IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

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Big: National Children's Study faces full-grown questions, ethical issues

"When does it ratchet up to something more complicated?"

In planning the recently launched National Children's Study (NCS), researchers knew that ethical and IRB issues would be front and center. The federally funded observational cohort study will follow more than 100,000 U.S. children from the womb to age 21, looking at the effects of environment, genetics and other factors on childhood diseases and conditions that include childhood obesity, diabetes, autism, asthma and mental health problems.

While the study has been deemed to be minimal risk, it still raises a number of ethical issues, including collection of biospecimens and use of genetic information, confidentiality and the distribution of results to participants and their communities.

John Santelli, MPH, MD, an adolescent medicine specialist at Columbia University in New York City, served on the NCS ethics working group during the planning stages of the study in the early 2000s.

"We looked at a broad range of issues – genetics testing, stored samples, when do you consent, when do you reconsent, how do you deal with community involvement in a multisite study?" Santelli says. "Is this study really minimal risk? None of the individual procedures are particularly dangerous, but we had a lot of minimal risk data collection going on – when does it ratchet up to something more complicated?"

The scope of the project – subjects will be recruited at 105 study centers across the United States, and many study centers have multiple institutions involved – only added to the challenge of coordinating IRB approval.

Study director **Peter C. Scheidt**, MD, MPH, says planners determined early on they would be unable to use a centralized IRB for this project, although the IRB for the National Institute of Child Health and Human Development is serving as the IRB of reference.

"We met with various study center IRBs' representatives, had several planning meetings and came to the conclusion that IRBs would not likely completely defer to a central IRB, so we would have to address that on a local level," he says.

But he says the project has gone more smoothly than he at first had feared. So far, nearly all the IRBs have classified the study as minimal risk and no study center has had problems with IRB approvals.

Scheidt says that with this type of long-term study, not every potential ethical issue can be resolved ahead of time – it's not yet possible to know what all those issues will be.

"The way we decided to address bioethical issues in general is to create mechanisms to deal with them as they come along," he says. "We understand that this is a moving target. Take the genetics issue: What is both available and viewed as genetic information today will be changing rapidly over the next two to five years.

"We need the ability to constantly reevaluate these issues and to respond to the specific problems that occur as a result of it as the study goes forward."

Stages of consent

The longitudinal nature of the study creates challenges for giving continuing, useful informed consent. Although pregnant women are initially recruited, their children will be asked to give assent when they are 7 years old, and consent when they reach adolescence, Scheidt says.

During that time, the mother and child will participate in periodic interviews, and will be asked to give blood and other biospecimens. Researchers also will take environmental samples from participants' homes.

As a result, says **Julia Slutsman**, a bioethicist with the study's program office, the informed consent process has multiple phases and documents.

"The informed consent process starts with a series of advance letters and materials to potential participants explaining the study for them and what ramifications of participation might mean for them and for their children," Slutsman says. "When women first come in contact with study staff in the field, they receive a general consent booklet that explains in plain, very accessible language the research procedures, the purpose of the study and the risks to participants.

"There's a separate informed consent form for the collection of environmental specimens and for biological samples," she says. "And it's very clear that they can choose to participate in certain elements of the study but not in others."

Slutsman says one unique feature of the informed consent process is a series of documents called visit information sheets, which are given to participants at every interaction they have with a representative of the study.

"There is a description of the particular research procedure that is to be done in that visit and they can then indicate whether they choose to participate in those procedures or not – they can refuse any aspect," she says. "So the

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• *Address:* 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: **Suzanne Koziatek** and **Melinda Young**.
Associate Publisher: **Coles McKagen**, (404) 262-5420 (coles.mckagen@ahcmedia.com).
Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Director of Marketing: **Schandale Kornegay.**
Production Editor: **Ami Sutaria.**

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informed consent process is designed to be tailored to the participants in the study and to give numerous opportunities to explain the procedures and to allow participants to choose not to participate in particular pieces."

Handling, distributing information

Among the major ethical issues that have arisen during the development of the study is the question of when and if to return individual information to participants, Scheidt says.

"We're collecting a great deal of information and just determining what's appropriate and especially what's inappropriate to share has been a big issue," he says.

