indiana University | 0-1,000 sliding scale | 0-500 sliding scale | 12/00 |
| Yale University | 1,200 | 800 | 2/01 |
| Children's Hospital Pittsburgh | 1,500 | 500 | 7/02 |
| UC San Diego | 1,400 | Included in initial fee | 11/01 |
| University of Pittsburgh | 1,500 | 500 | 7/02 |
| University of Texas | 1,500 | Unknown | 3/01 |
| University of Mississippi | 1,500 | 500 | 1/02 |
| University of Medicine and Dentistry of New Jersey | 1,500 | 900 | 7/02 |

Medical College. That's why the college opted to shift IRBs from the institution to a central IRB. "We looked at the increase in the personnel we would need, the paperwork we would have to do, even just the copying we'd have to do since there is no way you cannot make a copy of something. This was something we had to consider," she says.

### *Task force checks audits, staff numbers, etc.*

Konopka says the college looked at both moving the IRB function to an on-line service — "but that was really expensive" — and shifting it to a central IRB. A task force was created that looked at about a half a dozen different central IRBs before choosing Western IRB (WIRB).

Among the things it checked: whether there had been any FDA audits of WIRB, how many people were on staff, who those people are, and their areas of expertise. It also looked at who the IRBs' current clients were and made sure to check references.

At the time of the change, Albany Medical College was charging $2,200 per review. The first annual review didn't have additional cost, but after the first continuing review, the cost was $500. No charge was imposed for amendments and revisions. "Usually for cancer centers, you can have amendments and revisions almost weekly," she explains.

Over time, Konopka says she has come to the conclusion that "there is no way you can charge fees that will cover the costs of the IRB. You have to make a decision about whether the institution will support the board and pay for it another way, or outsource it."

By outsourcing, the number staff in her office was cut from six to three. They need three because grant-funded research still goes through the college

IRB, unless the grant comes from another institution and they already are using a central IRB. If all research went through WIRB, then the IRB at Albany could function with a single person, Konopka says.

### A seamless process

Under the current system, investigators submit their protocol to the Albany College IRB with a cover sheet and submission form that WIRB requires. Once that is checked off by internal staff, it's sent on to WIRB. The total time of that simple function is less than an hour per day. Konopka is kept apprised of all communication between investigators and WIRB.

For investigators, it's a good deal, too: The cost is $600-$1,300, and the turnaround time is just seven to 10 days.

It seems like an obvious solution to a problem that is often discussed on IRB listservs and forums, but Konopka says one reason many don't choose to go the central IRB route is prestige.

"There is an innate bureaucracy around IRBs," she explains. "People don't like to give up their turf or admit they are anything other than absolutely necessary. So they don't look at the practicality of outsourcing."

The idea may be catching on, though. The National Institutes of Health and the Food and Drug Administration (FDA) don't oppose it, Konopka notes. "They even came out and said recently that it isn't a bad idea." Not that one could really criticize the outsourcing process when it occurs regularly if an institution has a problem or is the subject of an FDA audit.

There are dozens of central IRBs to choose from, although she says reputation is important. "You don't want to just have a cursory review and have someone not paying attention to those things that might potentially be problematic in research."

Along with reviews, central IRBs also can help investigators develop consent forms, do consent reviews, and provide regulatory advice. They can even help principal investigators develop protocols.

"An institutional IRB would love to have the ability to help investigators with all that stuff, but we don't have usually have the time, the staff, or the resources." ■

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SPOTLIGHT ON COMPLIANCE

# OIG developing ethics guide to prevent fraud

*NIH grant recipients being targeted*

By **J. Mark Waxman**, JD
General Counsel
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Boston

One of the major fraud prevention efforts over the past decade has been the development and publication of compliance program guidance (CPG) for various aspects of the health care industry. Most recently, we have seen this effort with respect to the pharmaceutical industry and a focus on its relationship to health care providers.

