IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

FEBRUARY 2005
VOL. 5, NO. 2 • (pages 13-24)

Vioxx, NIH crises lead to questions about drug safety and IRBs' role

But are IRBs responsible for long-term safety of FDA-approved drugs?

The revelation that Merck's popular painkiller rofecoxib (Vioxx), as well as other drugs in the COX-2 inhibitor class, pose an increased risk of heart attack and stroke in patients who take them has led many in the research community to question whether the instiutional review boards at the sites where the drug was tested failed in their mission. Disclosure by investigators and FDA regulators that they knew of clinical data indicating a statistically significant number of adverse cardiovascular events among study subjects has only added to the controversy.

If IRBs are charged with protecting the interests of human subjects enrolled in clinical research, many wondered, how could a drug with such glaring risks be approved?

The debate has been further heightened by allegations by an internal investigator at the National Institutes of Health (NIH) that senior officials there conspired to cover up significant research misconduct that allegedly occurred during a clinical trial of the AIDS drug nevirapine, which was conducted on pregnant HIV-infected women in Uganda under sponsorship from the National Institute of Allergy and Infectious Diseases. The NIH whistle-blower, Jonathan Fishbein, currently is scheduled to testify before Congress about allegations that the researchers failed to adhere to the study protocol, mishandled study drugs, poorly maintained patient records, and failed to report many adverse events, including deaths. According to one internal NIH audit report, thousands of adverse events in the study were never documented.[1]

Such revelations lead many in the public and clinical research arenas looking for a single place to assign blame, and, unfortunately, that scapegoat has become the IRB, says **Paul Goebel**, CIP, vice president of Chesapeake Research Review Inc., a private biomedical and social science research support firm based in Columbia, MD, that provides a central IRB and scientific ethical review consulting for different institutions.

"Many seem to expect the IRB to be able to prevent abuse, misconduct, or an adverse event from occurring," he says. "Failing that, they expect the IRBs to know when these shortcomings occur and take prompt action."

But such expectations misconstrue the mission, structure, and functioning of IRBs as they have been traditionally established, Goebel points out.

Under the original federal regulations and guidance that established IRBs, they were charged with ensuring that a study protocol met federal guidelines and then periodically monitoring the study's progress to ensure that investigators do what they said they were going to do and follow the approved protocol.

"They were originally designed for an initial review of a project, and then a 'how is it going?' look after a period of time, usually annually," Goebel explains. "Most IRBs have now recognized that more frequent review is necessary for high-risk studies. For example, the IRB for the first artificial heart study performed a review after each installation before permission was granted to the researcher to install the next one. The investigator soon moved his research to another institution, in part because of the close IRB oversight of the study. The IRB was asking questions and demanding assurances that were viewed by some as excessive at that time, but would be considered normal and necessary today."

Informed decisions possible?

Currently, IRBs are simply unable to perform the added oversight functions that the public increasingly seems to be asking them to assume, agrees **Michael Goodyear**, MD, assistant professor in the department of medicine at Dalhousie University in Halifax, Nova Scotia. Goodyear currently is serving on a task force to recommend improvements in clinical research oversight to Health Canada.

"The public has far too much confidence in the system and a very incomplete idea of what IRBs are all about," he says. "In fact, IRBs are usually woefully underresourced. The IRB's primary role is the conduct of a study locally. On the other hand, there is nothing that stops IRBs talking to each other or to other bodies if they are concerned. I strongly encourage that."

Even so, he adds, IRBs and research ethics boards (their Canadian equivalent) are not meant to be "content experts, but principle experts."

However frequently they monitor progress or communicate with other boards, IRBs still are not structured to evaluate complex safety data, such as the occurrence of cardiovascular events in the COX-2 trials, adds Goebel.

First, they usually only get information about adverse effects occurring in subjects at their site —

IRB Advisor (ISSN 1535-2064) is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to **IRB Advisor**, P.O. Box 740059, Atlanta, GA 30374.

Thomson American Health Consultants designates this continuing medical education activity for up to 18 credit hours in category 1 toward the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Thomson American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Thomson American Health Consultants is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Provider approved by the California Board of Registered Nursing, provider number CEP 10864, for approximately 18 nursing contact hours.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, board members have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Belknap, Dr. Nelson, Mr. Goebel, and Dr. Sugar report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Mr. Isidor reports stock holdings in Merck and Pfizer. Mr. Waxman is general counsel to CareGroup Inc. and Beth Israel Deaconess Medical Center. Dr. Sugarman is a consultant to Family Health International, the FDA Advisory Committee, and NIH Data Safety Monitoring Board. Dr. Sugarman also is receiving funding from the National Institutes of Health for study on research ethics and receives ad hoc honorarium fees from institutions for speaking on research ethics topics. Dr. Hill reports no relationships with companies related to this field of study

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (ahc.customerservice@thomson.com). Hours of operation: 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.

