IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

December 2013: Vol. 13, No. 12
Pages 133-144

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Statement of Financial Disclosure: Editor **Melinda Young**, Associate Managing Editor **Jill Drachenberg**, Executive Editor **Russ Underwood**, Nurse Planner **Kay Ball**, and Physician Reviewer Mark Schreiner, MD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies related to the content in this CNE/CME activity.

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OHRP revisits standard of care vs. research issue

Controversy divides bioethics, research community

To some in the research community, the brouhaha over how standard of care is communicated in research consent documents is a tempest in a teapot. For others, it's a significant problem.

Whichever view one holds, it's clear that the Office for Human Research Protections (OHRP) is taking the issue and its critics seriously.

In late August 2013, OHRP held a public meeting about standard of care in research, and more than 200 people participated. Also, 75 people posted comments online about the issue.

OHRP will develop guidance about what constitutes reasonably foreseeable risk in research involving standard-of-care interventions and what is required to be disclosed to research subjects, says **Diane M. Gianelli**, OHRP spokesperson.

"This is an important issue that deserves thoughtful deliberation, so there is no timetable set for releasing the updated guidance," Gianelli says.

There is growing appreciation that the current approach to informed consent has serious flaws, states a letter signed by researchers involved with the Clinical Research Ethics Key Function Committee and the Child Health Oversight Committee of the Clinical and Translational Science Award Consortium (CTSA). The letter was submitted as a comment to OHRP.

"Informed consent documents are lengthy and difficult to understand," the CTSA letter states. "Numerous studies show that people can participate in the informed consent process and yet retain misunderstandings about the most basic facts about the research for which they have given consent."

The OHRP meeting and public debate over the use of standard of care in research resulted from a March 7, 2013, letter OHRP sent to the University of Alabama at Birmingham. The 13-page letter discussed the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) study, which involved 22 sites and was reviewed by at least 23 IRBs. The study enrolled 1,300 infants from 2004 to 2009 and was designed to learn about treatment with continuous positive airway pressure (CPAP) and to determine the appropriate levels of oxygen saturation in extremely low birth weight infants.

The study randomized infants to lower or higher levels of oxygen to test the effects on their survival, neurological development, and the likelihood of

developing retinopathy of prematurity (ROP).

OHRP wrote in the letter to UAB that, based on the consent form template and the UAB consent forms, "We determine that the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death."

IRB Advisor (ISSN 1535-2064) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (404) 262-7436. Website: www.ahcmedia.com. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to IRB Advisor, P.O. Box 550669, Atlanta, GA 30355.

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The OHRP letter further stated that the SUPPORT consent form did not identify a single specific risk relating to the randomization to high or low oxygen ranges, but did include a section with specific information about the possible benefits to participating infants.

More than 40 bioethical and medical experts responded to the letter, urging OHRP to withdraw its notification that SUPPORT failed to meet regulatory informed consent requirements. The bioethicists' letter was published on June 20, 2013, in the *New England Journal of Medicine* (*NEJM*).

"We believe this conclusion was a substantive error and will have adverse implications for future research," the *NEJM* letter states. "Allowing the decision to stand would be unfair to the investigators and institutions involved in SUPPORT. It would also set a precedent that would impede ongoing and future patient-centered outcomes studies."

That sort of response to OHRP's letter to UAB is puzzling, says **Leonard Glantz**, JD, professor of health, law, bioethics and human rights at Boston University, School of Public Health.

"Why do people react this way over such a minor finding?" Glantz says. "When you look at the OHRP letter it's incredibly gentle."

While the OHRP letter helped launch the broader look at the use of standard of care in research and, more specifically, how it's handled within informed consent documents, its overall tone is mild, he adds.

OHRP should stand by its letter to UAB and say that standard of care is just like any other research, requiring the same amount of IRB scrutiny, Glantz says.

"When you go to a doctor and you get care, it's because your doctor thinks it's good for you," Glantz says. "When your doctor is a researcher and is no longer acting like your doctor, then you need to know that."

OHRP decided to suspend compliance actions against UAB until after the agency issues new guidance to address risks and standard of care. The public meeting in August on the topic was a first step toward creating new guidance.

Several speakers at the public meeting spoke in favor of increased regulatory scrutiny of standard of care in research, and some took issue with OHRP's critics.

