

IRB ADVISOR

*Your Practical Guide To
Institutional Review
Board Management*

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Surveying teens about sex: Full disclosure, confidentiality key

Careful attention must be paid to the informed consent process

Behavioral surveys of adolescents always are a delicate proposition, requiring consent from parents as well as assent from the child and asking both to consider the possible implications of participation. Add sex to the mix, and it becomes a potentially volatile brew for IRBs, raising issues of confidentiality, public health, and parent-child tensions. But investigators dedicated to discovering more about the sexual behavior of teens say research can be done if careful attention is paid to informed consent and to the protection of the adolescents' interviews.

In fact, done properly, the surveys can end up benefiting the children and parents who participate, says **Elizabeth Waiters**, PhD, associate research scientist for the Prevention Research Center of the Pacific Institute for Research and Evaluation (PIRE) in Berkeley, CA. Her organization recently released results from a survey of more than 800 adolescents regarding their media consumption and sexual behavior.

"One of the good things that came out of the study was that a lot of parents were saying it opened up the lines of communication between themselves and their children, along the lines of sexual activity, in a way that they hadn't been able to talk to their children before," Waiters reports.

She says the knowledge gained from working with researchers on the sexual behavior survey has helped the organization's IRB better deal with tough issues in other surveys involving sensitive data.

"[IRB members] actually wanted to use this protocol as a prototype to present to other investigators when they were coming in front of the IRB, because they did such a good job of it," says Waiters, who served on the IRB when the study was reviewed and later joined the research team. "This was one of the first studies our IRB had to deal with of such a really touchy nature."

The largest study to date of adolescents, the National Longitudinal Study of Adolescent Health (Add Health), surveyed seventh through 12th graders across the country over eight years on a variety of topics including drug use, peer pressure, and sexual attitudes and risk behaviors. The

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surveys included in-home interviews conducted with more than 20,000 students.

The adolescents were asked detailed questions, not just about their sexual activities, but also about the identities of their partners in order to study networks of relationships, says **Peter Bearman**, PhD, one of the study's designers and chairman of the department of sociology at Columbia University in New York City. In later stages of the study, participants gave urine and saliva samples to test for sexually transmitted diseases.

Research projects using the data have examined the role of virginity pledges in sexual decision making, the relationship between maternal attitudes and teenage sexual activity, and religion's

influence on teens' decisions about sex.

Bearman described a complex study design that was intended not only to protect the teen participants from direct disclosure of their responses but also from so-called "deductive disclosure," in which a respondent's identity could be guessed from the use of known characteristics collected in the data.

Adolescents who participated would answer questions posed to them on a laptop computer to prevent even the interviewer from knowing their responses, a practice also used in the PIRE study. **Melina Bersamin**, PhD, associate research scientist at the Prevention Research Center and author of the PIRE study, says parents were given a separate, paper-and-pencil interview in a separate room to ensure that they wouldn't be around the teens while the survey was being administered.

Interviewers for the Add Health study were chosen from outside the survey's geographical area to avoid accidentally assigning an interviewer to survey someone he or she knew, she says.

The Add Health data were transmitted back and forth between the interviewing organization and a data manager in Canada, stripping away personal data so that the researchers didn't possess identifying information, even if they were ordered by authorities to produce it.

Bearman says that last safeguard was to prevent a situation such as a "frantic father example," in which a parent might learn of a child's sexually transmitted disease and attempt to compel the researchers to disclose the names of the child's sexual partners.

Because researchers would be obligated by law to release information when compelled by the government in a public health situation, Bearman says the critical link in the chain of data identification — a key matching an adolescent's ID number to a real person — was located outside the United States.

In fact, both PIRE and Add Health survey designers decided early on to avoid asking questions about sexual abuse and other reportable activities, because they would be compelled to immediately disclose them to the authorities.

Walters says the PIRE questions were carefully worded to avoid soliciting information about illegal activities, including consensual sex between a teen and an adult. "If it did come out in the interviews, parents had to know that that information would have to be divulged," she adds.

Bearman says the Add Health researchers also

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Editorial Questions

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used a system of describing geographical locations — also important in studying social networks — in a way that made it impossible to identify a particular neighborhood or school involved in the study. And certain data were removed to keep from unintentionally identifying respondents indirectly.

