IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

THOMSON
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Inconsistent interpretation of HIPAA creates research recruitment barrier

Researcher says IRB enforcement of privacy rule varies greatly

Researchers are finding the HIPAA to be a significant barrier to recruiting research participants, in part because of the inconsistent way in which IRBs deal with requests for HIPAA waivers.

In a March editorial in the *Annals of Epidemiology*, **Roberta Ness**, MD, MPH, a researcher at the University of Pittsburgh, wrote of her difficulties in recruiting patients for an ongoing study of preeclampsia in pregnant women.

Ness detailed her experience with recruitment after HIPAA became effective in April 2003, both with and without IRB waivers that allowed researchers to review maternity records at the university's Magee Women's Hospital to find potential participants.

The result: "With HIPAA in general, our average enrollment was cut in about half," she reports. "Because of changes in the leadership of the IRB, in part because the IRB at this particular hospital was merged with the main University of Pittsburgh IRB, we kind of gained and lost waivers. [When waivers were lost], the enrollment rate was cut in half again."

Without the waiver, researchers couldn't comb through maternity records to find participants, and so they relied on health care providers to identify possible subjects and refer them.

Ness and others are calling for the Department of Health and Human Services (HHS) to modify the privacy rule to make recruitment easier. "I'm very hopeful that HHS will produce clearer guidance on how to interpret these rules," Ness says. "I think that would be enormously helpful."

Recruiting for the PEPP Study

The Pregnancy Exposures and Preeclampsia Program project (PEPP) is an ongoing, single-institution study of women followed throughout pregnancy. The goal is to find the cause of preeclampsia, a potentially fatal complication of pregnancy.

The first phase of the PEPP study was conducted from 1997-2001. Recruitment for the second phase was delayed while the hospital tried to figure out how to enforce the pending medical privacy rules, Ness says.

From April to September 2003, the researchers were not allowed a waiver of HIPAA's authorization and disclosure requirements, and were unable to review any medical records for eligibility in the study except for those of women who had enrolled in a research registry. Ness says that only about 10% of women enrolled in that registry.

In October 2003, the maternity hospital's IRB granted a waiver, allowing Ness and her colleagues to review records again to look for prospective subjects. However, unlike pre-HIPAA days, she says, a woman's health provider had to gain assent from the patient before PEPP staff could approach her.

Ness says the study was once again complicated when the hospital's IRB merged with the main University of Pittsburgh IRB in June 2004; the waiver once again was lost, and researchers again lost access to the records.

"Early on, before the implementation of HIPAA, we were recruiting over 12 women per week into the study," she recalls. "Directly after the implementation and without a waiver, we went down to 2.5 women per week. Then we got a waiver and we went up to about six women per week. And then lost it again and went back down to three."

In the editorial in *Annals of Epidemiology*, Ness' assessment is blunt: "We cannot identify other systematic explanations for these trends other than the obvious: Local interpretation of the HIPAA regulations had a negative effect on the pace of our research."

Ness says the waiver recently has been regained. While she contends that the situation at research institutions in general has improved with time, she says there are institutions that still interpret HIPAA too restrictively.

"I don't think that HHS meant to have so much variability in local interpretation," Ness says. "Of course there's also an enormous amount of local interpretation in terms of the Common Rule, which we all see whenever we do multicenter studies. The same thing is true with HIPAA — it's yet another barrier being put in place very variably by institutions."

Not the only one

Ness is not the only researcher who has noted the negative impact of HIPAA on research recruitment. The American Association of Medical Colleges (AAMC) conducted a survey in 2003 of researchers, IRB members, privacy officials, deans, and others involved in the conduct and oversight of research.

Out of 331 responses, 74% reported that HIPAA

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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**.

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Editorial Questions

Questions or comments?
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had affected patient recruitment, says **Susan Ehringhaus**, JD, AAMC associate general counsel for regulatory affairs. Seventy-six percent reported an effect on data access, and 68% reported an impact on data acquisition.

Among the issues that the AAMC identified with the implementation of HIPAA:

— a longer and more confusing informed consent document that can overwhelm or intimidate potential participants;

— an increase in the time and money required to carry out the requirements of the privacy rule;

— inconsistent interpretation of the rule by IRBs, leading to confusion, particularly in multisite trials.