As an example, he points to one analysis, which will look whether certain environmental exposures trigger expression of autism in children. Based on statistics, Scheidt says the study expects to find about 600 of its participants are eventually diagnosed with autism.

Specimens may be taken from a baby and its home and then not analyzed until years later, when the child is diagnosed.

Decisions about when to reveal information will be made by an Independent Study Monitoring and Oversight Committee, which functions as the study's data and safety monitoring board.

"Its primary responsibility is to advise the study on what information should be revealed to participants and to communities," Scheidt says. "It's an independent committee, comprised of experts and scientists, bioethicists and community representatives."

Another mechanism in use in the NCS is a Data Access and Confidentiality Committee, which handles questions regarding what data can and should be released to study investigators, in public data sets and to other entities.

A Sample Oversight Group looks at all proposals that involve the use of biological specimens and environmental samples to ensure they are being used appropriately.

In addition to community representation on committees and on the overall study advisory board, a local community advisory board will be set up at every study center.

Scheidt says engaging the communities involved in the study is vital to its success.

"Awareness and a positive view of the study are going to be absolutely essential to enrollment and retention," he says. "So we're approaching this as not only a national study, but very much a study in 105 communities." ■

Study raises thorny questions about research on pregnant teens

Recruiting, who should give consent, can be tricky

Because of the unusual scope of the National Children's Study (NCS), it raises a significant range of ethical issues for its designers and for the IRBs that have been reviewing it at 105 study centers across the United States.

Although many of these issues have come up before in pediatric research, the multisite nature of the study meant that there were a number of areas where different IRBs might see things differently, says **John Santelli**, MPH, MD, an adolescent medicine specialist at Columbia University, New York City, who served on the NCS's ethics working group.

While the ethics working group's members obviously focused closely on federal regulations, many had IRB experience and also were trying to view the study in terms of dealing with IRBs, Santelli says.

"You know IRBs, they all see different sides of an issue," he says. "How do you coordinate all of that?"

Pregnant teens

The process, while lengthy has led to approaches that Santelli says may hold lessons for IRBs in reviewing other pediatric studies.

A case in point: Whether and how to recruit pregnant teens and teens who may become pregnant to the study in order to follow the progress of their children. Santelli says it's important to include pregnant teens in the National Children's Study, because they are more likely to have environmental exposures that may affect their children. But there were questions as to whether they could give consent on behalf of themselves and their fetuses to participate.

Santelli says the group looked closely at 45 CFR 46, subparts B and D, as well as state law, to try to arrive at some solutions.

One group Santelli was concerned about was teenagers who were not pregnant but were sexu-

ally active and could become pregnant. Plans were to recruit women over age 18 in that situation, but Santelli says dealing with teenagers raises some thorny issues.

Would it be ethical to recruit a teenager at risk of becoming pregnant without advising her about pregnancy prevention? Would requiring parental consent cause disclosure problems, since the teen might not want her parents to know she was sexually active?

In the end, it was decided not to attempt to recruit "pre-pregnant" adolescents.

"The IRB would have said, you can't just recruit 16-year-olds and 15 year-olds and expect them to get pregnant, you probably have to do some prevention," he says.

Who gives consent?

With pregnant teenagers come consenting issues – at what point is a teenage girl allowed to make her own decision to enroll in the study on behalf of herself and her fetus?

Santelli says different states have different laws governing medical treatment, age of majority and emancipation of minors. Pregnant minors in 28 states may consent for their own health care, while a similar number of states allow them to make health decisions for their fetuses.

He says the working group "pleaded for flexibility" from IRBs in dealing with these issues, since one pregnant teenager may be very different from another. Taking a firm position that a teen always should be the one to give consent, or never should, isn't practical.

"In some cases, the teen mothers are very responsible, in other cases you're going to find a teenager who's actually turned over the raising of the child to a grandmother," Santelli says. "If Grandma is raising the child and bringing the newborn in for health care and research visits, you've got to somehow recognize that, and if the mother is doing that job, you want to recognize that."

Santelli says he believes IRBs can use that same flexibility in dealing with pregnant teens in other research.