“If you knew somebody was in the study, you could then cross-classify a whole set of characteristics in order to uniquely identify a single individual,” he says. “For example, there are only so many girls in the school who are 16 years old who play on the volleyball team who have a certain weight or height, and sometimes, there’s only one.”

Add Health’s concern about confidentiality is so keen that researchers who use the restricted data in their own projects must agree to an IRB-approved security plan that includes using stand-alone computers or other methods to keep data off the Internet or an internal computer network.

At PIRE, an interviewer was fired after her laptop computer, which contained interviews, was stolen, Bersamin and Waiters report. Luckily, there was no identifying information in the data, Bersamin says.

“I remember that started a discussion on the IRB of the safety of monitoring that kind of information,” Waiters says. She says the IRB had an information technology expert talk to members about data encryption and other security measures for laptops.

Giving parents the facts

The end result of all of this attention to confidentiality was to reassure both parents and teens that the adolescents’ privacy would be protected, a process that greatly eased recruitment and informed consent, Bearman says.

“Parents didn’t have a problem because they believed in the security system,” he says. “And the interviewers didn’t have a problem convincing them because *they* believed in it, too.”

Waiters says the chief concern of the IRB reviewing the PIRE study was that parents understood that the survey their children would fill out included specific questions about sex.

She adds that the IRB asked researchers to rewrite a fact sheet for parents to more explicitly state that fact.

PIRE contracted with a data collection firm to provide them with a database of households that were likely to include adolescent family members. An initial phone call secured the parent’s permission to ask the child if he or she wanted to

participate. A formal written consent form was sent to families who agreed.

From the beginning, parents were told they would not have access to their children’s responses, Bersamin says.

She says the consent form explained to parents and teens that the researchers had obtained a Certificate of Confidentiality from the National Institutes of Health (NIH).

The NIH issues the certificates to protect identifiable information from forced disclosure in civil and criminal matters. However, researchers using them still are subject to state public health laws requiring disclosure of communicable diseases, a point that Bearman says made a certificate worthless for Add Health’s purposes.

In the PIRE study, both students and parents received nominal compensation for participating, Waiters says.

She says many of the parents who agreed to allow their children to participate in the PIRE study cited its focus — the relationship between media influences and teen sexual activity.

“When they found out it was a study of the media, of television in particular, most parents were really happy to participate,” Waiters recalls. “I know from the focus group interviews, parents had a lot of concerns about the amount of sexuality in television, and really didn’t know what to do about it.”

She and Bersamin say another point that reassured parents was a particular feature of the computerized survey, a “skip pattern” that automatically deleted questions from the survey if the respondent didn’t need to see them.

“So, if an adolescent indicates that they’ve never kissed anyone or held hands with anyone or made out with anyone, we’re then not going to ask them questions about sexual intercourse or anal sex or anything like that,” Bersamin explains.

Although Add Health did restrict questions about activities such as anal and oral sex to older respondents, Bearman says he thinks there’s too much concern about the potential harm of presenting a teen with such explicit questions. He says adolescents are more sophisticated and knowledgeable about sex than adults think they are.

“If an IRB worried that a 15-year-old could be disturbed by a question about sex, then I would think that they’re not paying attention to the larger culture around them, which is just infused with explicit and inexplicit comments about sex,” he says.

Bersamin says she worries that in an effort to

protect kids, IRBs are too quick to strike questions that researchers need to ask. For example, she says, in the past, surveys of teens shied away from asking about oral sex.

“And new studies have finally started putting that in questionnaires, and lo and behold, it appears to be more prevalent than sexual intercourse,” Bersamin says.

A ‘beneficial’ survey

Bearman notes that the Add Health survey asked a number of questions that he considered far more sensitive and potentially disturbing than ones that involved sexual behavior.

“There were a whole lot of questions about suicidality, about tensions that kids face, feeling lonely, having disrupted family lives,” he says. “One of the most sensitive questions in my opinion was, ‘Does your mother love you?’ For a 15-year-old who thinks his mother doesn’t, that’s a more sensitive question.”

In the event that a parent or adolescent did experience problems while being surveyed, both studies took pains to make professional help available.

Walters reports that for the PIRE study, every interviewer was armed with a list of referrals in case issues such as drug use came up during the interviews. All participants also were given a toll-free number to reach the IRB in case they had questions about the study.