"Soon after OHRP's findings regarding SUPPORT came to public attention, a group of individuals within the medical research establishment launched a well-orchestrated attack against OHRP in defense of the SUPPORT study," according to **Michael Carome** of watchdog group Public Citizen in Washington,

DC. Carome was the first speaker at the OHRP meeting.

"Many critics of OHRP's actions have sought to blur the line between research and clinical care and appear to view the process of obtaining informed consent as an unnecessary impediment to conducting clinical trials and advancing medical knowledge," Carome continues. "They want to change the rules to satisfy their research needs at the expense of subjects' rights."

The people who oppose the OHRP letter appear to oppose research regulation in general, Glantz says.

Research treatment and standard care are different, which is why ethical research requires voluntary informed consent, one expert told OHRP at the August meeting.

"In standard care, as we have heard, a doctor's fiduciary responsibility is to prescribe treatments that serve each patient's best interest adjusted in response to each patient's individual fluctuating need," said **Vera Sharav** of the Alliance for Human Research Protection in New York City.

"Research treatment is predetermined by a protocol that seeks to resolve uncertainty and contribute generalizable knowledge," Sharav said. "Every patient who is asked to volunteer for research should be informed honestly about potential risk of foregoing individualized care."

Researchers and IRBs should keep in mind the fact that inherent risks in treatment used in standard care may be magnified within the constraints of research, Sharav said.

However, in some comments to OHRP, experts point out that research treatment is not always riskier.

"It is a dangerous and outdated fantasy to simply view research as riskier than conventional treatment," writes **John D. Lantos**, MD, director of the bioethics center at Children's Mercy Hospital in Kansas City, and a professor of pediatrics at the University of Missouri in Kansas City.

"Care guided by protocols may be better or worse than care guided by individualized clinical judgment," Lantos adds. "Participation in a research study may increase or decrease some or all of these risks."

The only way investigators and IRBs can ensure that patients make a truly informed choice is to describe risks to potential study subjects in a way that is informative, empowering, clear and comprehensive, Lantos writes.

"And I hope that the federal regulations that come out of hearings like this acknowledge not just the risks of research but also the benefits — and parallel risks of non-validated therapies," he concludes.

Perhaps the real problem with the SUPPORT study was that more than 20 IRBs reviewed it and none had addressed the informed consent problems OHRP found, Glantz says.

"There is a problem when IRBs say, 'This is a national study; I'm sure it's fine,' and then they don't look too closely," Glantz says.

"You expect investigators to downplay the risk; you never see a proposed form where the risks are exaggerated and the benefits are downplayed, so IRBs should be used to that by now," he adds. "That's where the failure is." ■

IRB Series: Overseeing studies overseas:

[Editor's note: This story is part of a series about how IRBs are handling international research studies. In the November issue of IRB Advisor*, there were stories about how universities are focusing more on international research, and stories about best practices and guidelines for international research. This story on collaborations and human subjects protection of international study participants concludes the series.]*

Protecting subjects from 5,000 miles away

Collaborations can help grow research overseas

A first step in protecting human subjects in an international study is to ask researchers to discuss their motivation, preparation, and knowledge involving research in foreign countries, experts say.

"What do they say prepares them to conduct research in that location and with that subject population?" says **Michelle Watkinson**, IRB administrator at Rutgers, The State University of New Jersey, in New Brunswick.

"What are their attitudes and cultural sensitivities?" she adds. "In today's world it's about connections."

IRBs will also want to know about oversight, including having someone provide oversight for a graduate student who is initiating research overseas, she says.

"Who does the researcher know in that country, and what consultants have they gotten to do the work?" Watkinson asks.

A research protection office might provide some

education about research in international settings to an institution's faculty. The IRB also might seek input from experienced international researchers when creating new educational and training materials and programs, she suggests.

"We provide educational outreach and sessions," Watkinson says. "Last year we did a session for [the global affairs department] for international students, telling them what they needed to do to go through the IRB process."

Those kinds of programs are helpful in improving research compliance with international research rules, she adds.

Another strategy might be to speak with experienced researchers about ways to improve reviews of international studies. This can help create better submissions and reduce the time it takes to complete the review process, Watkinson says.

"It allows for reviewers and committee members to review things effectively and to know what their resources are if they have any concerns," she says.

The Rutgers IRB has guidance for international studies that addresses these questions. *IRB Guidance and Procedures: Evaluation of the Local Research Context for International Studies* provides guidance for handling both research involving greater than minimal risk to subjects, and research involving no greater than minimal risk to subjects.