The issue of privacy and research came to a head in California recently when hospitals closed down access to a process that had allowed epidemiologists to inspect cancer pathology reports very soon after a diagnosis.

The process, called Rapid Case Ascertainment, helps point out cases of very aggressive cancers, such as pancreatic cancer, at a point when subjects are still well enough to contact, says **Dennis Deapen**, DrPH, director of the Los Angeles Cancer Surveillance Program.

It requires that staff pore through all pathology reports, even those that turn up negative, to find prospective subjects. And post-HIPAA, says, hospitals balked at allowing that type of comprehensive access.

After months of negotiation with the California Department of Health Services, the lead hospital involved in the dispute, the University of California-San Francisco (UCSF), agreed to reinstate the review, with a few minor changes, Deapen says.

"Unfortunately, at this point, while UCSF has been resolved, many of these other hospitals have not yet allowed this to resume," he says.

And Deapen notes that the curtailment of access damages the ongoing studies that rely on the data. "All of those studies that were ongoing over those two years [of the dispute] that require this Rapid Case Ascertainment design, they are forever harmed. You can't go back and two years later find those cases rapidly."

Looking for solutions

In presenting the findings of the AAMC study to a subcommittee advising HHS on privacy issues, Ehringhaus laid out a number of proposed revisions that could help eliminate HIPAA's research burdens. Among them:

— **Eliminating the accounting of disclosures for research**. Currently, providers must stand ready to inform patients of disclosures of their records made to researchers. Deapen says hospitals are interpreting that to include even the mere viewing of a record to see if it qualifies for a study. In her presentation to the subcommittee, Ehringhaus called the requirement "expensive for providers and for their institutions, burdensome for the research enterprise and highly unlikely to provide information that is meaningful or relevant to individuals."

— Eliminating the requirement of authorization or waivers of authorization for disclosure. Ehringhaus testified that human subjects' privacy is appropriately covered under current federal regulations specific to human subjects research.

— Simplifying the de-identification standard for research purposes. While the AAMC supports the use of de-identified medical information, the standards in the current rule are so high as to render the resulting data useless for many research purposes, Ehringhaus testified.

Ness says proposed modifications to HIPAA that would make a number of these changes, including harmonizing it with the Common Rule, were presented to HHS Secretary Tommy Thompson before he stepped down from his position in December.

She and Ehringhaus say they're unsure where the recommendations are now, but Ness says she's hopeful that the new secretary, Mike Leavitt, will make it a priority.

In the meantime, Ness says, IRBs need to better understand the purposes of HIPAA when considering requests for waivers of authorization.

"HIPAA was never meant to cause any slowdown in the progress of research," she says. "There's all sorts of language in HIPAA that very clearly indicates that researchers who are working under normal IRB guidance, under normal Common Rule guidance, should readily be able to do what they had done previously without a lot of additional barriers from HIPAA.

"IRBs need to understand that these rules were not in fact meant to create barriers," Ness says. "And furthermore, impeding research progress, is really not in anyone's interest, or to anyone's benefit."

Reference

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Psychiatric research guidelines developed

Consensus can be difficult, but worth it

Patients with psychiatric illness pose a particular problem to researchers and to the IRBs that review studies involving them.

They can have widely varying capacity to give informed consent — and that capacity can wax and wane depending upon the progression of the illness and the patient's current treatment. Issues such as the use of placebo and the role of surrogates can be thorny.

After dealing with several such studies on a case-by-case basis, the Human Studies Committee at Washington University School of Medicine in St. Louis created a task force to tackle a set of guidelines to better delineate what is required of researchers who deal with this vulnerable population.

The resulting "Guidelines for the Evaluation of Studies in Persons with Psychiatric Illnesses" was one of two winners of the Health Improvement Institute's Awards for Excellence in Human Research Protection for Innovation.

John Csernansky, MD, a professor of psychiatry and chairman of one of the school's IRBs, says the need for the guidelines grew out of the high number of studies at the university into such illnesses as dementia, schizophrenia and depression.

"There's a lot of activity at our university around neuropsychiatric disorders, which would include subjects who might have compromised capacity to give informed consent," says Csernansky, who was one of the task force members. "Questions kept coming up at the committee level as to whether certain consent procedures were appropriate, whether certain aspects of research design were appropriate for the populations.