For participants in the Add Health study, researchers provided a 24-hour psychiatric help line, Bearman says. “Maybe two or three people used it. It was a useful investment. That’s the kind of thing that IRBs should be asking about. It meant that if anything serious happened, there could be some help around for the kid.”

Bearman also contends that IRBs should make an effort to ensure the survey itself is set up in such a way that it can potentially benefit the respondent. Both he and Walters say students were very enthusiastic about the surveys, approaching interviewers to ask to be included and having parents check back in subsequent years to make sure follow-up surveys were conducted.

“A well-designed survey instrument is fun to fill out because it’s revelatory of the self — the process of filling it out helps them understand their lives,” Bearman says. “The bad surveys just take analytic questions from academics’ minds and ask them, without any order, without any sense of the life. It’s a very different experience

and much more threatening to the individual, where they just become an object.

“What IRBs can look at is whether this survey is designed to work with the way people’s lives work. Does this instrument do something for the respondent? Because there’s no reason that instruments shouldn’t be beneficial.” ■

Here or abroad, informed consent is still a process

Three-phase approach proves effective

As IRBs move to improve the quality of human subjects protection in international research, they should pursue a model of informed consent that begins long before an individual signs a consent document — and continues afterward.

That’s the message from a researcher who has conducted HIV prevention trials in Africa, India, and the United States. **Cynthia Woodsong**, PhD, a senior scientist with Family Health International in Research Triangle Park, NC, is among a group of researchers participating in the HIV/AIDS Prevention Trials Network, which collaborates to develop and test HIV preventative approaches.

She and others involved in the network have used their experiences in cross-cultural research to develop a three-phase model of informed consent that is designed to better educate individuals and communities about research before, during, and after the official consent is obtained. The approach includes getting input from the community to understand cultural mores before recruitment begins; using props and other aids to ensure that subjects understand the study and all that is involved; and following up regularly to ensure that participants still understand the study and to dispel any myths or misinformation that may have arisen since the start of the study.

Woodsong notes that while their model may seem more labor-intensive, it’s both ethically stronger and scientifically smarter than a more perfunctory get-the-signature-on-the-form approach.

“We argue that yes, it does take more time, but you get better recruitment eligibility ratios, and you get better eligible-to-enrolled ratios,” she says. “If you pay attention to things on the front end, you’ll get people coming to enroll who are better suited to the study and will stay in the study. We argue that it improves retention and

adherence. So it should make a study tighter — make it run more smoothly and avoid problems.”

Her group published the model in a recent issue of the *American Journal of Public Health* [2005; 95(3):412-419]. Woodsong has been presenting the proposal at conferences of research ethics groups over the past year. Her hope is that IRBs will begin to adopt all or parts of the model when they review international research — or even research in the United States that involves different cultural groups.

Getting community input

The informed consent model Woodsong advocates attempts to take into account the relationship between participants and their community. This is particularly important, she says, in cultures that have a different concept of personal autonomy.

During a pre-enrollment stage, researchers would work with community leaders, possibly in the form of an advisory board. The board would represent different facets of the community, especially any groups being targeted in the study, such as women.

“You sort of do a general stakeholder assessment — who are the stakeholders, people who have a stake in the outcome of the research, and gatekeepers, people whose permission you have to have before you go into a community,” Woodsong explains. “That may be a village chief; if you’re going to recruit in a clinic setting, you’re going to have both the director of the hospital and maybe the matron of the nursing ward.”

Working with community members can help identify problems as early as possible so they can be addressed.

For example, Woodsong’s research deals with the use of vaginal gel microbicides to be used by women to prevent transmission of HIV. In some sub-Saharan African communities where she conducted the research, women expect to ask their husbands for permission to participate.

“Respecting persons means if in their culture, they don’t want to do something without asking their husband, you have to respect that,” she says. So as part of the pre-enrollment process, researchers developed materials specifically to explain the study to male partners.

Community input also can identify what forms of recruitment might be most successful, perhaps prompting the use of illustrated booklets, videos or drama skits in populations with low literacy.

Community advisers can educate researchers about the best way to translate materials for optimal understanding, provide insight into local practices, and help shape informed consent materials, particularly to explain difficult research concepts such as randomization and placebos.

The pre-enrollment process can be eased significantly if a researcher has prior experience with the community, or has good local contacts, notes Woodsong.

“If you’re working with an established site and local researchers, they know what kinds of recruitment strategies work,” she says. “Working with experienced teams, you can cut to the chase on a lot of this.”