For example, one guideline involves the use of consultants, and states that it is not acceptable for a consultant to be a friend or collaborator on protocols or grants with the investigator, or anyone who has personal or professional ties with the protocol investigator that would preclude him or her from speaking independently and objectively about the research project.

"This is because of objectivity," Watkinson explains. "We want a consultant who is knowledgeable, but objective."

Overseas consultants must understand the needs of the population, as well as have research knowledge and experience, but they cannot be connected to the investigator, she adds.

Domestic researchers could find a researcher at the international setting and ask to collaborate with him or her, says **Richard L. Sneed**, PhD, director of the Office of Research Compliance, University of Central Oklahoma in Edmond.

Working with consultants and collaborators also is a good strategy for conducting international research on a limited budget, he notes.

"We encourage collaborations, and one way we do that is to try to find more local universities or find universities with pre-existing relationships in those places," Sneed says.

"Given the global nature of education, if I want to talk with a researcher in Singapore, I can do it at a mouse click," Sneed says. "We can identify local researchers, ask them to collaborate, and then initiate a system of collaboration between our research endeavors and what the local researchers have in place."

Once an institution establishes a record of success, it can write about its track record in grant applications for international research, Sneed adds.

When the IRB is able to contact a consultant who is knowledgeable and objective, IRB members will be able to trust the consultant's input as they make a decision about the study, he says. ■

Help IRBs deal with common frustrations

IRBs can be part of problem

IRB members and chairs often deal with investigators' outrage over the IRB process, but sometimes it's their own frustrations that are difficult to resolve, an expert notes.

"There are two parts to dealing with frustrations to improve the process," says **Melissa Abraham**, PhD, chair of Partners Human Research Committee, Massachusetts General Hospital, Brigham & Women's Hospital, and assistant clinical professor, Harvard Medical School in Boston.

"First, you are dealing with the frustrations of trying to improve the process — dealing with the things that make an IRB member frustrated, and the other is dealing with frustrating investigators," Abraham says.

IRB chairs, reviewers, and investigators sometimes are outraged over perceived unfairness in the process. This perception can occur when IRB chairs are viewed as enforcers — those who discipline others — rather than as customer service representatives or allies who guide people to improve the review process, she notes.

"We need to recognize that IRBs contribute to this climate, one where it's difficult to manage misconduct, because there is so much mistrust on both sides," Abraham says.

IRB chairs and members should think about how they contribute to the frustrations and problems that erupt. For instance, mission creep is something an IRB could acknowledge as a potential issue, she adds.

"You have investigators who see this as a

bureaucratic exercise and want to get through it, and they can be defensive," Abraham explains.

Abraham offers these strategies for reducing IRB and investigator frustration:

• **Assess style of communication.** IRBs should look at their written and vocal communication. For instance, look at how staff answer the phone, Abraham says.

Also, communication should be focused on the business issues and avoid personal references. IRB members and staff should be very clear about what they expect and clearly state the remedies that need to be done, she says.

"Be specific and give facts, as opposed to making it personal," Abraham adds.

"This might mean the IRB will check in with staff to make sure the letters they're writing are polite and respectful," he says.

An example might be to slightly rephrase certain IRB directives: "Instead of starting a sentence with 'You must change the word on page 3 to this,' change it to 'Please change the wording of this to this word,'" Abraham suggests.

These small changes can make a difference.

Another example would be a change in phrasing in a letter requiring changes: "The IRB could start a letter with, 'We recognize it can be difficult to implement the recruitment methods that are required by our policy. However, requiring this extra phone is…'" Abraham says.

"Or the IRB could say, 'Please do this,'" she adds. "Those styles of communication make a big difference in how people perceive that letter."

A third example shows how a less direct approach to handling an investigator site that is resisting corrections in its faulty processes might succeed. An IRB could say in its letter that it doesn't understand why an investigator is doing what he or she doing, or it could write, "Please continue your thinking on this important problem," or "While it may be difficult to implement this…," Abraham suggests.

• **Do not always assume the other side did something wrong.** One of the results of mistrust between IRBs and investigators is that each side will think the other did something wrong when there's a mistake. IRBs should start with the assumption that they may have missed something, Abraham says.

"If you find when you review a study that it doesn't look like they've made the appropriate changes, then instead of saying, 'You still haven't changed that,' you can say, 'We may have missed something. Please indicate where in your file we can find the change,'" she says.

Also, move away from the assumption that investigators are trying to get in the IRB's way, Abraham says.