Subscription rates: U.S.A., one year (12 issues), $415. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. **Back issues**, when available, are $55 each. (GST registration number R128870672.)

Editor: **Suzanne Koziatek**.
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262- 5483, (lee.landenberger @thomson.com).
Managing Editor: **Alison Allen**, (404) 262-5431, (alison.allen@thomson.com).
Senior Production Editor: **Nancy McCreary**.

THOMSON
AMERICAN HEALTH CONSULTANTS

Editorial Questions

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

which may be only one out of several nationwide or internationally, he says. And, they often are only told that an effect occurred, not whether it was expected or unexpected, and whether other factors, such as subject compliance, were involved, Goebel adds.

"The IRBs do not get enough information about an adverse effect to enable them to make an informed decision. The IRBs are told that an event occurred. They do not have access to the complete study data. And, many IRBs do not have statisticians as members," Goebel continues. "Whether or not to continue a study often involves a statistical evaluation of the raw data. It is very rare for an IRB to stop a study. Most adverse effects do not present a black-and-white, clear-cut situation upon which to stop a study. The recent Vioxx and Celebrex heart problems only surfaced after sophisticated statistical evaluations of hundreds or thousands of uses."

Monitoring of this kind is and should be the purview of an independent data safety monitoring board (DSMB) established by the study sponsor, he notes.

DSMBs, the existence of which can be mandated by an IRB, function to evaluate the raw data collected by all of the study sites to determine whether any significant effects are discernible, Goebel says.

"In my view, this is the right place for such decisions to be made. NIH requires a safety monitoring plan to be in place for some studies," he says. "This framework could be extended to all studies conducted in humans for which the research could result in substantial or permanent harm to the subjects."

Research watchdogs also should not let sponsors, study monitors, and principal investigators off the hook when it comes to the occurrence of adverse events or disclosure of potential misconduct, Goebel continues.

Under federal research guidance, it is the responsibility of the sponsor to send site monitors to evaluate the conduct of the study at each site, and the responsibility of principal investigators to monitor the conduct of the subordinate investigators and research coordinators to ensure that subjects receive appropriate informed consent, are treated according to the study protocol, and that any adverse events are appropriately reported.

It is unrealistic, Goebel contends, to place the lion's share of the burden on an IRB already in charge of monitoring possibly hundreds of other ongoing studies at the same time.

"The people closest to the study are the clinical investigator and the study coordinator. They are the ones who are involved with the study every day," he notes. "The study monitors are charged with repeated oversight of the study. They visit the study site several times a year. The IRB is a distant third. A routine study is reviewed once a year, excluding changes in the protocol and adverse effect reports. So if we want IRBs to now assume the responsibility for close monitoring of studies, it will be expensive."

Improvement in oversight cannot be the sole responsibility of individual IRBs, but they can be empowered through changes in regulation or guidance to have more of a say in how drug studies are conducted, Goodyear notes.

"Yes the issues raised are outside the IRB scope. Yet the IRB is a component of a social structure set up to protect the public, and is entitled to a voice at the table on drug policy," he explains. "But ideally, IRBs should have a strong voice through a central umbrella organization. In terms of what we now know, IRBs can simply refuse to approve studies that do not meet minimal standards, such as an independent DSMB. The can also lobby to have these made mandatory, and for other national standards. However, to do this they will need the ear and support of the regulator. Usually what happens is sponsors play IRBs off against each other."

Reference

1. Associated Press. "NIH Dismissed Concerns About Drug Treatment." Dec. 14, 2004. Accessed on-line at: www.msnbc.msn.com/id/6707600/. ■

2005 issues: Stem cell research, noncompliance

PRIM&R panelist discusses issues on IRB radar

The work of IRBs will not get easier this year, if predictions from panelists at the fall Public Responsibility in Medicine & Research (PRIM&R) conference are on point. Some issues are old hat — informed consent, conflict of interest — and others will arise out of the new frontier of stem cell research.

"There are several ongoing challenges," says **J. Mark Waxman**, JD, general counsel for CareGroup Healthcare System in Boston, including, "ensuring the quality of continuing reviews, meeting the eighth-grade understanding level in informed consent documents, and finding the resources to

do all the work."

During the conference, **Thomas Puglisi**, PhD, senior consultant at PricewaterhouseCoopers LLP in Washington, DC, listed the following as "issues on the radar."

• **Systemic problems.** Such problems include failures in the informed consent process, such as limited or no discussion of benefits or lack of a statement that informs subjects that the study is research; failure to conduct adequate continuing review; and failure to maintain adequate documentation of IRB activities — all items frequently listed in warning letters sent to institutions. According to Puglisi in his presentation, 1,120 citations of noncompliance were issued between 1998 and 2002.

He says good clinical practices and an effective evaluation process should be in place to ensure that IRB processes are in compliance with federal regulations.