"After dealing with these kinds of issues on a case-by-case basis for some time, we realized that we really could benefit from some guidelines that committees could use, and for that matter that investigators could use as they prepared their proposals, he adds."

A task force was formed from about 10 members of various IRBs at the university — members included psychiatrists, clergy, and lay members such as a relative of a mentally ill patient.

The task force used schizophrenia as a prototype illness in creating the guidelines, because it had so many of the elements that make protecting subjects challenging, Csernansky says.

"Patients with this illness could have delusions, they could have hallucinations that interfere with their capacity," he says. "They could also have fundamental cognitive deficits — they don't remember. They're not invested in protecting their own self-interest because of their apathy. They may not be adequate advocates for themselves."

But he contends that the guidelines fit a variety of other psychiatric illnesses as well.

"We developed them thinking of all those aspects of the clinical situation that could come up in the context of research," Csernansky says. "Because schizophrenia is such a multifaceted syndrome, it made a good prototype to develop the guidelines around. If we could make it work for schizophrenia, in other words, it almost works for anything."

Breadth of opinion

The membership of the task force was varied in its viewpoints of the issues surrounding psychiatric research, a point that Csernansky says he found troublesome at first, but that he now appreciates for the breadth of opinion that was brought to the table. He credits the decision to Philip Ludbrook, MD, associate dean and chair of Washington University's Human Studies Committee.

"It turned out to be a very wise thing to do, because by coming to a consensus that we could all live with, those guidelines had broad appeal," he says. "It wasn't just one faction or one point of view that was represented, but we really did have to struggle to come to some sort of consensus or compromise, something we could all live with."

Reaching that consensus took about a year, with debate focusing on two main issues:

- **Placebo controlled experiments** — The panel decided that placebo controlled trials were justified only in very rare situations because of the danger of placing stable patients at risk for relapse.

The guidelines state that placebo controlled trials are generally acceptable only in cases where subjects have failed to respond satisfactorily to available standard therapies, or who have experienced unacceptable side effects on those therapies.

They also allow for giving placebos during a "washout" period, designed to allow a prior treatment to clear from a subject's system.

"Placebo in that sense would be used during a

brief washout period as a safety measure, but not to make the study easier to do and not for any purely scientific reason," Csernansky says. "It was justifiable as an additional safety measure but not as a purely scientific measure."

He admits that the decision was a little bit painful for him as an investigator who has done placebo controlled treatment studies in the past.

"There's no question that some studies are not being done now that were being done five years ago," Csernansky says. "By and large, we're talking about early Phase II studies, where the basic efficacy of the treatment is being evaluated. Some of the studies that would have been judged ethical five years ago or so would not be judged ethical now, because of the placebo issue."

• **Informed consent** — The guidelines treat informed consent as an ongoing process that requires monitoring of the patients to ensure they still have capacity to make decisions in their own interest.

Investigators are asked to make special efforts to procure consent, including a waiting period between consent and enrollment and asking subjects to paraphrase the major points of a trial. A qualified person independent of the research project should evaluate the subject's ability to understand what he or she has been told.

Subjects are given the opportunity to identify someone who can act as a surrogate in case they lose decision-making capacity during the trial. When a subject gives permission, the researchers can give their contact information to family or significant others, so that someone can be notified if a subject's condition changes.

"Sometimes a person is recruited into a study at one phase of their illness, when they may be relatively stable," Csernansky says. "But something could occur in the course of the study where that stability is interrupted or deteriorates and then of course the capacity has to be rejudged again."

Guidelines hold up over time

Csernansky says the debate at times was contentious, as the group worked to balance the competing concerns of scientific and lay members. But he contends that the difficult process of working out their differences actually made the guidelines more useful and less subject to being challenged later as inadequate.

"It would have been easier and quicker to have avoided that [debate]," Csernansky says. "We probably would have ended up with something that would have been wanting.

"I think we succeeded at finding a balance between protecting research subjects and yet creating guidelines that are usable by people who want to do this kind of research," Csernansky says. "We've used them now for a couple of years, and nobody has made any big demands to make revisions to them, nor has anybody strongly objected to them, so I think we must have had some sort of a balance." ■

Video helps patients with decision-making process

Goal was to dispel misconceptions

A video created to dispel patient misconceptions about clinical trials benefited from a diverse array of viewpoints — everyone from physicians and nurses to subjects and even those who decide not to take part in clinical trials, says the woman who spearheaded the effort.