• **Look for root causes of problems.** IRBs should ask a few questions of investigators to determine why a required action was not taken. It could be that the investigator thought everything was done correctly, but had not been the one to do that particular task.

If that's the case, then the root cause is improper delegation of a task, Abraham notes.

"The investigator might say, 'I didn't know this happened. I told the research assistant to take care of it,'" Abraham says. "So there was delegation without appropriate training."

When IRBs suspect there is a pattern of this, then they can send someone to discuss the issue with the principal investigator, she suggests.

"There are delegation logs, and they are supposed to keep track of key tasks and who these are delegated to," Abraham explains. "The first time it happens, assume it was a mistake; the second time, say, 'Maybe we're missing something, so help us understand how you are doing this.'"

• **Calmly deal with difficult investigators.** "Sometimes an investigator has no respect for the rules," Abraham says. "They'll say, 'Yes, we'll do that,' but there's no real learning curve, and no matter how much you educate, they do not make the changes going forward."

When this happens, the IRB can continue to be polite, avoiding hostile and sarcastic comments, but let the investigator know that his or her behavior is getting in the way of an expeditious review of the study, she suggests.

Let the investigator know that when the IRB sees a pattern of repeated problems, it results in IRB members worrying about the overall quality of the investigator's research operation, Abraham says.

"You can let them know they are hurting themselves," she adds.

Most investigators try to do the right thing, but there are always those who frustrate the IRB with their lack of concern for the regulations and rules, she notes.

• **Create solutions to common misunderstandings.** An IRB should assess the issues raised by investigators and research staff, looking for trends that could be solved systematically.

For instance, IRBs sometimes receive questions about quality improvement projects and whether a particular one will require an IRB review, Abraham says.

If this question pops up regularly, then the IRB could create a checklist, available online, that assists investigators with determining whether a project is

a quality improvement project or research, she adds. *(See sample checklist for QI vs. research projects, below.)*

Another area that can cause misunderstandings involves using deception in research, she notes.

"We developed a guidance document on when deception can be used and when not," she says. "We gave talks in the community about it."

"Bite off a piece you can fix and get information out there, publicizing it," Abraham says. ■

Make it a top goal to improve data collection

Capture data more efficiently

Whether an IRB relies on paper or is entirely electronic or has a combination of both, IRB staff can improve the office's efficiency. The simplest solution is to collect and use data wisely, an expert says.

"Every IRB collects data, although they don't necessarily recognize that they're doing this," says **Melissa Epstein**, PhD, CIP, IRB administrator at Albert Einstein College of Medicine of Yeshiva University in Bronx, NY.

Even IRBs that keep paper files can collect basic data about the number and types of studies they receive annually, she adds.

Some basic information IRBs can collect are on the first page of the study submission form, including these data: the principal investigator's name, department, the type of submission, topics covered, whether it involves bio banking, etc., Epstein says.

The real issue is: What will the IRB do with the collected data?

"And how could we collect it better?" Epstein asks. "Now that we recognize that we have information and are collecting it well, how can we measure

Sample items from QI checklist

Is IRB review necessary?

The Partners Human Research Committee at Massachusetts General Hospital in Boston uses a clinical quality improvement checklist to help investigators determine whether their QI activity is a clinical quality improvement/measurement project that does not need IRB review, or a quality improvement research project that does require IRB review.

The two-page checklist first provides examples of QI projects that do not require IRB review, including an evaluation of characteristics of patients with catheter-associated UTIs on a particular service for the purpose of minimizing the problem.

And it refers to whether the intent is to publish results of the project. This alone does not determine whether it needs IRB review. However, if the project is funded by an external research grant, then it should be submitted for IRB review, according to the checklist.

There are 10 items on the checklist. If an investigator answers "yes" to all of these, then no IRB review is needed. If there are one or more "no" answers, then an IRB review is required. Here are some examples of items on the checklist:

- The specific aim is to improve performance on a specific service or program in the hospital and is part of usual care. All participants will receive standard of care.
- The project is not designed to answer a research question or test a hypothesis and is not intended to develop or contribute to generalizable knowledge.
- The project is conducted by staff where the project will take place, and involves staff who are working at, or patients who are seen at the partner institution.
- The clinical practice unit (hospital, clinic, division, or care group) agrees that this is a QI project that will be implemented to improve the process or delivery of care (i.e., not a personal research project that is dependent upon the voluntary participation of your colleagues, students and/or patients).
- If there is an intent to, or possibility of publishing your work, you and your Department/QI Oversight group are comfortable with the following statement in your methods section: "This project was undertaken as a Quality Improvement Initiative at X hospital or clinic, and as such was not formally supervised by the Institutional Review Board per their policies." ■

what we do and feed that back into improving IRB performance?"