"The regulations provide a lot of flexibility about what is the best thing to do," he says. "You ought to use your common sense," he says. "I think IRBs often want to have one informed consent process that's kind of uniform for everybody. For most situations, that makes good sense – you don't want to have some people get the consent form and others not get the consent form.

"But when you're dealing with his kind of situation, you ought to be ready to deal with these realities. I think if you just use common sense, an IRB will come up with good solutions."

Reference

1. Santelli J, Geller G, Chen DT. Recruitment of pregnant, minor adolescents and minor adolescents at risk of pregnancy into longitudinal, observational research: The case of the National Children's Study. *Ethics and Research with Children: A Case-Based Approach*. Oxford University Press; 2005. ■

Famous obedience study recreated – at least in part

Changes to reduce subjects stress win IRB approval

The 1960s obedience experiments of Stanley Milgram have become a hallmark of social behavioral research, as well as a cautionary tale for those involved in human subjects protection.

Milgram showed that ordinary people could be induced to deliver what they believed were painful, potentially severe electric shocks to others at the direction of an authority figure. While the results were dramatic and illuminating, they also raised questions about the treatment of the subjects, who were subjected to the stress of hearing what they believed to be screams of pain and pleading.

Among researchers, Milgram often has been seen as an experiment that couldn't be done today, in part because no IRB would allow it.

Jerry Burger, PhD, a social psychology researcher at Santa Clara University in California, was among the doubters. But when ABC News approached him in the aftermath of the Abu Ghraib prison scandal to see if a replication of the Milgram study might be designed to help explain the behavior of prison guards, he decided to try.

The result was a scaled-back version that eliminated many of the objectionable details of the Milgram studies, while arriving at nearly the same conclusion.

"My findings indicate that the same situational factors that affected obedience in

Milgram's participants still operate today," Burger wrote in a January 2009 article in the jour-

nal American Psychologist.

He says he knew the study would be a tough sell to his IRB, which normally doesn't tackle subjects with such potential for controversy.

"The easy thing for them to do would be to say no," says Burger, who himself had previously served on the board. "If I was on an IRB and I got this proposal, I think my first inclination would be to say 'This is impossible.' Fortunately they didn't do that, and they gave it careful consideration."

Lessening stress

In designing the study, Burger made a half-dozen important changes to the original Milgram experiment (see accompanying story), all designed to lessen stress on participants. Most notably, he cut off the experiment before the "shocks" they delivered (actors actually feigned responses to non-existent shocks) reached a level that participants might see as severe or distressing.

Before he even attempted to submit a protocol to the IRB, Burger sought out the advice of others in his field.

"I consulted with people who were experts on Milgram and experts on the ethics involved," he says. "I wanted to make sure I wasn't off base here – if they had all told me, 'No, no, that's crazy, you can't do that,' then I would have stopped at that point. But their judgment was that would probably be an ethical way to get some relevant information. That was encouraging."

One of those he sought out was **Steven Breckler**, PhD, a social psychologist who is executive director of the Science Directorate of the American Psychological Association in Washington, D.C. Breckler has written about the ethics of the Milgram experiments.

"Obviously the APA doesn't approve or disapprove of studies, that's not their role," Burger says. "But he wrote a nice letter for me that I was able to pass along to the committee with his permission, saying he had looked this over and thinks it is within the guidelines."

Burger says he thought Breckler's support was reassuring to his IRB.

"If I was on this committee and I wasn't sure, seeing that this person who's obviously in a very responsible and knowledgeable position has made this assessment – I think that made it easier for them."

Burger also offered to provide the IRB with a list of experts whom they could consult about the study.

"I tried to anticipate what all their objections might be," he says. "I gave them a very lengthy description of the procedure, and they met many hours discussing all the fine points. In the end, they told me they had decided right away it was probably okay to do the study."

Television broadcast issues

The IRB did ask for two changes. The first related to the potential for video from the experiment being broadcast on television. While all subjects had to give permission for the use of their images after they were told the true purpose of the study, the IRB wanted more assurance that a participant wouldn't give permission and later change his mind. As a result, participants were contacted by phone and by mail afterward, to make sure they did not want to withdraw permission.