Using props and aids

During the enrollment phase, Woodsong says she relies on a whole array of aids and props to help women understand the studies for which they’re being recruited.

A woman might be shown a speculum to help explain a vaginal exam. Instead of simply being told that blood will be collected, she’s shown the actual vials that must be filled, so that she knows how much blood will be taken (this came in response to rumors during one study that the five “vials” to be filled were Coke bottles).

To explain an abstract concept such as use of placebo and blinding, Woodsong says researchers can use glasses of orange juice, explaining that one is vitamin-enriched and that it’s impossible to know from drinking them which has been enhanced. Or a researcher could use hair creams, with and without curl relaxer, to explain the idea that you can’t tell from looking at a treatment which one is active.

Some cultures don’t understand the idea of flipping a coin or playing the lottery to describe randomization, so the idea of drawing straws or casting lots might be more appropriate, she says.

“The idea is to spend some time with your local staff and local community advisory board members or community stakeholders to find out what mechanism of explaining would help,” Woodsong says.

She says it’s vital at this point to understand how the community views individual decision-making, particularly when research involves women, who may have limited individual autonomy to make decisions about participation.

While it’s important to respect cultural norms, the informed consent process still must respect an

individual's absolute right to decide for herself whether to participate — or to let others in on the process.

In her work with vaginal microbicides, “a woman may want to use them without her husband knowing about them,” Woodsong points out. “Asking a husband's permission may be tantamount to accusing him of fooling around or suggesting that she herself is unfaithful.

“So you may want to help give women the opportunity of making a decision without involving their husband,” she says. “However, if they want a husband's or partner's involvement, it's incumbent on the research team to make that information available.”

Comprehension drift

Once a subject is enrolled, the job of informed consent isn't over, particularly in longitudinal studies where comprehension can drift over time, Woodsong says. Researchers must keep in touch, both at the individual and community levels, to make sure that the study is still well understood and to counter any rumors that might have taken hold and could threaten continued participation.

“If word gets out, for example, that they're selling the blood [drawn in the study] to Satanists, then people might drop out,” she says. “This happens a lot with HIV studies where blood is taken. All kinds of rumors get going about what's being done with the blood — that it's being sold or being used in inappropriate ways.”

She says in another study that measured children, rumors cropped up that the children were being measured for coffins, since the children who were randomized into the active ingredient were expected to sicken and die.

Woodsong says quizzing participants periodically on informed consent information can have a dual benefit — reinforcing any issues that participants are unclear about, and identifying problems in the informed consent process.

For example, if follow-up quizzes show that women don't realize the gel they're using comes with a risk of skin rash, researchers can be prompted to remind them at their next visit. Or they can monitor which staff seem to have trouble explaining details about the study to see if they need help.

“So it becomes a quality improvement tool as well as a good ethics documentation tool,” says Woodsong.

She says the three-phase informed consent

model currently is in full use in a clinical trial being conducted by the HIV/AIDS Prevention Trials Network. Parts of it are being used in other clinical trials, and Woodsong says she's gotten a lot of positive feedback from her discussions of the model at various conferences.

“People are saying yeah, this will help, it makes sense,” she says. “People may be reluctant to do all of it. They may want to do the visual aids, but won't do much with the rumor monitoring.”

She hopes that as more information is generated about the model's effectiveness, more IRBs will ask for this type of enhanced informed consent from researchers.

“If this approach catches hold, an ethics committee might say to someone going in front of their IRB, ‘Have you thought about having any visual aids handy to explain randomization?’ IRBs might start asking for how things are going to be translated, how things are going to be explained,” Woodsong says.

While all of these ideas aren't necessary for every study, Woodsong says they are particularly useful in large longitudinal studies of populations other than the researchers' own.

“With those types of studies, it's a solid front-end investment of a little extra time that would pay off with better science as well as stronger ethics,” she says. ■

Cues prove helpful to schizophrenia patients

Multiple-choice questions aid comprehension

Obtaining informed consent from people with schizophrenia is a process fraught with difficulty, as the condition can impair a potential research subject's ability to recall the consent information he or she is given. But an Oklahoma researcher says he's found evidence that a simple, inexpensive method of testing informed consent can greatly improve schizophrenia patients' understanding of the facts of a study. In fact, even control subjects who didn't have the disease did better when tested on the facts of the study using the method.