The goal was to get across to patients that the decision about whether to take part in a clinical trial is a personal one — there's no one answer that's right for everyone, says **Christina Parker**, MD, assistant director for faculty activities at Dana-Farber Cancer Institute in Boston.

The video, "Entering a Clinical Trial: Is it Right for You?" was developed to address concerns that patients were getting the wrong idea about cancer trials, Parker says.

The video was one of two winners of the Health Improvement Institute's Awards for Excellence in Human Research Protection for Innovation.

"People think that when they enroll in clinical trials they're getting the best treatment possible," she says. "Clinical trials aren't really about getting the best treatment possible. They're about figuring out what's better. So we set out to try to make an educational tool that would make that more clear to people. There are videotapes that exist, but they often give the impression that to be in a clinical trial is better for you than to not be in one."

She says that while IRBs often pay attention to the informed consent aspects of individual trials, it's also important to look the larger issue of explaining what a clinical trial is meant to do.

"I think that's really critical to a patient's

understanding of whether or not they want to go into a clinical trial," Parker says. "As much effort needs to go into making sure that patients understand those basic elements as needs to go into patients understanding specifics of an individual clinical trial."

Video tailored to patient needs

In determining what would be in the video, Parker first consulted with a committee of health care providers, IRB members, and medical ethicists to arrive at what they wanted to say. Based on those decisions, Parker began setting up videotaped interviews, and even took steps toward editing the final product.

But as they got further into the project, and consulted other groups, they saw that they only had a piece of the total picture.

Research nurses pointed out that they were the ones patients interacted with most and needed to be more visible in the video. The institute's patient and family advisory council suggested a number of changes, including inclusion of more minority faces and explanation of insurance issues.

Most importantly, Parker says, the patient and family advisory council provided a completely different perspective on the message the video needed to convey, Parker says.

"They said, 'Yes, you get across the point that clinical trials aren't there to cure you, but the reality is that they provide hope, and that part of the equation cannot be ignored or left out,'" she recalls. "They were very, very clear about that. In our desire to tell the other side, to make it clear that we don't know that [the trial is] going to work, we left out the reality that it might be better.

"But the patients stood up there and they said, 'You have to put this in.' And so we went back to our videotaping, and fortunately we had that piece." Parker continues.

The format of the 22-minute video is a series of interviews with health care providers and patients, intercut with scenes of patient treatment and lab work. Because Dana-Farber is a cancer treatment facility, the patients interviewed are all cancer patients, and much of the discussion is cancer-specific. But Parker says the video's content would be appropriate for anyone contemplating a clinical trial for treatment of a life-threatening disease.

"It wouldn't be suitable for somebody who's in a trial that doesn't carry much risk associated with it," she says. "It might be a little bit too scary for somebody who's just gonna sit there and have their blood drawn. But we're a cancer institute, so that's what we chose to focus on."

In the video, the head of the IRB talks about what an IRB considers when it reviews a clinical trial. Physicians and a research nurses describe the different phases of clinical trials and what they mean. And there are a number of interviews with patients who had different experiences with trials.

In one case, a patient who was in a trial describes how she had to withdraw because of a side effect. Another interview subject, a nursing professor, considered a clinical trial but ultimately decided not to enroll.

"The fact that she was a professor of nursing was very valuable because it really validates the fact that it's OK to say no — that people who are smart say no, who are very knowledgeable medically," Parker says. "That doesn't mean it's the right choice to make, but it does mean that it really is OK to make it."

Right videographer is critical

Parker's group didn't stumble across these interview subjects entirely by chance; they sought them out, asking IRB members, staff, and patients for suggestions. In some cases, however, serendipity did play a role, she says.

"Between our scheduled [interviews], while we were waiting, we were in patient spaces, and patients agreed to be interviewed, just out of the blue," Parker says. "And they gave some of the nicest discussions of the issues."

Parker says they conducted many interviews for the each of the different points that they wanted to make in the video, so that they could choose the best person for each scene.

"We interviewed three or four different doctors and asked them essentially the same questions," she says. "And we ended up with one who's almost a narrator. Even though it's a spontaneous conversation, she says things with sound bites that are just right for leading into the next section, even though she wasn't interviewed for that purpose."