Puglisi tells *IRB Advisor*, "If an IRB or institution discovers serious noncompliance, it should 1) take whatever immediate action is needed to safeguard current subjects; 2) self-report the problem to the FDA and/or OHRP; and 3) propose a corrective action plan to address the identified problem and any systemic issues to which the problem might be related."

The consequences of noncompliance range from suspension of the study to negative media attention to financial loss. "If discovered by OHRP, federally supported research could be halted until corrections are made," Puglisi says. "If FDA discovers the problem, the IRB could be prohibited from approving research until corrections are made. Clinical investigators could be sanctioned or even prosecuted if violations are serious enough."

• **Human and fiscal resources.** It's a common complaint: IRBs are shorthanded and overworked. "Generally, the amount of effort required is underestimated," says Waxman.

Further, many IRBs are dependent on institution support, points out Puglisi, and as institutions experience budget constraints, IRBs may be the first to feel the impact.

Two ways to solve the issue of lack of resources, says **Stephen Kopecky**, MD, medical director for the Rochester, MN-based Mayo Alliance for Clinical Trials, are to work smarter and charge for services. "An IRB has a huge job to do and requires a large amount of resources both in terms of finances, personnel, and information technology. I think for the near future, IRBs should focus on incorporating IT [information technology] processes that will streamline the protocol reviews and help educate investigators and coordinator as they are going through the steps."

Additionally, IRBs could pool resources he says. "One way to stretch resources is to have IRBs work together," Kopecky says. "For instance, if a study is done at 50 institutions around the country, then have one or two IRBs take the lead role in reviewing the study to ensure protection rather than having every individual IRB repeat the work. Groups such as the MACRO [Multicenter Academic Clinical Research Organization] group are working together with common IRB review protocols."

(Editor's note: MACRO is a consortium of five institutions — Vanderbilt University, Washington University School of Medicine in St. Louis; the University of Pennsylvania; Baylor College of Medicine; and Partners HealthCare System, a Massachusetts-based health care delivery network — that have pooled IRB resources. Protocols are submitted to the group, and one institution is appointed lead reviewer. Though all participating institutions receive review documents, only the designated lead performs a full review.)

On the issue of financing activities, Kopecky says, "One way to recoup costs is to charge a fee for review of a protocol and for annual review. This is done commonly by centralized IRBs, and we should start to incorporate this more at academic institutions."

• **Rogue investigators.** A rogue investigator, said Puglisi during his presentation, would include researchers who failed to adhere to the protocol approved by the IRB, failed to maintain adequate records, failed to report adverse events, or failed to provide appropriate information for informed consent.

Whereas a true rogue is highly unlikely, those who repeatedly make honest mistakes can create problems for an IRB or institution. Investigators who fail to comply typically tend to do so not out of malice but out of inadequate training, Puglisi said during his presentation at the PRIM&R conference. Investigator noncompliance also could be related to lack of adequate assistance from clinical trial coordinators, typically because they are overworked, and a sloppy monitoring program, Puglisi said.

• **Adverse events.** "Adverse events are a challenge. Which ones are truly related to the trial and which are not continues to be a problem," says Waxman.

"IRBs receive a huge number of safety reports

from the industry that are virtually impossible to interpret because the IRB does not receive sufficient context on the incident and/or sufficient information about the total number of subjects in the trial," Puglisi says.

"Adverse events are troublesome for an IRB in that they often see the numerator — how many patients have an adverse event at their institution — but don't often see a denominator — total number of patient in the study at all institutions," says Kopecky. "The IRBs main role is to protect patients, and they should have data that helps them do this by looking at both the instance and the severity of the adverse event among the total patient population. IRBs often fall short because they don't have access to this data."

One way to improve data gathering, Kopecky says, is to utilize data and safety monitoring boards (DSMBs). "It is the DSMB's role to review adverse events and make suggestions regarding discontinuing the study as appropriate. IRBs should work closer with DSMBs, rather than repeating the role of the DSMB," he says.

• **Privacy of medical records.** There are privacy concerns discussed in the Health and Human Resources IRB guidebook, and there is the Privacy Rule that came out of HIPAA. "Although they use similar language, the requirements of the HIPAA Privacy Rule and the human subject protection regulations are different in many important details." For example, the guidelines do not offer clear criteria for evaluating whether a protocol might involve an invasion of privacy or breach of confidentiality; they merely instruct members to take a sensitive, common-sense approach. HIPAA has specific criteria for when and how a subject's private health information can be used.

Whether or not the Privacy Rule is adhered to is not an IRB responsibility, and the IRB shouldn't make it one, Kopecky says. "The HIPAA rules are really here to ensure privacy of a patient's records," he says. "IRBs are overwhelmed as it is and really can't get into the role of policing and regulating privacy issues."