The more IRBs integrate their information systems with the IRB's workflow, the more IRBs can address the needs of their research communities, she adds.

"Data can be used to help you place your resources," Epstein says.

For example, if an IRB finds that only a small number of principal investigators submits more than one or two studies per year requiring full board approval, then this information can be used to prioritize education and training, she says.

"You might want to designate a staff member to design a training manual because you won't have the resources to train each investigator individually, or you may want to reach out to research coordinators and provide group training," she adds.

Epstein offers some strategies for improving data collection and analysis, including the following:

1. **Collect categorical data rather than continuous data.**

Categorical responses are when a data sheet gives the user a list of possible answers. This data type can be analyzed. Continuous responses are fill-in-the-blank answers, which are far more difficult to analyze and compile, Epstein explains.

"If you have a spreadsheet and want to know how many studies you receive per department, then you don't want people to type out the department's name because they could write, 'cardiology' or 'heart disease' or 100 different ways of describing the department," she says. "What you need is a pull-down list with department names to select."

"If you have free responses, these may be really informative or interesting from a review perspective, but they're useless from a data perspective," Epstein says. "If you want to hold onto information and analyze it, then you need to collect it as a categorical question."

Most electronic IRB submission systems are able to query any field, but someone on the IRB needs to know how to make the system do this, she says.

"Someone needs to know about data analysis, and some systems make this easier than others," Epstein adds.

2. **When collecting data, ask one question at a time.**

For instance, an IRB submission form may include a categorical question of whether the study involves bio banking. It is not a good idea to place a continuous question, such as "If yes, describe your mechanisms for data confidentiality here," in the same box, Epstein advises.

"If you put all of that in one box, people often don't answer the entire question," she says. "People try to load as many questions as possible in one space, but this can be disastrous."

The form's users might respond to only three of the five questions asked when the questions are compounded in one space, she adds.

"If you have one question at a time, some will lead to analysis and others don't," Epstein says. "If you write these questions as 1a through 1e, then it's much more likely that people will answer all five of them."

3. **Know your institution's data collection interface capability.**

"Hospitals and universities tend to have all sorts of in-house systems with information about patients, but getting the systems to communicate is not always easy," Epstein says.

When an institution improves its electronic system interfacing, it will make the IRB's and researchers' work easier and more efficient, she adds.

"If you have an IRB database and are generating information from the meeting minutes, can you generate from information the principal investigator has already put into the system?" Epstein says. "Can you have the principal investigator do some of the work for you?"

For example, Epstein asks investigators to write the information about their protocols exactly the way they'd like to see it appear in official IRB documents. Once they type it into the field the way they want, then every letter the IRB sends out to the PI will have the information listed in that exact same wording, she says.

"Then it's not my responsibility to type it in the way they want it anymore," Epstein says.

4. **Use data to better dedicate staff time.**

Just collecting data on how long it takes to complete a study review is one issue, but there are even easier metrics to collect that could be as useful, Epstein says.

"You should know how many new protocols you get in a year," she adds. "That's very, very informative."

With these data, for instance, an IRB administrator might be able to make the case to institutional leadership that the IRB office needs more staff and resources, she says.

"A lot of IRBs don't know how many amendments they get because maybe they do amendments in a haphazard way, and nobody understands why the IRB worker is behind," she says.

IRBs also should know what their investigators' research portfolios look like so they can prioritize education and training, Epstein suggests.

"If you get a Veterans Administration application

once every 10 years, then you shouldn't worry about those until one comes in," she adds. "But if you see a department of education study four times a year, then you may want to learn those education department regulations."

5. **Design data collection to deconstruct certain information.**

It's important to track the time between submission of a study protocol and the full board review or full board approval, Epstein says.

"You can do that on an Excel spreadsheet, and it's not elaborate or nuanced," she says. "If you have an electronic database, you should at the very least be achieving that."

With a sophisticated database, an IRB could measure specific lengths of time in the study review process.

For instance, the IRB could measure the precise amount of time that the study was in the principal investigator's office while the IRB waited for a response to questions, Epstein says.