"In fact, nobody did," he says. "Something like 90% of the people eagerly signed saying yes, they were willing to be on television and even though they were given multiple opportunities to take back that permission, they didn't."

The second point raised by the IRB was the use of clinical psychologists to screen potential participants to identify anyone who might be unduly stressed by the study. The IRB asked that the psychologists chosen be people that Burger didn't know personally in order to avoid potential conflicts of interest.

Breckler says he wasn't surprised that the IRB ended up approving Burger's replication.

"I think some IRBs probably would not approve it, but I do think his procedural solutions minimized the risk to participants," he says.

Breckler says Burger's experiment may be a good case lesson in how an IRB can balance risks against potential benefit in social behavioral research. He notes that Milgram's original experiment was an attempt to understand the behavior of Nazis during the Holocaust, and that Burger's replication came in response to prisoner abuses at Abu Ghraib.

"I think you could see this study as an example where the potential benefits of understanding this behavior could outweigh the risks by a huge amount," particularly when there's been an effort to minimize those risks as much as possible, Breckler says.

He says the American Psychological Association encourages researchers to collaborate with IRBs in this way when they're setting up

studies.

"You like to hear stories like this – it's refreshing to see the ability of IRBs and researchers to engage in a partnership," he says.

Reference

1. Burger JM. Replicating Milgram: Would people still obey today? *Am Psychol* 2009; 64(1):1-11. ■

Comparing two studies: A painful balancing act

Participants still believed they were delivering shocks

In trying to replicate the Milgram obedience experiments, social psychologist Jerry Burger had to balance the goal of getting useful results that were roughly comparable with Milgram's, while providing more protection for participants from severe stress.

Stanley Milgram actually conducted a whole series of obedience studies, but most were variations on his first experiment, conducted in 1961 at Yale University. /Prompted by Nazi war crimes trials, Milgram wanted to explore how people could follow orders to commit such atrocities.

He devised an experiment in which a participant was assigned the role of "teacher," and told that the study looked at the effects of punishment on learning. The participant watched as a "learner" (actually a confederate of the researcher) was strapped into a chair in an adjacent room and electrodes were attached to his body.

The participant was told to administer a test to the learner, and to deliver incrementally more powerful electric shocks when he answered incorrectly.

As the dial was turned to higher settings, the participant could hear the learner's cries of protest and demands to be let out. Meanwhile, an authority figure in the room would tell the participant to continue. The experiment would continue until the participant repeatedly resisted instructions to keep delivering shocks. At the highest settings, the cries of protest would end, suggesting that the learner no longer was capable of responding.

The shocks, of course, were not real.

Milgram found that 65% of participants were willing to continue delivering what they believed to be severe electric shocks, all the way to the end of the machine's range, at 450 volts.

"I've seen the film that Milgram produced, and common sense tells you that this is way too stressful to put anybody through," says Berger, PhD, a social psychology researcher at Santa Clara University in California. "If you've ever seen the images and heard the screams coming through the wall – a man screaming 'Let me out! I can't stand the pain!'

"It is unbelievable. I knew it would never be acceptable – it wouldn't be acceptable to an IRB, but it also wouldn't be acceptable to me."

Screening subjects, dialing down shocks

Burger took a number of steps to protect subjects:

- First, he screened potential participants, using a phone interview, written tests and a final interview with a clinical psychologist, in order to identify people who might experience undue stress if they participated.
- Participants were told at least three times, twice in writing, that they could quit the study at any time and still receive $50 for participating.
- Like Milgram, Burger had participants experience the electric shock for themselves; while Milgram's experiment called for a 45-volt test shock, Burger's participants received a 15-volt shock.
- Most importantly, Burger stopped the experiment at the 150-volt level, which was the first time in the Milgram version where participants began to hear protests from the learner. Burger says 80% of Milgram participants who went past that point continued on to the 450-volt level. So knowing how Burger's modern participants would act up to and at 150 volts was useful, and stopping the study immediately after that point would spare participants from greater stress, Burger says.
- The experimenter running the study was also a clinical psychologist who was instructed to the stop the session immediately if the participant showed any signs of excessive stress.
- Within a few seconds of the end of the session, participants were told the true nature of the study and allowed to see that the learner was unharmed.