• **Stem cell research and gene transfer therapy.** Both issues will appear on IRB radars this year, Puglisi said during the conference. "Multi regulatory and ethical issues surround the use of stem cells and gene transfer research," he tells *IRB Advisor*. Issues include questions about the level of protection human embryos deserve and at what stage of development, the appropriate use of stored biologic materials, and the possible mutation of vectors used in gene transfer therapy into active diseases.

"Clinicians are just scratching the surface on this and we need to have both clinicians and experts in gene issues involved when putting together guidelines," says Kopecky.

(Editor's note: Puglisi suggests these web sites for more information on the ethical considerations related to stem cell research — www4.od.nih.gov/oba/; www.georgetown.edu/research/nrcbl/nbac/execsumm.pdf; or www.georgetown.edu/research/nrcbl/nbac/hbm_exec.pdf. Information on gene transfer therapy can be found at www.dnapolicy.org/genetics/transfer.jhtml.)

• **Accreditation.** In 2001, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) formed. AAHRPP is a voluntary accreditation program requiring that applicants meet a rigorous set of performance standards and submit to an on-site evaluation. To date, they have accredited 18 institutions.

Right around the same time, the National Committee for Quality Assurance (NCQA) developed an accrediting program for the Department of Veteran Affairs. In 2003, NCQA and the Joint Commission on Accreditation of Healthcare Organizations formed the Partnership for Human Research Protection (PHRP) accreditation program. To date, PHRP has accredited seven organizations, four of which are independent review boards.

"Accreditation remains an issue, but not a critical one. Right now, it is in the 'Wouldn't it be nice' phase, as opposed to 'We need to do it now.' In three years, this may not be the case," Waxman says.

Accreditation should be global first, then individual, says Kopecky. "First is institutional accreditation; second is individual and coordinator [accreditation]. We have to be more diligent in educating our principal investigators as to the proper way to perform research. In the not-too-distant future, we will all understand that clinical research has to be done by individuals who are trained in it." ■

IRB application helps educate researchers

Submission process made easier

A new computerized tool developed at Vanderbilt University in Nashville, TN, provides investigators with information about IRB policies

and human subject research regulations at a critical point in the research process — when they're filling out their IRB applications.

Project PROTECT — PROvide Teaching of Ethical Clinical Research through Tactical Support — creates a computer-based IRB application that has links to relevant guidance and regulations buried in its text. By clicking on "Help" arrows, an investigator can get immediate answers to common questions about the application.

The new enhanced application helps not only the researchers, but IRB staff who otherwise would be spending more time answering questions from investigators, says **Tonya Yarbrough**, RN, a research nurse at Vanderbilt who helped develop the tool.

"We felt like our protocol analysts in the IRB were spending an enormous amount of time answering questions for investigators, the same questions over and over again," she says. "'How am I supposed to answer this question?' 'Where am I going to find this information?' 'Why is this so important?' 'How do I answer it if it doesn't apply to me?'"

Yarbrough says the institution also wanted to find a better way to educate investigators about human subjects protections than a tutorial that might not spell out the relevance to their own research. "We wanted to have some information right there so they would know exactly what it was that they needed to be thinking about with regards to their own study," she says.

"And the idea was to have it be electronic so they wouldn't have to go anywhere else to find the policies and procedures or the regulations or the template language when they are filling out the application. They could just click on an arrow right there in the application and have access to all of that information immediately."

Yarbrough says the enhanced application is part of a push by Vanderbilt's assistant vice chancellor for research, Gordon Bernard, to find ways to help investigators overcome roadblocks to doing clinical research while still protecting human subjects.

"That's our main goal: To make sure that our subjects are protected, but we also need to figure out a way that research can still get done," she says. "This was just one very small part of this very large restructuring process we're doing."

When an investigator goes to the IRB web site and downloads the application to a computer, he or she will see a number of colored arrows below each question. Each arrow links to a different category of the Help function:

— clicking on a red arrow explains "Why does the IRB ask this?"

— a dark-blue arrow brings up "Investigator help," or suggestions to help answer the question properly;

— a yellow arrow links to "IRB Policy" for that

Project PROTECT Sample Question

In the enhanced IRB application, a series of arrows next to each question provides the applicant with additional information.

Using the example of question 24C: **Is there a data safety monitor or board/committee to review this study for safety and adherence to the study protocol?**

— **Clicking the red arrow ("Why does the IRB ask this?") brings up this response**: "The IRB must determine if the method and degree of monitoring is commensurate with the degree of risk involved in participation in a study as well as for the size and complexity of the study."

— **The dark-blue arrow ("Investigator Help"):** Explains the purpose of a data safety monitoring board/committee, how it is chosen and its responsibilities.

— **The yellow arrow ("IRB Policy"):** One policy is referenced for this question: "Reporting of Unanticipated Problems or Adverse Events Involving Risk to Subjects, DSMB Section." The applicable section of the policy is quoted.