Now, the OIG has turned its attention to the research arena and announced that it is developing CPG for recipients of extramural research grant and cooperative agreement (grant) awards from the National Institutes of Health (NIH). To facilitate that process, it also is soliciting input from those who might wish to implement CPG, principally colleges, medical schools, and other entities committed to furthering biomedical research.

### The nature of a compliance plan

The elements of a compliance plan are based upon the U.S. Sentencing Guidelines, which were developed by the United States Sentencing Commission. They were designed to not only to create uniformity in sentencing but also encourage organizations to develop their own compliance (re: ethics) programs. The guidelines apply to almost all types of organizations including corporations, partnerships, unions, not-for-profit organizations, and trusts. One significant aspect of the guidelines is that each organization is responsible for the wrongful acts of its employees as long as the employees were acting in their official capacity. The theory is that each organization shares a degree of culpability if an employee acts in an unlawful manner, even if the organization did not know of or approve of their actions. It is, therefore, in the best interest of organizations involved in research to develop a compliance plan that includes:

• Written policies and procedures that foster a commitment to compliance. In this context, the organization will likely need to address policies and procedures for both the administrative and billing components, as well as the IRB oversight functions.

• An effective training and education program.

• A designated compliance officer and compliance committee.

• Effective lines of communication.

• Internal monitoring and auditing.

• Enforcement of standards through disciplinary guidelines.

• Prompt response to problems, with implementation of corrective action plans and timely reporting to the NIH, Food and Drug Administration, or other relevant federal agency.

The OIG has addressed a number of areas specific to research that it will consider for this particular CPG. First, it notes that consideration will be given to an additional CPG element — "Defining roles and responsibilities and assigning oversight responsibility." While no particular comments are made informing us as to what OIG may have in mind, presumably it will be looking for comment as to whether clear guidance is required when both a medical school and hospital are in the same corporate structure, or whether clear determination of delegated authority must exist as between an IRB, research administrators, or entity finance personnel.

Second, OIG seeks input on the scope of the CPG and the types of activities that should be subject to it. It seems fairly obvious that the scope should be at least commensurate with the risks to improper expenditures of funds. A real question, however, exists as to whether it will extend into the clinical side of the research enterprise and those areas already subject to IRB oversight.

Third, the OIG notes that its fraud investigations to date have identified the areas of internal controls as problematic enough to "warrant attention" in a CPG. Internal controls in this context likely refers to the process of allocation funds or time spent among various grants, as between a grant and services provided to Medicare or other fee paying patients, or between various time periods over the course of a grant. This will address not only how this activity is to be conducted, but by whom and under whose supervision.

Indeed, the OIG notes that risk areas it has "tentatively identified" relate to charges allocations, "time-and-effort" reporting, and the use of program income. One interesting question in this latter area that is not addressed, but has been highlighted by the OIG elsewhere, is the interrelationship between routine Medicare service reimbursement and research activities and funds.

The implication of the OIG notice is clear, and is not the product of only this notice. Given the increasing amount of taxpayer funds that are pouring into research in the life sciences, particularly with bioterrorism likely to provide a new funding impetus, the OIG feels an increasing need to take those steps necessary to protect both the public and taxpayer dollars. OIG also may recognize that the research infrastructure within the nonprofit institutions that conduct much of the NIH-funded research is in need of all the help it can get, given the incessant budget pressures and the overall newness of many involved in the research process, including the board of directors of many of these entities. ■

# Once enrollment and data collecting stop, then what?

*Determining when to close the file*

As long as local protocols continue to enroll subjects and collect data, they must submit to annual reviews by the institutional review board. But what happens once the study concludes, enrollment is closed, and all data are collected? What obligation does the IRB have to continue monitoring the study?

According to the Office for Human Research Protection (OHRP), protocols must continue to be reviewed annually while any data are being collected or analyzed or any interaction with human subjects continues. However, studies are eligible for expedited annual review once the following three situations occur:

• (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects;

• no subjects have been enrolled and no additional risks have been identified;

• the remaining research activities are limited to data analysis.