The results from Burger's replication showed that modern participants behaved much as Milgram's did. In one group, 70% of participants not only were willing to administer shocks of up to 150 volts at the authority's instructions, but were

ready to continue on, even after hearing the learner ask to be let out. At that point, the experiment was halted.

A 'personal standard'

Burger says that as he devised his study, he tried to keep in mind how he would feel if his own grown son were participating.

"Would that be fine with me? And if a researcher asks that question and says, no, I don't think I'd like that, then I think we have no business putting anybody else in that study. I think that's a pretty good barometer to use. Even if the IRB approves it, there's still the personal standard that everybody needs to live up to."

He says he's been contacted by other investigators about the possibility of replicating his study and he cautions them to consider two points carefully. The first is the amount of stress participants are subjected to, and the possibility that they could have a negative experience.

The other point, he says, is trickier – the conflict between a participant's right to leave the study at any time, and the necessary actions taken in the obedience study.

"Ordinarily, if somebody says, 'I don't want to do this anymore,' I always tell my experimenters that the study is over at that point. You don't coerce people into staying if they say they don't want to be there," Burger says. "But in this Milgram replication (as in the original), we didn't immediately let them go; we made them say repeatedly that they wanted to stop. And even though this may only last for a few seconds, it gets back to the question of whether we're putting people through something that you shouldn't.

"It's a tough question, and the lingering question for me that I still wrestle with. In this case, given how it worked out, nobody was upset that they weren't released as soon as they said they were uncomfortable. But that's something I think researchers need to think about if they're going to do something like this." ■

Cyber-age tech raises novel ethics for IRBs

Virtual environment can create real stress

Researchers at the Institute for Simulation and Training at the University of Central Florida in Orlando, FL, are studying physical interventions used in a virtual world. Their work opens new horizons for rehabilitation clinical care, but also raises new questions for ethics review boards.

For instance, should IRBs require investigators to inform participants about potential uses for stored brain wave mapping that do not yet exist except perhaps in science fiction novels?

Or, if a virtual environment causes participants to feel anxiety, much as they would in the real environmental setting, should the virtual world study be handled any differently by the IRB?

"Our IRB has been very proactive in dealing with the best course of action when new technologies come out," says **Cali Fidopiastis**, PhD, associate director for applied cognitions for active lab at the Institute for Simulation and Training.

The IRB anticipate future problems and discusses how to handle new types of data and unique issues related to technological advances, she adds.

The institute's work delves into areas that most people have never imagined.

For example, the institute has created a virtual environment in which people with traumatic brain injuries can learn their daily activities of living.

This is similar to how rehabilitation facilities teach patients how to adjust to their new limitations. Such facilities typically have small kitchens where patients might practice making coffee or baking cookies.

But the virtual environment takes this a step further by recreating a particular person's own kitchen. **(See story about virtual reality studies and risks, p. 32.)**

Similar study in stuttering

In another study, researchers studied the emotional response of people afflicted with stuttering problems, using wireless skin conductor equipment. They had stutterers sit in a virtual restaurant, ordering from a fictional menu.

"Once they got into the experiment they started to immerse themselves into the task of ordering from the menu, and we had them interacting with real [people as] waiters and hostesses," Fidopiastis says. "When they started that process, we saw changes in skin-conducted responses and their engagement that

modeled a real world setting."

The virtual restaurant was designed to give the stutterers an experience with first a compassionate waiter/actor and, secondly, with a less helpful waiter/actor, she adds.

"When the bad waiter came in, you could see a change in skin conductive response," Fidopiastis says. "They still were engaged in the environment, but they were more emotionally-aroused than they were in the presence of comforting waiters."

Investigators told the IRB that the virtual restaurant experience would not be as emotional as a real restaurant experience. Plus, it would be impractical to take people with stuttering problems out to a real restaurant and then switch waiters in that setting, Fidopiastis notes.

"We could do this in an experimental setting and not have a person in a situation where they would be embarrassed," she says. "It's a controlled environment, so the person doesn't feel bad about him or herself."

The IRB's chief concern involved safety with the wireless skin conductors, she notes.