Parker has advice for institutions that are considering creating their own patient information video:

- **Start with a group of people who can hone down what you think your message will be:** "And I emphasize 'think,'" she says. In her case, that group included health care providers, medical ethicists, and the IRB.
- **Then, bring in a group of patients who are**

prepared to watch the evolving product three or four times. Use their input to help identify who the important players are — nurses, doctors, patients, family members — to set up interviews.

• **Finding the right videographer is critical to the success of the project.** Parker found hers through a suggestion from an IRB member who also was a divinity student.

"She said, 'You should go with this guy; he really wants to get things right. He's very ethical,'" she recalls.

Parker says that after speaking with the videographer, she decided to use him even though he lived six hours away, rather than contract with someone in Boston.

For those who lack the resources to create their own video, Dana-Farber's project is available, and can even be personalized a bit for other healthcare institutions, Parker says.

"We made two copies," she says. "One is for use in our center, and it has pictures of our institutions at the beginning. And then we made what I call a generic version — it's exactly the same movie except that we took out the pictures of the institutions at the beginning and replaced them with clinical scenes. So now there's no pictures of our institutions other than the insides where we filmed, and we don't explicitly identify those as part of our institution."

She says that several health care web sites already have plans to use a version of the video.

The video can be viewed on the Dana-Farber web site at www.dana-farber.org/res/clinical/trials-info/. A high-speed Internet connection is necessary. For more information about using the video, contact Parker at christina_parker@dfci.harvard.edu. ■

States move to mandate drug trial registration

Maryland, Texas would require publishing results

Reacting to allegations that clinical trials showing unfavorable results often go unpublished, two states are proposing legislation that would require clinical researchers to register their studies with the NIH's clinical trials database if they involve studies designed to evaluate a drug's safety or effectiveness.

Although one measure would prohibit IRB approval of an unregistered study, passage of the laws should not affect IRB procedures significantly, experts say.

A bill currently under consideration in the Texas legislature (HB 1029) would prohibit IRB approval of any study designed to "evaluate the safety and effectiveness of a drug" unless the principal investigator agrees to register the trial with the NIH database and publish the results.

And three separate proposals before Maryland lawmakers would require registration of safety and efficacy studies of drugs and biologics, with one proposal calling for a penalty of $1,000 per day on researchers who fail to comply.

• Maryland Senate Bill (SB) 289 would require registration of all research designed to determine whether a treatment is safe and efficacious. It prohibits an IRB from approving the research unless the results will be made publicly available and it will be registered with the NIH web site.

• Maryland SB 681would include research that involves asking human volunteers to answer specific health questions, and any drug and biologic trial conducted under an IND. It requires the trial to be registered before Maryland residents can be enrolled, and provides a $1,000 per day penalty for not enrolling.

• A competing House-sponsored measure, Maryland HB 54, would only require sponsors to submit trials to the NIH data bank. It is limited to trials testing the effectiveness of drugs and biologics under an investigational new drug (IND) application.

As this issue of *IRB Advisor* went to press, the state House of Representatives approved its measure and the others were still under consideration in the senate, says **Jack Schwartz**, assistant attorney general in Maryland Attorney General's Office.

"The House bill, which deals only with registration of trials, was amended and passed the House unanimously," he explains. "The amendments to that bill basically conformed the state definition of 'clinical trial' to the federal one, and also eliminated the monetary penalty. But, they retained the authority of the attorney general to seek to enjoin a trial that should have been registered but wasn't."

The amendments probably served to assuage concerns by research institutions and pharmaceutical companies that Maryland would not be hindered in its ability to attract clinical research and the funding that accompanies it, he adds.

The two Senate bills still are in committee, but

Schwartz says does not see the IRB continuing to be the body in charge of ensuring compliance with the new requirement, he said.

"I anticipate that, if the provisions on IRB approval remain, they will be modified so that the responsibility for compliance will rest with the PI, who would be responsible for carrying out commitments about registration and disclosure of trial results contained in the protocol submitted for IRB approval," he adds.

The current proposals should not significantly affect the IRB review process, says **Paul Goebel**, CIP, vice president of Chesapeake Research Review, an independent IRB and research consulting firm in Columbia, MD.