The major benefit is that expedited reviews can be conducted by a smaller group of the local IRB and not by a convened meeting of the entire IRB,

says **Don Workman**, CIP, director of the Office for Protection of Research Subjects at the University of Illinois at Chicago (UIC).

"A convened meeting must be attended by a majority of the IRB members, including at least one nonscientific person," he explains. "An expedited review can be conducted by the IRB chair or by one or more experienced reviewers designated by the chair from among the members."

Though a less formal review, the OHRP has been clear that they expect to see a thorough examination of the study design, the questions the study is attempting to answer and what progress has been made, the number of subjects enrolled, the adverse events reported, and how those risks have been addressed and minimized.

The IRB also must have an established protocol for how to communicate information about the studies receiving expedited review to the entire board, and must demonstrate that the review process is not just a cursory glance, he adds.

"A lot of IRBs have gotten into trouble by lumping 10 protocols up for continuing review and taking one motion, something like saying, 'Does anyone have an issue with any of the studies up for continuing review?'" he explains. "You shouldn't have these blanket approvals. You need to review each one individually."

The procedures for reporting adverse events throughout the trial and the procedures for annual review both serve as feedback loops for the IRB to monitor the study's progress, with the adverse events serving as a sort of daily check and the annual review as a time for the IRB to comprehensively look at all of the information gathered over the course of the previous year, Workman says.

The smaller subset of the IRB that conducts an expedited review is not able to disapprove a study — that can only be done in a convened meeting — but they can require the study to be suspended while the investigators address any critical issues found.

That requirement prevents situations in which one person might be able to hurt another's research, but allows problems to be addressed pending the review of the entire board.

### When it's finally over

But at what point can the IRB stop conducting annual reviews?

That question is not explicitly addressed in the regulations, says Workman, but it is generally accepted that a study is concluded once all interaction with study subjects has ceased, and all data have been collected and analyzed.

At that point, continuing review no longer is needed.

However, there is no broad consensus about what constitutes proper analysis of the data, Workman says.

Investigators usually prepare some sort of final report to the IRB indicating that the study has concluded and what the results were, he notes. "Otherwise, you would just end up with these protocols with lapsed approvals, and you need to know what the status is."

However, some experts feel that IRBs should continue review until there is some sort of publication of the study results or the information is made public in some way, Workman adds.

Human subjects agree to participate in research with the knowledge that the information will be put to use. IRBs must be careful to not support or encourage investigators to abandon data, particularly if it happens to be data that the study sponsor is just not happy with, he notes.

There is a great concern among research ethicists now about pressures, both real and potential, on investigators to not publish results that are unfavorable to a sponsor's test drug or product.

"Sometimes you just have a study and the results are just not what the investigators expected, or they just don't reveal anything in particular," Workman notes. But there are journals that publish null results — and even that type of publication is useful in that it prevents other researchers from duplicating a bad study. "That's not what everyone wants. There's not a lot of incentive for journals to publish the results of a study that went nowhere, but there is value in it."

At St. Jude Children's Research Hospital, where Workman worked prior to UIC, a group of investigators started a small-scale study whose design was picked up by the Children's Oncology Group, which expanded it, he notes.

The original researchers then closed their study, but the local IRB did not want to abandon the information collected from the participants there.

"They really worked with the investigators and kept them coming back until they found some forum to publish the data," he notes. "Now you are talking about uncharted waters, because there is certainly nothing in the regs that says an IRB can keep a study under review until the investigators find a journal willing to publish, but because of the ethical concerns, they and the investigators were willing to." ■

## Reader Question

# COI policy: Address potential conflicts

*Policy should be threefold*

By **John Isidor**, JD
CEO
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Cincinnati

**Question:** Should an IRB have a conflict of interest (COI) policy? If so, what should be in it?

**Answer:** Yes, an IRB should have a COI policy. The IRB should consider three potential sources of COI: member conflicts, institutional conflicts, and investigator conflicts.