— **The green arrow ("Federal Regulations and Guidance"):** Links to two guidance documents: "Establishing Data & Safety Monitoring Boards — NIH/National Heart, Lung and Blood Institute;" and "Guidance on Data & Safety Monitoring for Phase I &II Trials — NIH/National Heart, Lung and Blood Institute." The investigator also can link to the "National Cancer Institute Policy for Data and Safety Monitoring of Clinical Trials," but there is a warning that clicking on this link will take the user outside the Vanderbilt web site.

— **The light-blue arrow ("Examples, Suggestions, and Template Language"):** Missing because it was not needed for this question.

Source: Vanderbilt University, Nashville, TN.

question, taking the investigator directly to the applicable section of the policy;

— a green arrow links to "Federal Regulations and Guidance" regarding the question;

— a light-blue arrow links to "Examples, Suggestions, and Template Language" the investigator may use to craft his response. **(See box on p. 18 for an explanation of how Project PROTECT works for one question on IRB application.)**

Yarbrough reports that when Vanderbilt first began developing the new application, it was planned as part of a switch to iMedRIS software for web-based on-line IRB applications. But that switch has taken longer than anticipated, so her group went ahead with the project, enlisting the help of a computer programmer to help create the interactive application.

Creating a system that can easily move the reader from the application to nearly 300 linked documents has proven challenging, Yarbrough says. To access the application, which was created in Microsoft Word, a researcher goes to the IRB web site, pulls up the application, and saves it to his or her own computer to fill it out.

"We had to do a lot of testing to make sure that we weren't locking people's computers up," she says. "And we found that we were in a lot of cases, because we were taking them from our server to the IRB server where template language and policies and procedures and things like that were."

Their answer was to put everything on a dedicated server, which has lessened the problem somewhat.

"We've made it clear that when you click on something, that it'll keep you on our server," she says. "But if, say, you're in an FDA regulation and it references another document, it will say in there 'This will take you outside of our server,' and that way people will know that there's a chance it might lock up their computer."

Technical support crucial

Yarbrough believes that when Vanderbilt goes to an entirely web-based system there will be fewer problems. That development also will make it easier to update the links as federal regulations and IRB policies change.

"Then, we'll be able to just pull in the new policy from the federal government and whatever links they had within their policy would still work when it's web-based," she says. "Right now, it doesn't work that way, so we actually had to create links for everything that's linked within a document so that slowed us down a lot."

Yarbrough says one important factor in creating this application was finding the right technical help. The computer programmer for the project had previously worked with the IRB, which gave her a useful perspective.

"You need someone who's really familiar with computer programming and who can adequately test the process to make sure it works," she says. "Because there's nothing more frustrating to either an IRB protocol analyst or an investigator than to go into an IRB application and it not work like it's supposed to work. That took the most time, just making sure that everything worked appropriately."

Yarbrough also advises anyone interested in a similar project to test, test, test.

"Because there are so many different computer systems out there, we had to do a lot of testing — people access our IRB application from home, from the football field where the kids are playing, all different places."

The system has been up and running since July 2004. Since that time, Yarbrough says she has heard enthusiastic responses from investigators and research coordinators.

"But the people who surprised us the most were the actual protocol analysts in the IRB, who have found that when they get a telephone call now, they go to the IRB application and to the Help [function] to answer the question from the investigator on the telephone," she says.

"One of the things they like most is that they can send the investigator to that application and they have access immediately to the policies and procedures and the regulations. So that if an investigator is questioning why they have to do something or what's the reasoning behind it, they have information to provide to them right there at their fingertips."

Having input from many different perspectives helped tremendously, Yarbrough says. Her team asked for feedback on the application and the Help function from the protocol analysts in the IRB, as well as investigators, nurses, and a research support services team that works with the IRB.

The director and assistant director for the IRB also reviewed it. "When you start reading through it, it kind of sparks your memory about something you did that you had to ask a question about so, we got lots of good suggestions," she says. "So it was really a collaborative effort."

(Editor's note: The Vanderbilt IRB application can be viewed at https://pulmonary.mc.vanderbilt.edu/IRB-help/.) ■

New web site centralizes multicenter submissions

IRBNet designed to improve communication

Developers of a new web site for researchers and IRB administrators hope it will help streamline review of multisite research by centralizing protocol creation and enhancing communication among research sites.

IRBNet.org, which went on-line a little more than a year ago, was developed by Dartmouth College and the Children's Hospital of Philadelphia.

Kristin Nowak, MPH, IRBNet project manager based at Dartmouth in Hanover, NH, says the goal of the site is to allow for cooperative review of multisite studies, which would help ease roadblocks for researchers and allow institutions to communicate among themselves regarding the studies.

"In these multisite studies, IRBs weren't talking to each other at all," she explains. "You could have a concern that an expert on the committee at one site may bring up because they have more knowledge about the subject area, but at another site you may not have that sort of expertise, and the issue may never come up."