"All of the devices had to be connected to the individual as he walked through the environment, so it was more of a safety issue," Fidopiastis says.

Another major ethical concern with the institute's advanced technology involves the collection of individual brain waves.

While the collection of brain waves seems innocuous, its use might not be entirely safe.

For instance, brain waves might be used to activate a device, such as a cursor, Fidopiastis says.

Also, there's a theory that brain waves could be captured to study higher order thinking.

"So how do you store this type of data and protect it?" Fidopiastis says. "And with the latest technologies coming out, this is a burgeoning field, and many engineering firms want to get into this field."

IRBs need to know why investigators will store the data and for how long it will be stored, she adds.

"We designate it as a special type of data that needs to be handled with care," Fidopiastis says.

For example, brain waves from people who've had brain injuries could be stored in a database that gives researchers the information they need to better understand head injury, she suggests.

"We need to stipulate with the IRB what the researcher is using the data for," Fidopiastis explains. "And the participants need to be aware of this purpose."

If the data is simply being stored for possible future research purposes, then the participants should be told that the information could be used in future research work, she adds.

Key questions to ponder

IRBs also might ask these sorts of questions:

- How are you going to store the brain waves?
- What would happen if a person's brain waves were used to operate a brain wave interface device?
- What stipulations should an IRB put in place to protect participants?
- Is there a risk of invasion of privacy?
- How do you protect the brain waves?
- What do you tell participants about how the waves will be used over time?

"What stops researchers from saying, 'I collected this data in 2006, and now new technology allows me to extract features and use the data in a different way,'" Fidopiastis says.

"Most researchers don't know what they have," she says. "They're trying to get on the research bandwagon, going in the direction funding is going."

And IRBs lack experience in dealing with data made available through new technologies, she adds.

"I don't think IRBs are prepared for the ramifications, especially when people are using biosignatures to identify people," Fidopiastis says.

"Your brain pattern is like a fingerprint," she explains. "Some researchers believe that even showing that data — whether single or combined — is like showing a naked picture of a person, and that's a huge ethical concern that hasn't been worked out." ■

Brain-injured pt studied in a virtual kitchen

IRB must review alternative screening method

As virtual space technology improves, researchers are beginning to study how it can be used to help patients who've suffered traumatic brain injuries or other impairments that require rehabilitation.

At the Institute for Simulation and Training at the University of Central Florida in Orlando, FL, researchers worked with a man whose brain

injury had impaired his memory to the point that he couldn't remember anything that happened after his accident, says **Cali Fidopiastis**, PhD, associate director for applied cognitions for active lab at the Institute for Simulation and Training.

"When we saw the patient in the clinic, he didn't remember who we were and didn't remember doing this type of therapy," Fidopiastis says. "But he still had an implicit memory system in which under a level of consciousness, he still had memory for a task."

So the institute replicated his apartment in virtual space, recreating his coffee maker and oven in a 3-dimensional display, she explains.

The room was replicated using basic construction materials to make cupboards and table tops, all of which were painted a color that allowed chromoscheming, Fidopiastis says.

"It's like when the weather person projects a map of a city and state and shows the weather coming through," she says. "We did the same thing with a head-mounted display."

The patient wore a head mount that combined video stream of the real kitchen.

"The participant stood in a 3-dimensional environment with painted plywood and would see the textures of his own kitchen, and he could walk in that 3-D space because it was a real space," Fidopiastis adds.

"We reconstructed the kitchen almost to scale and had the patient walk in this environment," she adds. "Within six, one-hour training sessions he was able to go home and maneuver around his own kitchen, finding pots and dishes in the cupboards."

Before the virtual training sessions, the patient was unable to use his own kitchen, she says.

This use of virtual reality is an exploratory research design that is making no marketing claims that would make it subject to Food and Drug Administration approval, Fidopiastis notes.

"Once we go forward and show this kind of therapy could be used in a therapy environment we would need FDA approval," she says.