• **Member conflicts.** An IRB must have a COI policy regarding its members. 21 CFR 56.107(e) and 45 CFR 46.107(e) state that:

— No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

— Accordingly, an IRB should develop a COI policy that covers a member's financial, personal, and professional conflicts of interest.

— A financial COI might exist if the investigator has a financial interest in either the sponsor of the research or the test article. Financial interests also arise from owning stock in the sponsor's company, having a consulting relationship with the sponsor, or being a spokesperson for the sponsor. The IRB should consider what level of financial interest would create a COI requiring the IRB member to be removed from IRB deliberations and voting.

— A personal COI arises when the IRB member is asked to review research being sponsored and/or conducted by a close friend or relative.

— A professional COI might exist when an IRB member is asked to review research being sponsored and/or conducted by a supervisor, such as a department chairperson.

— The COI policy should require the conflicted member to leave the room during deliberations and voting about the research in which the conflict exists.

• **Institutional conflicts.** Institutional conflicts of interest arise when institutions have equity interests, licensing agreements, or investments in the sponsor [HHS Draft Guidance on Financial Conflict of Interest in Clinical Trials, 68 *Fed Reg* 15,456 (March 31, 2003)].

The Institution should create a COI committee to deal with institutional conflicts of interest. The institutional COI committee should ensure that a mechanism is available to communicate institutional conflicts of interest to the IRB. Upon receipt of information regarding an institutional conflict, the IRB can decide on appropriate management of the conflict.

• **Investigator conflicts.** A conflict exists when an investigator has professional or financial interests that compromise or appear to compromise the investigator's independent professional judgment in any aspect of the conduct of a clinical trial.

As with IRB member conflicts, investigator financial conflicts can arise from financial interests in the sponsor or test article. They also may arise from a compensation structure using milestone payments and/or incentives that reward investigators for rapid and/or high-volume enrollment of subjects. Professional conflicts could exist when an investigator attempts to recruit subjects from his or her own patients or employees.

As with institutional conflicts, the institution can establish a COI committee to review investigator conflicts and communicate those conflicts to the IRB. The COI committee and the IRB should jointly determine what types of COIs will be communicated to the IRB and how to manage them. For example, the COI committee

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might decide that certain conflicts, such as ownership of a small number of shares of stock in a publicly traded company, are so minor that they need not be reported to the IRB.

Institutional and investigator conflicts can be managed in a variety of ways. Effective ways of management include disclosure in the consent document, third-party monitoring of the consent process, additional monitoring of the research, use of a data safety monitoring board, divestiture of the financial interest that creates the conflict and preventing the conflicted institution or investigator from participating in the research.

Lastly, it is vitally important that institutions, investigators and IRB members educate themselves about COI. Available resources include professional association guidelines, the draft NIH guidance referenced above, the Internet, and conferences sponsored by groups such as PRIM'R/ARENA.

*(Editor's note: If you have questions regarding IRB responsibilities, federal regulations, adverse event reporting, and day-to-day functions, we'd like to know. Please forward questions to alison.allen@thomson.com and each issue we'll ask an expert in the field to provide an answer.)* ■

# CE/CME *questions*

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

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

13. Which of the following might be included in a data safety monitoring plan?
A. How will risks/adverse events be minimized?
B. How will subjects be treated if an adverse event occurs?
C. Who is going to be monitoring the safety data for each subject?
D. All of the above

14. IRB fees for initial review typically are:
A. $2,200
B. $1,500
C. $1,000
D. $500

15. Expedited annual review is acceptable under which of the following conditions?
A. The research is permanently closed to the enrollment of new subjects
B. Half of all subjects have completed research-related interventions
C. The research no longer conducts follow-up of subjects
D. None of the above

16. A compliance policy/program should include which of the following?
A. An effective training and education program
B. Internal monitoring and auditing
C. Enforcement of standards through disciplinary guidelines
D. All of the above

**Answers: 13-D; 14-B; 15-A; 16-D.**