Another feature of the site allows a researcher to create a protocol and consent form on-line using a best practice model that follows International Committee on Harmonization guidelines. The web site then could serve as a distribution center for the study documents and an archive for past and current studies, allowing investigators to check on the progress of submitted studies at various IRBs.

Nowak says IRBNet was the brainchild of Elizabeth Bankert, MA, director of Dartmouth's IRB, and Robert Nelson, MD, PhD, chair of the IRB at The Children's Hospital of Philadelphia, who pooled NIH Enhancement Grant funds to start it up.

As Bankert gave presentations on IRB review, Nowak says she heard the same complaints from researchers about the cumbersome process of gaining approval for multisite clinical trials.

"Whenever Liz was going out, she was hearing from researchers what a big hassle it was to deal with IRBs," Nowak recalls. "When you're only dealing with one IRB, you're going to have a decent sort of sense of what they want. But if you're the lead site of a multisite trial, every IRB is generally going to want things in their own format and they're going to have their own schedule as far as their submissions and renewals."

They developed a plan for IRBNet, which still is evolving, Nowak says.

Currently, it features a three-phase process of study design, distribution, and communication:

• **Study Design —** An investigator can either upload previously created protocol documents to IRBNet or create new study documents using IRBNet Study Designer, a document "wizard" that leads the investigator step by step through the process of creating a protocol or consent form. Because the Study Designer uses the ICH's best practice model, it promotes standardization of studies.

"[Documents created by Study Designer] should contain everything that anyone would need to submit a document to their IRB," Nowak says, while acknowledging that some IRBs might have different institutional requirements. "Our hope would be that eventually everyone would accept documents produced by IRBNet, but we're aware that at this point in time, that may not be entirely realistic."

• **Study Distribution —** Using IRBNet, researchers can give their collaborators access to study documents during the design phase, distribute the documents to local researchers at various sites, or transfer ownership of the documents to another researcher or sponsor, all on-line.

Nowak says a researcher can create a database of all the studies he or she has created and all the documents that researcher has been working on.

"You can see whether they've been submitted, what the review status is, who they've been shared with," she says.

• **Communication —** An important aspect of IRBNet is the ability it gives IRB administrators to communicate with each other regarding multisite studies they're involved in, Nowak notes. An administrator at an IRB involved in a study can see the status of reviews of the study at other sites — including any comments that are available for review.

"They would be able to communicate with other IRBs if it was a multisite trial as to why a review status was as it was," she says. "If something was not approved, why it was not approved, if it needed revision in some manner or another."

Nowak says the site still is in the process of signing up a multicenter study that could be completely created using IRBNet. While there's a lot of enthusiasm about the idea — IRBNet already has more than 400 registered users — finding a study that could be begun on the site, registering everyone needed and getting all the documents

into the system has taken some time, she says.

"We really want to get a multisite study through the system because it will also help us see where some of our weaknesses lie," Nowak says. "I can go through and test the site all that I want and can think everything is fine, but it's not until multiple people are actually using it as it's intended to be used that certain things will come up."

Nowak says IRBNet has the capacity to customize forms or add new ones if an IRB was willing to use the study plan but wanted a different version of say, the consent form. The form could simply be available for download and submission, or in a more time-intensive process, IRBNet could put the form into the system so a researcher could be guided by a wizard as he or she filled out the forms.

"There are lots of possibilities for how IRBs could get what they want out of it, or how it can be made most useful and acceptable for IRBs," she says. "The goal is that this will streamline the process and also increase communication between IRBs. That would be the ultimate goal."

There's also the issue of funding, since the NIH grants that started IRBNet will be ending soon. While applying for new grants, Nowak says the developers also are considering charging fees to sponsors or physician consortiums that run protocols through the system — perhaps customizing the site to meet their specific needs.

(Editor's note: Registration at IRBNet.org is free, but must be approved by a site administrator.) ■

Newborn subjects, vulnerable families

IRBs' challenge: Truly informed consent

They're among the most vulnerable research subjects — newborn babies, born with problems, spending the first days of their lives in neonatal intensive care units.

Their parents are vulnerable, too. After sometimes traumatic deliveries, mothers are exhausted, and perhaps on medication. Fathers are frantic with worry about both mother and baby.

Some question whether it's even possible to get true informed consent for research under those circumstances.

Recent studies bear out the fact that the stress of making decisions for a newborn can impair parents' abilities to understand and remember what they're agreeing to. A study last year indicated that a substantial percentage of parents who had agreed to allow their children to be part of one neonatal research project didn't fully understand the study. Some didn't even remember allowing their child to be enrolled.