The key is providing cues to the participant in the form of multiple-choice questions, rather than asking open-ended questions that require the participant to recall the information in whole.

Dennis Combs, PhD, assistant professor of psychology at the University of Tulsa (OK), says he began studying ways to improve informed consent for patients with schizophrenia at the request of his IRB at Louisiana State University, where he was pursuing his doctorate.

"That seems to be the direction that the IRBs I work with are moving in," he says. "They really want to make sure the person understands it. The methods that this project developed, we're using now in our research."

Previous research has shown that people with schizophrenia have deficits in their ability to understand consent form information.

"There are so many cognitive problems there," Combs points out. "They may not be attending to it, they may not remember it. So anything that can help them do that is beneficial."

He says methods of obtaining informed consent usually have been based on research in the general population, which could prove risky to schizophrenia patients.

Some projects have attempted to boost recall of consent form information by using methods such as videotaped presentations and interactive approaches. Combs' group instead tested a lower-tech approach of creating multiple-choice questions about the study to be administered to participants.

"When you put it in the form of a [multiple-choice] question, they seem to remember it better than if you just ask them to tell you what they remember," Combs says, "because it has context to it. They can remember reading that section and they can identify the correct answer."

His team studied the ability of two groups — one of patients with schizophrenia and one of college students — to recall information from a consent form in two different ways.¹

Each group first was asked eight questions about the consent form — information such as the name of the principal investigator, the purpose of the study, the risks and benefits, and the consequences of withdrawing from the study. No cues were given. A point was given for each correct answer, but no information was given to the participant about how well he or she did.

Each participant then was given the cued test, with the same information presented in a multiple-choice format.

Patients with schizophrenia did significantly worse on the first, uncued test than the control group. When the cued responses were provided, there was no difference in recognition scores

between the two groups.

Finally, both groups demonstrated significantly higher recognition scores on the cued test than on the uncued one.

"The recognition stuff is always generally better than free recall, where you just answer questions," Combs explains.

He says while many studies working with patients with schizophrenia employ technology to improve understanding, "this is a cheap, easy way to do informed consent. It's not expensive to come up with some items to test."

Thanks to the success of this study, Combs now employs a version of it in all of his schizophrenia research. He asks patients focused questions about the study with multiple-choice answers.

"We go back over the ones that they miss and make sure they get that information," he says. "We want to make sure they understand every part of the consent form."

In addition to working with schizophrenia patients, Combs says a colleague is testing the cued method in informed consent with multiple sclerosis patients.

"I think it can be applied to any population that has cognitive impairment — that this might be a way to do it better," he says.

In addition to changing informed consent testing for schizophrenia patients, Combs also suggests working with the informed consent document itself to improve readability.

"We're trying to get them at about a sixth-grade reading level, and that seems to help a lot," he says.

Reference

1. Combs DR, Adams SD, Wood TD, et al. Informed consent in schizophrenia: The use of cues in the assessment of understanding. *Schizophr Res* 2005 Sep 1; 77(1):59-63. ■

Advisory board tackles life sciences issues

Board examines dual use potential

Research into the intricacies of the human genome has opened up a new era for biologic and biomedical research. Investigators are poised to explore the almost unlimited potential to diagnose, treat and possibly cure and prevent many

diseases once thought untreatable.

But such advances also have a dark side — the more scientists learn about how our bodies function at the molecular level, the higher the potential that such knowledge can fall into the wrong hands.

A new advisory board for the Department of Health and Human Services (HHS) has been charged with the task of developing criteria to determine when life sciences research has the potential to be used in unintended and harmful ways, and how such research can be properly secured.

On June 29, HHS Secretary **Mike Leavitt** announced the appointment of 24 members to the new National Science Advisory Board for Biosecurity (NSABB). Following the appointments, the board held its first meeting June 30-July 1 in Bethesda, MD.

The possibility for misuse?

International cooperation and the rapid sharing of information across national borders yielded impressive results during the SARS crisis and in the effort to combat the spread of avian influenza, NIH director **Elias Zerhouni**, MD, noted in remarks to open the first meeting. But this new age of discovery and cooperation poses significant risks.

“There is no doubt that research intended for the benefit of humankind can also be used for malevolent purposes,” he said. “Because of advances in recombinant DNA research, molecular genetics, and other life sciences disciplines, we have come to the root, the real root of life systems and biological systems. We have increasing abilities to routinely alter biological systems to explore the mechanisms of human, animal, and plant disease. Yet it is an unfortunate fact of life that there are individuals who would use these technologies and discoveries to terrorize nations and threaten public health.”