Fidopiastis suggests that any IRB reviewing a protocol that uses virtual reality technology would have some basic safety concern questions to ponder, including the following:

- Is there any potential for shock from the headset?
- How will simulator sickness be prevented and handled?
- Is there any potential for the gel used with the headset to cause irritation to the skin?
- Is there an issue in hooking up multiple devices to one participant?
- Is there a bigger risk for participants because they have multiple electronic devices attached to them?
- Are there any concerns about a participant's emotional state beyond what is normally experienced?

"The IRB understood these issues," Fidopiastis says. "Even with the head trauma patient, we had to show the patient wasn't experiencing anything that would be outside the normal every day activity despite the fact the patient is wearing a head-mounted display."

Working with a brain-injured participant poses its own ethical challenges, particularly when screening tools use questions that require at least short-term memory.

With the brain-injured patient, it quickly became apparent that the screening tool used to assess whether a person is experiencing simulator sickness would not work.

"We gave him the questionnaire, and he'd say he was totally fine," Fidopiastis explains. "He wasn't wandering all over the place, but he couldn't touch his fingers to his nose."

A more hands-on screening method was necessary.

"The typical simulator sickness questionnaire gives you written feedback, and this patient doesn't know after five minutes what he experienced five minutes ago, so that test isn't appropriate for this population," Fidopiastis says. "So we had to go with a more physical type of testing that correlated to the simulator sickness questionnaire."

There are three parts to the questionnaire, including ocular motor, nausea in general, and disorientation, and we had to pick a task that could be performed by the participant for each of those parts, she explains.

"We'd have the patient walk in a straight line and we'd ask questions at the beginning of the hour and at the end of the hour about how the patient felt," Fidopiastis says.

The IRB approved changes to the screening method, and a therapist stayed with the patient while he was in the virtual space, she adds.

"There wasn't a time when the patient was by himself," Fidopiastis says. "He could see the therapist, and she could see him." ■

eIRB will integrate IRB with everyone else

Efficiency, ease of use are benefits

The IRB office at the Washington University in St. Louis, MO, (WUSTL) will soon have an electronic system that will connect the IRB submission with every other application principal investigators (PIs) need to make.

WUSTL first implemented an electronic system in 2004 and replaced it last year, says **Diane Clemens,** DC, CIP, the eIRB education specialist at WUSTL.

The old system collected only serious adverse events (SAEs), which helped the IRB office learn more about working within an electronic system, she notes.

"We decided to get our feet wet and learn a lot, which we did," Clemens says. "Now we're going into the second phase of a much more in-depth system."

PIs can submit all of their AEs to the new system, and the system will triage the reports according to those that appear to be unanticipated problems that will be reviewed by an expert IRB reviewer, and those that will be placed in a report that's available for the full IRB to see during a continuing review session.

The new eIRB system also can be used for IRB review submissions, and it can communicate with other review boards at WUSTL.

"Now we can do new IRB applications, amendments, IRB notifications, continuing reviews, and final reports," she says. "We're still rolling out some applications."

The goal is to fully integrate the eIRB system with all 34 ancillary bodies that will conduct reviews of research studies, and to have all of the submission and approval processes conducted and documented electronically, Clemens explains.

For instance, the university has a review group that monitors all cancer studies and another that reviews research involving radioactive drugs.

"All of these different groups are separate entities and they have their own internal review process," Clemens says.

When the eIRB is fully implemented, it will be a one-stop shop for investigators and IRB members.

The eIRB application contains trigger questions for the ancillary review committees. When PIs submit their IRB application electronically, the eIRB system automatically will route the application to all of the other boards that would need to review the protocol. Many ancillaries use the same information as the IRB, but some of the trigger questions also trigger additional questions in the application specific to the ancillary review.

The current system involves multiple applications, duplicate questions, is time-consuming and somewhat confusing, Clemens notes.

"Especially when there is a change requested by any of these review processes, it will throw investigators for a loop," she says. "They submit to all of these different areas and then get changes requested from different directions, and it can be very confusing."

The different review bodies have different priorities and their interests sometimes conflict, she adds.

"Investigators wonder, 'Do I respond to one review body, or do I let everyone know about the change?'" Clemens says.

One goal for the eIRB is to streamline the entire research application process, she says.

So PIs and others will find links to the eIRB through a research Web page, called the Research Gateway, which is an on-line resource that Washington University faculty and staff access to view research tools, resources, forms, and applications.