"We know the literature tells us that parents are very unlikely to be able to make a true informed consent at all," says **Lisa Golec**, RTT, BSc, MHSM, clinical research coordinator for the NICU at Sunnybrook and Women's College Health Centre in Toronto. "But we also know that we need to do research. Research is how we provide the care that we can provide for these babies. Research is what has given us the technologies and therapeutics to provide the exceptional care that we can to the point that we are saving 24-weekers."

The challenge, for investigators and in turn, for IRBs, is to figure out ways to do the most necessary neonatal research while providing sufficient safeguards to tiny patients and maximizing their parents' ability to understand and consent.

Golec and others involved in neonatal research say that's possible through a combination of respect for traumatized families, seeking input from the entire care giving team, a truly comprehensible informed consent document and frequent checks to ensure that parents understand the research and still agree to it.

Parents don't remember details of study

The study, published last year in the *Journal of Perinatology,* looked at newborns in the NICU at the University of Kentucky Medical Center in Lexington who had been enrolled in the NEOPAIN study, a multicenter trial that evaluated the effects of morphine infusions in newborns who were on mechanical ventilation.[1]

Researchers surveyed parents who had signed consent forms, and whose children had survived to discharge. Parents were asked about their memories of the informed consent process, as well as their understanding of the NEOPAIN study itself.

Five of the 64 parents contacted (7.8%) had no memory of the study or of signing a consent form. Of the remaining parents, 40 (68%) recalled the purpose of the study. Most parents (95%) who knew the purpose of the NEOPAIN study could describe its possible benefits, but only two (5%) remembered any potential risks.[2]

A total of 14 parents (37.5%) didn't know they had the right to withdraw their child from the study at any time.

Those results don't surprise Golec.

"Happens all the time," she says. "[Parents are] getting pummeled with information, they're getting to know the unit, they're seeing all this equipment they've never seen before. They're trying to digest all this and they're recovering and they're exhausted and they're emotionally fraught. Who can remember everything they're given?"

Mothers have been through labor, in some cases, labor with serious complications, and often are receiving pain medications or magnesium sulfate, which is often used for toxemia. Even without medication, new mothers often are subject to short-term memory loss, says **Lori Shook**, MD, a neonatologist at the University of Kentucky Medical Center who co-authored the study surveying parents of NEOPAIN babies.

"They may be answering you, they may be signing things; and 10 minutes later, they may have no idea what you're talking about," Shook says. "That's something you really have to be on the lookout for as a researcher and from the IRB perspective."

A model for protecting families

Fathers are contending with their own anxieties regarding the health of the mother and the baby. A surprising finding in the University of Kentucky study was that despite medications, mothers generally remembered the details of the study in which their babies were enrolled better than fathers did, Shook says.[2]

"Our hypothesis was that the dads would probably be better to approach for this type of thing in that situation, but they really aren't," she says. "We actually had a father who was a physician give consent. And he swore up and down he knew everything about it, and he got every answer wrong."

Time often is a crucial, complicating factor in neonatal research requiring that parents be approached only hours after their baby is born, at a time when they're just dealing with the shock of having a sick baby and are least able to process the information.

Shook says one current study being conducted in the NICU at her institution requires that babies be enrolled and on the study drug by 12 hours after beginning ventilation.

And Golec notes that because the research population in question is so small, families often are approached multiple times in the first several days of life to inquire about enrolling their child in various studies.

So how do IRBs balance the urgent need for neonatal research with the real vulnerabilities of both the babies and the parents who must make decisions for them?

Golec has proposed an optimal model for research recruitment in the NICU, based on many of the practices in place at her institution. Among her suggestions for IRBs considering research in the NICU:

• **Ask who will be approaching parents to gain consent.** Golec says the chair of Sunnybrook's research ethics board (REB, the Canadian version of an IRB) believes it to be a conflict of interest for a principal investigator to approach a family for research, and prefers that someone such as a research coordinator make the inquiry.

"In the NICU, it's frequent that a PI would be an attending physician, so you can see where the conflict would come in," Golec says. "How likely are [the parents] to want to say no, knowing full well that you're the attending and you're taking care of their 24-weeker?"

• **Ask for input from bedside staff.** Golec says caregivers in the NICU are notoriously fiercely protective of the families and establish strong bonds of trust. As a clinical research coordinator, she often consults with them regarding which families are good candidates to approach, or regarding families who previously may have agreed to research but later seem not to understand it.

At Sunnybrook, bedside staff are involved in research projects from the beginning. They're given the opportunity to review the proposal before submission to the REB, and to give their input. Golec says they often make suggestions that can lead to changes in the protocol.

"As a researcher, I may think I've thought out every possible nuance of the study, and then they'll say, 'Don't you think that's a lot of blood to take?' and the researcher will say 'You know, I never thought about that,'" she says. "As a researcher, you become so hyperfocused that sometimes you miss things and it's always nice to have somebody who comes in who's subjective."

The researcher also is required to do multiple inservice programs with the bedside staff just before enrollment in the study begins, so that the staff can answer families' questions. This type of approach could lead to families better understanding the study, Golec notes.