"You can measure how much time it sits with the IRB and how much with the investigator and how much with the IRB staff," she says.

"A lot of these metrics are not available because it requires a fine grade level of tracking information, but if you can find these data it's great," she adds.

With information that is broken down into specific chunks, an IRB might learn that a specific IRB reviewer is taking a very long time reviewing studies. Or the IRB might discover that protocols submitted to the IRB on Thursday will take a week longer than others because the intake clerk only checks the pile on Wednesdays, Epstein says.

"The more fine-grained you can get the information, the more likely you can identify problems," she adds. ■

HRPP shares ideas for restructuring

Improved staff retention, turnaround time

In the fall of 2011, Indiana University's Human Research Protection Program was in crisis. Turnaround time for review of protocols was "horrendous," says **John R. Baumann**, PhD, now the executive director of the HRPP at IU. In what Baumann calls a "perfect storm" of challenges, staff turnover was high, electronic systems were adding to problems rather than addressing them, and there was a large backlog of studies waiting for review. Researchers' assessment of the Human Subjects Office was dismal.

"I don't believe it was a problem of having the wrong people — there just were not the right processes and procedures in place," he says. "In addition, a new program for processing had been partially implemented and created a need for workarounds — it was sort of a perfect storm."

In November and December 2011, the leadership team worked to identify key issues in the program structure and began a reorganization of procedures and workflow in January 2012. Baumann was named the full-time executive director of the program in February 2012.

Creating more accountability

One of the first changes, he says, was to restructure the teams in the office. Previously, the HRPP office was divided into four teams, with Team 1 in charge of exempt studies. Every person on the team could review the studies, but only one person had the authority to sign off. Baumann and colleagues' first step was to divide the office into three teams by academic unit — teams 1 and 2 have biomedical studies, while Team 3 has social and behavioral research. Each team has full responsibility over studies, from submission to closure and even post-study audits.

"In our opinion, there was not an alignment of responsibility, accountability, or authority," Baumann says. Studies had dividing points, including intake, screening and review, and outtake. Associate directors had responsibility for screening, but not for intake or outtake. "We said that doesn't make any sense, and now each team has responsibility for studies from soup to nuts, from when it comes in the door, to closure and audit," he says.

In order to eliminate the backlog of exempt studies, approval authority was expanded throughout the team. Members who have been in the office for a minimum of six months can participate in specialized training in order to gain authority to confirm exempt status. "We didn't do that and turn a blind eye; everyone who got the authority was monitored for six to eight months after completion to make sure they were meeting appropriate standards," Baumann says. Mean turnaround time for exempt studies is now at seven days, down from a mean time of 47 days in fiscal year 2012.

Another problem the office encountered was waiting for response from researchers if protocol review determined questions or issues with a study.

"That clearly affects turnaround time because in every human research protections office, the time a study spends in the hands of the researcher is a significant part of the turnaround time," Baumann says. "If you give people 30 days to respond and they respond in 28, you can't have turnaround time of less than 30 days."

In response, the HRPP created a policy requiring researchers to respond to questions within two weeks, or the study would be administratively withdrawn. That would not be punitive, or the end of the study, Baumann stresses; at resubmission, the process would be picked up where it left off. "What we found was that very few people complained," he says. "There were staff quite concerned about the faculty response, but there were very few complaints. This [policy] tells us that the researcher is ready for the study to be processed."

Improving turnaround time

Also contributing to approval delays was the repeated tabling of studies. Baumann notes that there were numerous cases in which a study would be tabled and not resubmitted for 60 days — and then it would be tabled again. The HRPP's new policy states that studies cannot be tabled more than once, and resubmission must occur in time for the committee's next meeting, 30 days later. At second review, the study must be approved or disapproved. "We did not do that in a punitive fashion — it just meant that studies didn't sit out there, lingering," Baumann says. The IRB offers resources for researchers whose studies are tabled; they can speak to an IRB member for guidance on study design, attend an IRB meeting to answer questions, or use other resources for help. "Researchers found it more helpful, and reviewers like it because they don't have to keep looking at the same study," he says.

The policies have decreased turnaround time significantly: In the second quarter of fiscal year 2012, full board studies had a mean turnaround time of 92 days. A year later, the mean time is 31 days.