"An agreement to publish the results should not delay IRB review. Though, as written, there are no details on how soon after completion of the research the results must be published," he says. "And there is no indication of whether each trial must be published individually or whether similar trials can be combined into one article. Nor do they prohibit sponsors of multisite trials from publishing one article to cover all the sites in multiple states."

Trial registration is going to quickly become a fact of life, anyway, he notes. Most medical journals will no longer accept publication of data from trials that have not already been registered.

"There could be a requirement for registration to be completed before IRB review. This might delay the start of studies, but should not be a burden on IRBs if it is made clear the sponsor is required to do the registering and provide documentation to the IRB prior to review," Goebel says. "What would be a concern is if the bills did not require registration first, but then required IRBs to follow up after the fact and make sure registration is accomplished and publication is done."

The way the bills are written still does leave gaps in what types of trials would fall under the new requirement, with some drug and device trials still falling outside the jurisdiction, he notes.

"Most of the bills are limited to clinical research to show safety and effectiveness for FDA approval," he says. "Maryland SB 681 includes surveys and drug and biologic trials, but not device trials. So the coverage is spotty. Many trials of drugs and biologics are not conducted under INDs or IDEs [investigational device exemptions]."

More information on the Maryland proposals is available on the Maryland Attorney General's website at: www.oag.state.md.us/Healthpol/. ■

Settlement reached in Gelsinger death

More IRB oversight mandated

The 1999 research-related death of Jesse Gelsinger achieved one more step toward resolution with the announcement of a settlement between the federal government and researchers and research institutions involved in the case.

U.S. Attorney Patrick Meehan announced the settlement in February. As part of the agreement, two institutions — the University of Pennsylvania and Children's National Medical Center in Washington, DC — will pay $517,496 and $514,622, respectively, to resolve the government's allegations. The institutions also agreed to changes in the conduct of their human subjects protection programs.

The three researchers named in the case — James Wilson, MD, PhD; Mark Batshaw, MD; and Steven Raper, MD — will have restrictions placed on their clinical research for several years.

"Perhaps most significant is the impact that these settlements will have on the way clinical research on human participants is conducted throughout the country," Meehan says. "This action covers two major research centers which have instituted important changes in the conduct and monitoring of clinical research on human participants.

"We hope that these settlements will now serve as a model for similar research nationwide."

Gelsinger, 18, was a volunteer in a Phase I safety study examining an investigational drug to be used to treat a deficiency in an enzyme, ornithine transcarbamylase (OTC). Patients with OTC deficiency cannot properly convert nitrogen in the body to urea for excretion as urine. Although severe OTC deficiencies can cause death, Gelsinger had a less severe form of the disorder, which was controlled by medication.

In the study, participants were injected with a genetically engineered adenovirus, which would deliver the OTC gene to the patient's liver to produce the missing enzyme.

Gelsinger had a reaction to the treatment and died four days later from multiple organ failure.

The government has alleged that the study should have been terminated before Gelsinger's involvement because of previous problems. The government further alleged that false statements and claims about the study were submitted to the NIH and the FDA.

Both the researchers and hospitals involved deny the allegations and contend that their conduct was lawful and appropriate.

Terms of the settlement require that the University of Pennsylvania increase IRB oversight of clinical research; conduct mandatory training for investigators and staff that includes good clinical practices, informed consent and conflicts of interest; use an independent contract research organization to monitor and oversee research; and create an Office of Human Research to focus on participant safety.

Officials at the University declined to be interviewed, but issued a statement saying that in the past five years, "Penn has established what is now a national model for the conduct of research, including the mandatory training of investigators and staff coupled with a comprehensive internal monitoring program for research involving volunteers."

As part of the settlement, Children's National Medical Center agreed to increase IRB staff from two to five; increase the IRB's budget by 50% between 2001 and 2004; add a position of RN quality improvement coordinator; and add a research subject advocate, a bilingual pediatrician/ethicist who would review all pediatric clinical research center protocols and consent forms prior to IRB submission. The advocate also would seek feedback from families and participants regarding recruitment and informed consent.

In its statement, Children's National defended the hospital and Batshaw, its chief academic officer.

"Despite his complete cooperation with the investigation, and acknowledgement of opportunities for improvement, Dr. Batshaw and CNMC, as participants in the aforementioned studies, deny that the they engaged in any unlawful activity and to the contrary, contend that their conduct was at all times in good faith, appropriate, and in the best interest of the study participants."