• **Require an informed consent process that gives families as much time as possible to deliberate.** Parents need time to discuss the study with each other, and if possible with other family

members, clergy or friends, Golec says.

"I think we need to look at the process of consent as being continuous in nature," she says. "It's not just a single moment in time when you go and talk to somebody; it's touching base with them again."

• **Ensure informed consent documents are understandable.** While this should be a requirement for all research, it's especially important when asking consent of parents who are in a vulnerable state, Golec says.

"For parents of neonates, we know they don't remember — they don't remember participating in a study, they don't remember saying yes," she says. "Would they be more likely to remember if they weren't just scanning something that didn't really make a lot of sense to them because the verbiage was so advanced?"

Golec says Toronto is a highly diverse city, so her health center's NICU sees parents from varying cultural and educational backgrounds. Too often, she points out, the informed consent forms she sees are written too high an educational level and contain too much jargon.

Teenaged decision makers

Shook agrees, noting that many parents of premature infants are themselves only in their teens.

"Had they not just had a baby, they wouldn't be able to really consent for themselves, and now suddenly because they've had a baby, they're considered emancipated and able to do that," she says. "If you plan to include emancipated minors in a study, things have to be written well enough so that they can understand them. Are you really explaining them in a way that a 13-year-old can understand?"

Shook also suggests that parents can be approached to begin the consent process before labor, when they're more likely to be able to understand what's being said.

Researchers at her institution often check in with obstetricians to see if there are mothers admitted who are expected to go into labor soon with babies who have problems. The researcher may or may not attempt to get a signed consent form beforehand, but will talk with the parents to begin the process of informing them about the study.

At the University of Texas Health Science Center at Houston, the IRB employs another method that can be used to ensure better understanding of research in the NICU, reports **Paula Knudson**, the center's special advisor for research involving human subjects.

A research intermediary, who is hired by the IRB and reports to it, can be assigned when the IRB approves a protocol that it believes requires special attention.

While the intermediary is not part of the initial consent process, she is notified as soon as someone from that protocol has signed a consent form, Knudson says.

"She immediately goes to talk with them, and she ascertains whether there is real comprehension about the study," she says. "It's before the intervention begins, if we have that luxury, and it provides a liaison between the families and the research staff for questions that come up."

If the intermediary believes that the family doesn't understand the study or wants to withdraw, she can make sure that happens, Knudson says. "It's not something she does easily, but if they really feel differently about it, or feel obligated in some way to be part of the study, we make it possible for them to come out gracefully."

Knudson contends that because it's so difficult to get true informed consent from parents of newborns, neonatologists should petition to be able to use a waiver of consent, similar to how it is used in emergency medicine.

"I think there are ways we could manage this," she says. "IRBs should assist neonatologists in petitioning for inclusion in this waiver of consent. But it has to come from the neonatologists. They have to say, 'There's work we're not able to do, and we need to do it in order to determine what really works for these babies.'"

References

1. Ballard H, Shook L, Desai N, et al. Neonatal research and the validity of informed consent obtained in the perinatal period. *J Perinatol* 2004; 24(7):409-15.
2. Golec L, Gibbins S, Dunn M, et al. Informed consent in the NICU setting: An ethically optimal model for research solicitation. *J Perinatol* 2004; 24(12):783-91. ■

COMING IN FUTURE MONTHS

- The 2005 Congress — What can IRBs expect?
- Technology helps improve adverse event monitoring
- Using audit teams to investigate noncompliance
- MACRO model for review

CE/CME objectives

For more information on this program, contact customer service at (800) 688-2421; e-mail: customerservice@ahcpub.com.

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

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **describe** the regulatory qualifications regarding human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research;
- **apply** the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- **explain** the potential for conflict of financial interests involving human subject research;
- **discuss** reporting adverse events during research. ■

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 to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

5. In the story on the Vioxx, NIH crisis, an NIH whistle-blower charged that researchers in one study engaged in misconduct by failing to do which of the following:

A. Obtain informed consent.
B. Adhere to the study protocol.
C. Submit protocol for continuing review.
D. Submit protocol for initial IRB review.

6. If an IRB or institution discovers serious non-compliance, it should

A. Take whatever immediate action is needed to safeguard current subjects.
B. Self-report the problem to the FDA and/or OHRP.
C. Propose a corrective action plan.
D. All of the above

7. In a study of parents' ability to remember details of neonatal research for which they'd given consent, who was more likely to remember the studies best?

A. The mother
B. The father

8. What step is one that is NOT recommended to help improve the quality of informed consent in the NICU?

A. Seeking input from bedside staff
B. Focusing on readability of consent documents
C. A time-intensive tutorial for parents on the research process
D. Giving parents time to deliberate

Answers: 5-B; 6-D; 7-A; 8-C.