The process for prior approval of research assistants was also simplified. "Any time there was a new person added or subtracted from a research team, it needed prior approval," Baumann says. "We were requiring co-investigator updates from everyone, no matter what." Instead, researchers are required to identify key and non-key research personnel, and only key personnel are required to have prior approval. Researchers still have to submit financial disclosures and proof of education for staff, but prior approval is no longer required for non-key staff. "We also implemented a monitoring procedure. Randomly during the year, we take a look at non-key personnel and make sure they completed educational training and disclosures before starting. So far, we have found no noncompliance. We regularly monitor a couple of times a year at random and never had a problem."

Executive committee

Another change focused on enhancing the utility of the IRB executive committee, which includes the chair and vice chair of each of the seven IRBs "Over time, the meetings lost focus and it became more of an opportunity for staff to report what was new," Baumann says. To enhance the function of the committee, the team implemented a new structure and the committee now has a chair, a vice chair, a new mission statement, and identified areas in the HRPP that would need its approval. "With the development of the new structure, they began looking at the processes and responsibilities of the committee members," he says. "The chairs became more active players in the process, and the committee is a more active group."

Pilot program

One of the HRPP's most innovative pilot programs, Baumann says, involves getting studies to a convened meeting more quickly by reducing the back and forth between staff, researchers, and sponsor. For example, if staff had a question about an issue such as informed consent, the comments would go back to the investigator — and be bounced between investigator, sponsor, and committee multiple times. "Different offices do different things with the study — some administratively process it, some screen it and critique a lot," he says. "We were doing a lot of the screening."

Working with the IU cancer unit, the HRPP implemented a pilot program in which the study would be sent for review along with the staff's comments, if all the basic study elements were there. The IRB would get the review and see the original edits and comments. "It eliminated one set of communications," Baumann says. "It was successful in getting reviews done quicker." The HRPP expanded the program to Team 1 and select units of Team 2. "The pilot is now standard operating procedure," he says. "We're always looking to see what we can do differently, with no sacrifice to protection of subjects, to be more efficient." ■

Streamlining protocol review with checklists

Lists can help focus on the small details

Four years ago, the research program at Connecticut Children's Medical Center in Hartford looked at its process for proposal review of pediatric studies and decided to strengthen and streamline the process.

"The idea was to have a more standardized approach to review, especially with things that are repeated over and over again [in the process]," says **Francis DiMario**, MD, CIP, associate chair of academic affairs, Department of Pediatrics, medical director, Human Research Protection Program, and Division Head Emeritus, Pediatric Neurology, at CCMC. "We wanted to make sure reviewers did not overlook the simple things."

To accomplish this, the Connecticut Children's IRB devised checklists to assist reviewers in completing the process. The New Protocol Reviewer Checklist was first developed four years ago, and the lists have been revised over time as needed. The IRB also has checklists for new submissions, full board reviews, submissions for expedited processes, amendments, continuations, and new proposals.

IRB members use the New Protocol Reviewer Checklist for new submissions, expedited submissions, and for full board reviews. It was developed by DiMario and the HRPP staff. "Quite a few people were involved and we shared our experiences using checklists," DiMario says. "I didn't think I'd be a big fan of it, and I think most people felt the same way — 'Oh no, more things to fill out.' I think it does help to improve efficiency and makes sure each review is done the same way. Everybody gets the same look."

DiMario says the review checklists have improved the depth and quality of protocol review. "I think the most important use of checklists was to assist people in a logical and thorough review process," he says. "Members felt that the checklists should be updated periodically and revised, that they have an educational value in and of themselves as well as guide the review process." As a result, the lists are revised as needed to make them more streamlined and user-friendly, DiMario says.

Sample questions

The New Protocol Reviewer Checklist is about seven pages long and includes sections on inclusion/exclusion criteria, scientific design, informed consent, risks and benefits, resources, privacy and confidentiality requirements, compensation, and other considerations. The end of each section includes space for reviewers to leave questions or comments for the principal investigator. There are also attachments for waivers or modification of informed consent.

Here are some sample questions from the New Protocol Reviewer Checklist:

Specific aims, background, and significance

Are the study aims/objectives clearly specified?

Are there adequate preliminary data to justify research?

Is there appropriate justification for this research protocol?

Inclusion/Exclusion Criteria:

Are the inclusion/exclusion criteria clearly stated and reasonable?

Is the selection of subjects appropriate and equitable?

Are minorities, women, children, or other vulnerable populations included in the study design?

Is the inclusion or exclusion of minorities, women, children, or other vulnerable populations justified?