The NSABB is needed to develop criteria to determine what types of research have the potential for such “dual use” and to recommend ways to prevent discoveries from being used in ways that would be harmful.

The federal government has passed laws regulating the use of specific biologic and chemical agents, but a “dynamic, evidence-based, aggressive approach” by the advisory board is needed to ensure that the international scientific community can continue to cooperate across borders,

while preventing discoveries from being misused.

Overly strict security measures could do more harm than good, if they stifle good cooperation in an effort to prevent bad, he added.

“At the end the day,” Zerhouni concluded, “it is my personal belief that the goal will be achieved when a scientist himself or herself asks themselves a question, could this be misused? What could I do to protect that from happening? That culture of responsibility is probably the task all of us as leaders of agencies and of this committee are going to have to develop and find way to get to.”

A code of conduct

The board’s overall charge is to develop criteria that can be use to identify dual use research and to develop guidelines that can provide for oversight of such research and research results, says NSABB executive director **Thomas Holohan**, MD, a physician serving in the NIH Office of Biotechnology Activities, which will manage and administer the board’s work.

Specifically, the board will advise the HHS and NIH on developing national policies to govern local review and approval of dual use research studies, including guidelines for case-by-case review by institutional biosafety committees. The board also may develop criteria and processes calling for referral of specific classes of research or specific studies for review at the national level by the NSABB itself.

“The board is also asked to provide recommendations on the development of a code of conduct for scientists and laboratory workers,” Holohan notes. “It will also advise on the development of mandatory education and training in biosecurity for scientists and laboratory workers at federally funded institutions, as well as recommend national policies for publication and communication and dissemination of methods and the results of dual use research.”

The board will meet quarterly, with special meetings called on an as-needed basis by the secretary of Health and Human Services, and all meetings will be open to the public unless HHS deems it necessary to close a meeting, Holohan said.

An archived webcast of the meeting’s proceedings is available on the NSABB web site at www.biosecurityboard.gov, and more information on the agency’s mission and work is posted there as well. ■

Ethical practice starts when study is designed

Winning back the public's trust should be the goal

Public trust in clinical trial research was damaged in the past year because of conflicts of interest issues that arose with the NIH and by front-page media reports about drugs that had been studied and approved, yet were found later to result in deaths among some people who used them.

"What people don't often realize is that virtually every decision we make has an ethical component to it," says **Evan G. DeRenzo**, PhD, bioethicist at the Center for Ethics at Washington Hospital Center and an adjunct faculty member in the graduate program in biotechnology at Johns Hopkins University in Baltimore. "We live in a world where we compartmentalize things. [Researchers] think of it as science, and then they think about ethics after thinking about science; and that's not the way it works."

Many researchers often fail to understand the ethical components to their decisions, including their ties to industry that could be construed as conflicts of interest, several ethical experts say.

Likewise, most researchers will think of conflicts of interest with regard to financial matters, but there also are other types, including process conflicts, says **Edward Fuchs**, PA-C, MBA, a research associate on the faculty at Johns Hopkins University School of Medicine in Baltimore. Fuchs also is the associate director of the Johns Hopkins Drug Development Unit.

"Investigators, in order to get promoted, need to publish and get data; in some ways, that poses as great a conflict as financial conflict," he says.

Because of these ethical challenges, the NIH Director's Council of Public Representatives held a workshop in Bethesda, MD, last fall — "Inviting Public Participation in Clinical Research: Building Trust through Partnerships." More than 80 participants discussed issues related to public participation and trust and developed a set of recommendations designed to enhance and improve the state of clinical research and build trust.

Regulatory guidelines, recommendations, and an institution's own policies regarding conflict of interest and ethical responsibility all are part of the base foundation for the house of ethical decision making, notes **Linda Strause**, PhD, executive

director of global site development at Cancervax Corp. in Carlsbad, CA. Strause also is the chair of the IRB for San Diego Hospice and Palliative Care.

Strause, Fuchs, and DeRenzo discuss some of the chief ethical issues the clinical trial industry faces today:

- **Addressing inherent challenges in physician-investigator roles.** "I believe physicians make decisions based on what's best for the patient," Strause says. "However, that decision may be conflicted when the physician is also the investigator and the patient is also the research subject."