Paul Gelsinger, Jesse's father, says while the settlement addresses the role the institutions and their IRBs played in the study that resulted in his son's death, it does little to ensure that a similar accident won't occur at another institution. He did not support the settlement, because it did not require an acknowledgement of wrongdoing or an apology from the institutions or researchers involved.

"While I commend [the institutions] for the improvements that they have made, those improvements should have occurred long ago," Gelsinger says.

He says he would like to see changes outlined in the Institute of Medicine's book, "Responsible Research," applied to the oversight of clinical research, in particular recommendations to address conflicts of interest.

"It will take legislation with severe financial and criminal repercussions to actually get all of research to pay attention and upgrade their oversight systems," Gelsinger says.

The lesson he believes IRBs should take from the entire matter: "Question the ethics of everything being done. Dig deeply into financial and professional conflicts of interest, no matter the importance of the person conducting the research or the potential benefit to the patient population, knowing that you and the researchers and your institutions will someday be held accountable for the way that the research is conducted." ■

Center for Pediatric Bioethics set for Seattle

Children's Hospital receives federal appropriation

Should a terminally ill 10-year-old have a say in determining her end-of-life care? Can a teenager make an informed consent to treatment? Questions of this type will be the mainstay of the Center for Pediatric Bioethics, the nation' first center for bioethics solely dedicated to pediatrics, which will be located at Children's Hospital and Regional Medical Center in Seattle. A $340,000 federal appropriation has been secured, and Children's Hospital has dedicated $1 million in start-up funding for the center.

"The center is integral to Children's mission to foster a spirit of inquiry aimed at preventing illness, eliminating disease, and reducing hospitalization and its impact on children and families," according to **Treuman Katz**, president and CEO of Children's. "By addressing the complex ethical issues that affect patients, families, health care institutions, and research involving children, the center will promote the highest standards of medical ethics and protections of patient rights in pediatric research and health care."

The center will focus on four primary areas of pediatric bioethics:

- researching pediatric bioethics;
- educating medical students, health care professionals, and the public;

• providing a resource for families and health care professionals facing ethical dilemmas in clinical care;

• serving as an advocate for children who are receiving care and participating in research.

First of its kind in the nation

"The Center for Pediatric Bioethics will be the first of its kind in the nation, and it will provide a model for the study of policies, practices, and standards in ethical issues in pediatric research and health care that can be applied nationally and internationally," according to **Norman Fost**, MD, MPH, director of the Program in Bioethics at the University of Wisconsin. "This center has the potential to dramatically increase our understanding of ethical issues in the way health care and research for children is conducted."

The study of pediatric bioethics is particularly important because it requires more than simply adapting the concepts applied to adult health care. Delivering health care to children and the involvement of children in research raises different questions.

For example, the extent in which children can participate in the decision making for their health care varies with each child and each situation. The relationship and communication that occur between a parent, health care provider or researcher, and a child are critical in assuring that the best interests of the child are served.

"Building on the strengths of one of the premier children's hospitals in the nation, the center will explore key issues faced by health care professionals, researchers, and parents, and will help create an environment that supports families in making informed choices about research participation and the use of innovative treatments," says **Wylie Burke**, MD, PhD, professor and chair of the department of medical history and ethics at the University of Washington.

The center's first undertaking will be to encourage collaboration among national experts in pediatric bioethics by hosting the first Conference on Pediatric Bioethics in July. The first of its kind in the United States, the conference will be a forum for institutions, researchers, and physicians to discuss the relationship between pediatric research, health care, and the pharmaceutical industry.

"We hope the center will become a national resource for physicians, researchers, policy makers, parents, and patients," says **F. Bruder Stapleton**, MD, pediatrician-in-chief at Children's and chairman of the department of pediatrics at the University of Washington School of Medicine. "We have initiated the recruitment of a world-class pediatrician-bioethicist to direct the center and serve as chief of the newly created Division of Bioethics in the Department of Pediatrics." Doug Diekema, MD, MPH, a respected bioethicist, will serve as interim director, according to Stapleton.

Bioethical challenges the center hopes to tackle include the involvement of children in research; quality of life for children with terminal illness; end-of-life decision making; and religious considerations in health care decisions for children.