For subjects vulnerable to coercion or undue influence, are additional safeguards included to protect the rights and welfare of these subjects? E.g., prisoners, mentally ill, economically/educationally disadvantaged, employees.

Subject recruitment & enrollment

Are recruitment methods for all groups well defined?

Are the location, setting, and timing of recruitment acceptable?

Are all recruitment materials submitted, if applicable? If YES, is the text and formatting deemed non-coercive and easily understandable?

Are there acceptable procedures for screening subjects prior to recruitment? Mailings, record reviews.

Scientific design

Is the scientific design adequate to answer the study's question(s)?

Is the scientific design (e.g. randomization, placebo-control) adequately described and justified?

Are the study aims/objectives likely to be achievable within the given time period?

Research Procedures

Are the rationale and details of research procedures

adequately described and acceptable?

Is there a clear differentiation between research procedures and standard of care and evaluation?

Are there adequate plans to inform subjects of specific research results?

If no, is this acceptable?

Data analysis

Is the rationale for the proposed number of subjects reasonable? NOTE: all studies, except pilot studies, require a formal sample size.

Are the plans for data and statistical analysis defined and justified? (stopping rules, endpoints)

Are there adequate provisions for monitoring data? (Data Safety Monitoring Plan) NOTE: required for all biomedical/behavioral intervention trials and GCRC research. ■

Study: Registered trials are going unpublished

Nearly one-third of registered clinical trials go unpublished five years after completion, a *BMJ*-published study found.[1]

By law, certain clinical trials and research studies involving human subjects must be registered on ClinicalTrials.gov, and results published on the website and/or in scientific journals. There has been some controversy involving studies that remain unpublished, including a group of researchers calling for the release of lost or unpublished trial data.[2]

In order to estimate how many trial outcomes go unreported, a group of researchers from Cooper Medical School of Rowan University in Camden, NJ, and the University of North Carolina, Chapel Hill, looked at 585 registered trials with at least 500 participants that were concluded before January 2009. The earliest registration date was November 1999, and the median date April 2006. Of those 585 trials, 171 (29%) were not published by November 2012. Of the unpublished trials, 133 did not publish results on ClinicalTrials.gov, as is required by the Food and Drug Administration Amendments Act. Thirty-two percent of the unpublished studies were industry-funded, while 18% were funded through universities, government, or grants of some sort. Eleven percent of the examined trials received some sort of federal funding; 80% were industry trials.[1]

"The non-publication of trial data also violates an ethical obligation that investigators have towards study participants," the study authors write. "When trial data remain unpublished, the societal benefit that may have motivated someone to enroll in a study remains unrealized."

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1. Jones CW, et al. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ* 2013;347:f6104.
2. Doshi P, Dickersin K, et al. Restoring invisible and abandoned trials: a call for people to publish the findings. *BMJ* 2013;346:f2865. ■

COMING IN FUTURE MONTHS

- Strategies for fairly listing risks and benefits in IC
- Develop policy for handling UP trends
- Update on Common Rule changes
- 2013 Salary Survey results

CNE/CME OBJECTIVES & INSTRUCTIONS

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

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

Physicians and nurses participate in this continuing education program and earn credit for this activity by following these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

CNE/CME QUESTIONS

1. The Office for Human Research Protections (OHRP) recently held a public meeting on the topic of standard of care in research. Which of the following issues was OHRP's chief concern regarding standard of care in the SUPPORT study, a multisite trial enrolling low birth weight infants?
   A. Unanticipated problems reporting
   B. Risks described in informed consent form
   C. Guardian consent approval
   D. Determining payer of standard of care procedures

2. IRBs might improve trust and communication between the board and researchers by making some changes to their wording in letters and emails, an expert says. Which of the following is a good example of one of these suggested changes?
   A. Reword directives, changing "You must change…" to "Please change…"
   B. When there is missing information, say, "You still haven't changed that," instead of "We may have missed something. Please indicate where in your file we can find the change."
   C. Change wording from "We don't understand what you did to solve this problem" to "Please continue your thinking on this important problem."
   D. All of the above

3. Which of the following is not a good strategy for improving data collection and analysis, according to Melissa Epstein, PhD, CIP?
   A. Collect categorical data rather than continuous data.
   B. When collecting data, ask one question at a time.
   C. Use only electronic data.
   D. Design data collection to deconstruct certain information.

4. According to John Baumann, PhD, specialized training programs to authorize staff to sign off on exempt studies is a good way to decrease protocol turnaround time.
   A. True
   B. False

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