Part of the challenge is the traditional relationship between doctors and patients in which patients ask their doctors to tell them what to do, she explains. In the case of a physician serving in the role of investigator, the doctor cannot make this decision and cannot apply any influence over the patient/research subject's decision-making process, Strause notes.

- **Being aware of changes in ethical perceptions.** Research in recent decades has relied on an ethical model based on the Belmont Report, focusing on issues of respect, beneficence, and justice, Fuchs reports. "We may be in a period where we're looking at something beyond the Belmont Report. In some cases, it's described as a relationships model."

According to the relationships model, there is a relationship established between the investigator and community and the investigator and research subjects, and this relationship begins before the trial and should continue after the trial has ended, he explains. "There are issues that may not be what one considers directly relevant to the trial, but they play a role in issues of trust and perception."

For example, although HIV investigators visited sites in the developing world and tried to do everything they could to protect subjects, the communities haven't always felt enough was done, Fuchs notes. "The community wondered whether the subjects would receive the standard of care that the individual with HIV in the United States would have and, if so, whether they would get access to those medications once the study was concluded."

That disconnect between investigators' ethical perceptions and the community's ethical perceptions resulted in some trials being closed briefly until investigators met with local leaders to discuss and define the investigators' obligations to the community, Fuchs explains.

- **Learning an ethical process or analysis.** DeRenzo has been working on an ethical process

Thinking through Issues

The following questions should be part of an ethical analysis:

- Who are all the possible interested parties? Think broadly — include not only persons and categories of persons, but institutions/organizations/professions/communities.
- What are the full range of duties and obligations of each potentially interested party? Or at least the primarily interested parties? Think of parties as not only individuals, but institutions and groups, also.
- How might various duties and obligations clash/conflict?
- What might be short-/long-term consequences of each possible course of action? How confident are you of your predictive accuracy?
- What ethical principles are at stake? In tension?
- What might be the intentions of the various players? Evaluate the praiseworthiness, or lack thereof, of persons'/organizations'/institutions' motives.
- What appears to be the full range of the possible courses of action?
- Weed out those possible courses of action that appear not to be justifiable based on potentially bad consequences, inability to meet duties and obligations, and/or the ethical soundness of intentions.
- With the possible courses of action that are left, make explicit — either to oneself, or with colleagues/friends/family whenever possible — the justifications for taking each. Then vigorously scrutinize whether or not those justifications are ethically robust.

Source: Evan G. DeRenzo, PhD, Baltimore.

model that would apply to whatever issue arises, and the result of this is an 11-step approach to decision making. (See **ethical analysis**, above.)

• **Incorporating ethics into the entire research process.** Ethical decision making should be a part of the thought process from the time a study is imagined, DeRenzo says.

“Right from the get-go, ethical issues are going to be embedded in every aspect of running a clinical trial,” he adds. “So not to approach clinical research and development and design of clinical trial and its context with a heightened sensitivity to moral issues embedded in the study puts us at risk of ignoring those things and not paying enough attention to those things.” ■

FDA senior advisor discusses GCP goals

Look for new guidance on risk-based approaches

[Editor's note: In this Q&A, **David A. Lepay, MD, PhD**, senior advisor for clinical science and director of Good Clinical Practice (GCP) Programs, for the Office of Science and Health Coordinator, Office of the Commissioner, U.S. Food and Drug Administration, provides readers with an update on federal regulations and guidance governing the clinical trial industry.]

Question: What is the FDA's most important focus these days with regard to the clinical trial industry?

Lepay: The most important is research subject safety and communications on safety. That's been a big focus for our agency and office as a whole and it will continue for some period of time. We held a hearing on March 21 on IRBs, and this is a hearing we will follow up on several levels. At the hearing, we heard a consensus opinion that there are problems in the system of reporting of adverse event, and that's a systemwide view. It's not a problem restricted to IRBs; it's an issue we have to deal with at the most fundamental level of how adverse event information is acquired, how it is synthesized, how it is interpreted, analyzed, and ultimately how it is communicated and reported among the parties.

We heard very much from IRBs that single serious adverse event reporting coming to an IRB are almost uninterpretable, and clearly we have to go back and look at what kind of information could be provided in this system. Right now, of course, the drug and biologic regulations don't provide for direct communication of information between the sponsor and IRB. They all move through the investigator, which also creates a large amount of paper and office time for the investigator and puts them in the very difficult role of interpretation. So we are going to have to look at making some changes in that fundamental direction into which information flows.