Best interest of the child

At the center, experts will assist health care professionals and families with difficult decisions by looking for ways they can work together to determine what is in the best interest of the child. Pediatric bioethics also helps children to participate in their own medical decisions, which can include determining if innovative therapies or participation in research studies is appropriate.

In addition to faculty bioethicists, the center will be staffed with pediatric-trained patient advocates who will work directly with patients and families to ensure appropriate safeguards and to facilitate and enhance communication with medical and research staff. ■

Public opinion of FDA sliding in Vioxx wake

Public confidence in the FDA is waning, according to an opinion poll released amid a pair of Senate committee hearings in March on the agency's drug approval process and safety record.

"We have seen America's confidence in the FDA decline in recent months," says **Celinda Lake**, president of a Washington-based survey company called Lake, Snell, Perry & Associates Inc. "An overwhelming majority of Americans want to either increase FDA's capacity for oversight and

regulation, or at least keep it at current levels."

The agency has found itself under fire with regard to drug safety after questions surrounding the COX-2 inhibitor class of pain drugs and non-steroidal anti-inflammatory products. The market withdrawal of the multiple sclerosis drug Tysabri this week, which occurred after the poll was taken, cannot have helped the FDA's image.

Lake, the survey's chief pollster, backed her statements with a number of results on confidence in the FDA's ability to protect the public. The poll surveyed 1,000 people, with an error margin of ±2.5%.

Overall, 14% said they had a great deal of confidence in the FDA. Two-thirds favored an independent body to conduct a full review of all of the agency's practices and procedures, while 70% supported strengthening the FDA's collection and reporting process on drugs and devices that have been found to cause harm after approval.

Opinions were mixed on the issue of sponsor company fees collected by the agency for its reviews, but Lake says the poll showed that by an overwhelming margin, "the industries regulated by the FDA have too much influence over the agency's decisions."

That feeling was echoed by **Arthur Levin**, the director of the Center for Medical Consumers, who in commenting on the poll's finding also referred to conflict-of-interest issues that arose following the FDA's recent three-day hearing on COX-2 inhibitors. After the meetings, it was revealed that a number of people who sat on the agency's advisory panel, of which Levin was a member, had consulting relationships with the pharmaceutical companies that produce the pain reliever drugs called into question.

"Whether it's real or perceived," he says, "it's just not a good thing for the public to see industry having too much influence over the FDA process."

Lake says the cardiovascular risks with COX-2 drugs have brought regulatory worries to the forefront of political opinion right now, concurrent with other high-publicity issues, such as Iraq and Social Security. ▼

CAM therapies must meet standards

In a new report, the Institute of Medicine calls for conventional medical treatments and complementary and alternative medical (CAM) treatments to be held to the same standards for demonstrating clinical effectiveness to make it easier for health care providers and the public to make evidence-based decisions about CAM use.

The report says the same general research principles should be followed in evaluating both types of treatments, although innovative methods to test some therapies may have to be devised. It says randomized controlled trials are the "gold standard" for providing evidence of efficacy, but that other study designs can generate useful information on treatments that do not lend themselves to such trials.

The National Institutes of Health (NIH) and Agency for Health Care Research and Quality sponsored the study to help NIH develop research methods and set priorities for evaluating CAM products and approaches. More than a third of U.S. adults report using some form of CAM, which includes chiropractic and acupuncture to herbal remedies. ■

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- **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.
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13. In a survey of IRB members, investigators, and others involved in clinical research, what percentage of respondents reported that HIPAA had affected recruitment of research subjects?
    A. 15% C. 74%
    B. 51% D. 83%

14. It is permissible, under guidelines developed by Washington University, for psychiatric patients to be allowed to enter a placebo-controlled study under certain circumstances.
    A. True
    B. False

15. How should a study involving psychiatric patients address the possibility that subjects may lose their decision-making capacity during the course of the study?
    A. Investigators should screen subjects to exclude those who could lose their decision-making capacity.
    B. Patients should be given an opportunity to identify a surrogate who can make decisions on their behalf should their condition deteriorate.
    C. Both A and B
    D. Neither A nor B

16. A proposed Texas bill (HB 1029) would prohibit IRB approval of any study designed to "evaluate the safety and effectiveness of a drug" unless the principal investigator agrees to register the trial with the NIH database and publish the results.
    A. True
    B. False

Answers: 13-C; 14-A; 15-B; 16-A.