"The login process for eIRB goes through the Research Gateway," Clemens says. "In addition to trying to streamline information, we're minimizing the number of passwords investigators use by having a single, sign-on process that we share with other university systems, including human resources."

Research staff will use the same password to review the status of a protocol as they would to view their paycheck.

This also provides an additional benefit of discouraging PIs from sharing their passwords with their staffs, Clemens notes.

"So when we require investigators to submit an item to the IRB, we'll have greater confidence they actually logged on and did it themselves," she explains.

The new eIRB system currently has new submissions and amendments in a pilot phase, and the IRB notifications and final reports are implemented fully with more than 8,000 users, Clemens says.

The complete roll-out had been set for early summer 2009, but likely will be a little later than that, she adds.

However, training is underway.

"We have identified several levels of training, including a basic system navigation training and an application-specific training," Clemens says.

As PIs and research staff learn how to use the eIRB system, they'll be able to find easy and fast answers to their questions.

For example, if a PI wants to know the review status of his protocol, he can look that up on-line and not have to call the IRB for that information, Clemens says.

"We anticipate receiving fewer questions once people are more familiar with the electronic process," Clemens says.

Another benefit to the eIRB is that it incorporates some efficiencies that were lacking in the paper system.

"Many institutions use an electronic application that looks similar to the paper application, and that's not the case here," Clemens says. "We combined the biomedical and behavioral IRBs at the same time we developed our electronic application so we had a merging of forms and review processes that has made it look very different from the two separate paper processes." ■

Informed consent flexibility needs to be taught to PIs

Process begins with the first conversation

IRBs that deal with social-behavioral-educational research might need to give investigators who also conduct biomedical research updated information and education about how to handle informed consent.

"Biomedical and social-behavioral research are different and have different challenges in terms of gaining informed consent," says **Tracy Arwood**, MS, director of research compliance at Clemson University in Clemson, SC.

"From a biomedical perspective, we're looking at the volume of information that is a challenge in terms of communicating it to patients," Arwood explains. "From the social-behavioral perspective, it's not the volume as often as it is the process we used to inform the subject and gain their informed consent."

From a compliance perspective, it's important to talk with investigators about the flexibility permitted in regulations, Arwood notes.

"We explain that informed consent is a process that begins with the first conversation with the subject, which could be a flier in the mail, and it continues through the end of the study," Arwood says.

"Also, depending on the type of study they're doing, we'd like for them to propose what makes sense for that study population," she adds. "We evaluate the protocol's informed consent in terms of [regulatory] criteria, and we see if it works in terms of documentation waivers and so forth." ■

CNE/CME Objectives

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

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

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

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

- Comparing views of IRB and REC in the developing world on HIV vaccine trials
- Texas cancer center's IND monitoring wins human subjects protection award
- Here's how to build long-term bridge between PIs and IRB
- When updating electronic system software, follow this advice
- Researchers/IRB training program has broad appeal

CNE/CME *questions*

9. True or False: Participation in the National Children's Study requires consent from the pregnant mother, assent from the child when he or she reaches age 7 and consent from the child at age 18.
   A. True
   B. False

10. The original Milgram study stopped participants from increasing the "voltage" of shocks they were delivering at what level?
    A. 15 volts
    B. 45 volts
    C. 150 volts
    D. 450 volts

11. When IRBs review studies that involve the use of virtual reality settings, which may require a headset, which of the following is a question they should ask?
    A. Are there any concerns about a participant's emotional state beyond what is normally experienced?
    B. How will simulator sickness be prevented and handled?
    C. Is there any potential for the gel used with the headset to cause irritation to the skin?
    D. All of the above

12. Which of the following statements describes the best informed consent process?
    A. Informed consent begins with the first conversation with the subject, which could be a flier in the mail, and it continues through the end of the study
    B. Informed consent involves a research associate sitting down with a prospective subject, reading the informed consent form aloud, asking if there are any questions, and having the subject sign the form
    C. The informed consent process begins with a physician mentioning a study to a patient and ends when the patient signs the informed consent document
    D. None of the above

Answers: 9. True; 10. D; 11. D; 12. A.