I expect we're going to do as much as we can through guidance. This will be coordinated very closely, not only with the FDA, but also with other agencies that have a stake here, particularly the Office for Human Research Protections (OHRP). I think that would be, probably, one of the very large areas of focus for us.

Question: So do you have any proposed changes or committees that are going to look at making any changes, such as allowing direct communication from the sponsor to the IRB?

Lepay: That would require a regulatory change. We'll see what we can do in terms of the way the regulations are currently written, what kind of guidance we can provide both to the IRBs under their regulations as well as the sponsors under their regulations. We can see how far we can take that. Ultimately, regulation development and writing is a much slower process.

Question: What's another area that is of top importance these days?

Lepay: We're looking very much at the issue of risk and risk-based approaches. We're trying to figure out how best to use resources in the clinical trials enterprise to achieve the greatest benefit from the standpoint of both subject protection and data quality. This is part of a broader initiative within the agency: The critical path initiative, which also is very much focused on trying to streamline processes in a risk management-based fashion. This is an area where we have solicited public comments and public information with the intention of providing a synthesized list of those comments and the opportunities or areas in which streamlining may be possible, based on those public comments.

But it extends as well to GCP and our oversight of clinical trials. We're trying to apply risk-based approaches internally, within FDA, in the way we develop assignments and the way we choose sites for inspection, in the way we talk with industry about study monitoring and study oversight. Fundamentally, when we're talking risk-based approach, the concept here is some sort of analysis of risk goes on prospectively during the developments of the study and development of a monitoring plan. By corollary, a risk-based approach would say, 'You're going to put more of your resources into those areas that are of higher risk than you're going to put into those areas of lower risk.'

Question: What are other big areas and hot points that you've been speaking about in FDA updates?

Lepay: There are a few other areas also in the forefront and one is the international. At that level

we certainly recognize the positive contributions that GCP harmonization has made between ourselves, Japan, and the European Union since the advent of ICH [International Conference on Harmonisation]. The recapitulation of some of those successes now in the device arena, as harmonized standards are also being embraced, not only in drug and biologic studies, but also in devices studies through harmonization efforts there.

But a lot of our efforts are being directed as well, to the extent that we have resources to do these sorts of things is working with international or foreign regulatory authorities to assist them in capacity building. We try to assist them in putting into place internationally recognized standards, as well as mechanisms to be able to ensure those standards are implemented and enforced. So we're working with a large number of governments in the world who are interested in developing their own GCP review or GCP inspection unit. We're also working quite closely with the World Health Organization (WHO), which in October should be coming out itself with some implementation guidance on GCP that is fully harmonized with other venues, such as ICH, which we have worked with, but which WHO will provide more directed implementation information.

We certainly recognize that the pharmaceutical industry is ever globalizing and information that is coming to FDA as to other regulatory authorities is not coming from within a single country. And we have to find ways to be sure there are real-time systems to ensure the quality not only for us when it comes to FDA but also for subjects who are participating in those trials.

The other big issue we're trying to work through is to increase consistency across government and to work more closely with other government agencies, particularly those within our own department, be that the OHRP, the National Institutes of Health, the Centers of Disease Control and Prevention, the Office of Research Integrity. As we are now working to develop guidance in these areas, we're also working to share our thinking as well as our contributions to these guidances from one agency to another. ■

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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.

9. Researchers who obtain a Certificate of Confidentiality from the NIH do not have to comply with state public health laws requiring reporting of communicable diseases.
A. True
B. False
10. Which of these approaches might explain the concept of randomization to a potential research participant?
A. Comparing the process to drawing straws
B. Displaying vials of blood
C. Adding vitamins to a glass of orange juice
D. None of the above
11. When schizophrenia patients and college students were tested on informed consent information using both cued and uncued tests, which group's score improved with the cued test?
A. Schizophrenia patients
B. College students
C. Both groups
D. Neither group
12. Which of the following questions should be part of an ethical analysis?
A. Who are all the possible interested parties?
B. What might be short-/long-term consequences of each possible course of action?
C. What might be the intentions of the various players?
D. All of the above

Answers: 9-B; 10-A; 11-C; 12-D.

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