IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

July 2010: Vol. 10, No. 7
Pages 73-84

IN THIS ISSUE

Statement of Financial Disclosure: Editor Suzanne Koziatek, Editor Melinda Young, Executive Editor Coles McKagen, Managing Editor Gary Evans, Nurse Planner Kay Ball, and Physician Reviewer Mark Schreiner, MD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies related to the content in this CNE/CME activity.

Internet research raises data storage, informed consent issues

Few IRBs have policies for Internet studies

Internet research has been an issue for IRBs since its roots in the 1990s, and the challenges ethics boards face in reviewing such studies are in pioneer territory.

For instance, twelve years ago, IRBs might not have known how to handle informed consent for studies that involved interviewing people met through Internet chat lines. Now the problems have evolved to determining how to protect research subjects when private Internet research information suddenly becomes public, says **Elizabeth Buchanan**, PhD, director of the center for information policy research in the school of information studies at the University of Wisconsin in Milwaukee, WI.

"I've sat on two different IRBs, helping them understand the complexities of Internet research," Buchanan notes. "One was a medical school board and one was a social science board, and there are different ways of thinking about the issues from the different disciplinary models."

Buchanan decided to study this issue by surveying IRBs in the United States. Her project was funded through a grant from the National Science Foundation.

"No one had been looking empirically at what was happening," she says. "IRBs are seeing more online surveys and interviews, but the boards don't talk to each other about it and there's a real gap in the literature base and understanding of what is happening at the national level."

Buchanan and co-researchers spent a year surveying IRBs and received more than 300 responses that formed an interesting dataset of how IRBs were handling Internet research.

Based on 2007-08 data, the study found that about half of the IRBs surveyed considered Internet research a concern or of interest to their boards. The study also found that less than 8% of IRBs had Internet research protocols, including checklists, review tools, policies, and guidelines. Another 17% said these protocols were under development, according to study findings presented at Office of Human Research Protection

AHC Media LLC

(OHRP) Research Community Forum 2010, held May 21, 2010, in Chicago, IL.

"IRBs are starting to get more and more of these Internet studies, and the most frequent are Internet survey tools," she says. "Some boards are more comfortable with these than others."

Plus, IRB members might find Internet research somewhat confusing, and the issues that concern them are varied.

Online consent

For example, one issue is how investigators might gain consent online. Should they use a checkbox that is similar to an iTunes or software company disclosure that asks you to read the rules and then check the box saying you approve and will proceed?

"Is that an acceptable model of consent?" Buchanan says. "Some IRBs say, 'Yes,' and some say, 'We don't know.'"

And if a checkbox consent form isn't acceptable, then what alternative do researchers have?

Other major issues involve privacy, data ownership, and terms of service.

Buchanan outlines these other ethical issues in Internet research:

Is it possible to have an equitable or fair representation in subject pool when most subject selection is based on type of site?

How does the researcher enter the research space to begin recruiting?

What if some people in a community agree to consent to the study, but others do not? Do researchers have plans for this reality?

With Internet research there are more unknowns in the area of data control, Buchanan notes.

"Suppose a researcher wants to study Facebook data," Buchanan explains. "Those data do not belong to individuals on Facebook or the researcher — they belong to Facebook."

In this type of case the stock phrases informed consent documents might include — about how the data will be kept confidential in a storage file for a set period of time and used only for research purposes — do not apply, she adds. *(See related story, p. 75.)*

"We can't use that language anymore because we can't make those assertions," Buchanan says.

If the research involves obtaining answers to questions given online and through the Internet, it is reasonable to assume those answers will exist beyond the researcher's hard drive.

Internet research is subject to cloud computing: "When we store things offsite, we may have a copy of the data on our desktop, and that's well and good," Buchanan says. "But there may be another set of data in the clouds, and we don't know how long that will last."

For instance, when an investigator conducts an observation online or interacts with a specific Internet community, the researcher will generate a log or transcript, keeping a copy, Buchanan says.

IRB Advisor (ISSN 1535-2064) is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to IRB Advisor, P.O. Box 740059, Atlanta, GA 30374.

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 18 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 15 Contact Hours.

This activity is intended for clinical trial research physicians and nurses. It is in effect for 36 months from the date of publication.

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

SUBSCRIBER INFORMATION

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcmedia.com). Hours of operation: 8:30 a.m. -6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.
Subscription rates: U.S.A., one year (12 issues), $399. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Back issues, when available, are $65 each. (GST registration number R128870672.)
For recent permission, please contact: Stephen Vance, Telephone: (800) 688-2421, ext. 5511 • Fax: (800) 284-3291 • E-mail: stephen.vance@ahcmedia.com • Address: 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: Suzanne Koziatek and Melinda Young.
Executive Editor: 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.

Editorial Questions

Questions or comments?
Call Gary Evans at (706) 310-1727.

Concerns to consider in reviewing web studies

Internet research expert offers advice

Internet technology and its impact on society have evolved so quickly in recent years that researchers and IRBs lag far behind in their efforts to understand and use this new forum.

IRBs need to understand the different kinds of Internet research they're likely to see in protocols, as well as how this type of research might change the informed consent process, says **Elizabeth Buchanan**, PhD, director of the center for information policy research in the school of information studies at the University of Wisconsin in Milwaukee, WI.

Buchanan suggests IRBs consider these questions and concerns:

- What are the practical challenges in obtaining informed consent with regard to fluidity and changes in group membership?
- How do you verify understanding of informed consent?
- Will something placed on a public Internet space come back to haunt the researcher or participants?
- Should researchers be permitted to use archived quotes that were never intended to be represented in research?
- Should an informed consent use blanket statements, such as "I understand that online communications may be at greater risk for hacking, intrusions, and other violations. Despite these possibilities, I consent to participate?"
- How might researchers use blogs, which might not meet the definition of human subjects research? ■

Participants and the Internet community's administrator also will have a copy of the interaction. So the questions that an IRB will have to address are as follows:

- Who owns the information?
- How long will the e-data last?
- Has the researcher informed participants about the data's longevity and potential risk of data intrusion?

A quick study

This uncertainty puts a burden on researchers and IRBs to learn the new Internet rules quickly.

"Researchers and IRBs need to learn and adopt new languages to protect themselves and subjects," Buchanan says.

IRBs also might encounter research collection methods that begin to cross ethical boundaries.

For instance, Buchanan has encountered the case of a researcher who wanted to learn more about people's online political views. He proposed studying this by creating a fake Internet persona with which he'd befriend people in an online community.

"He wanted to know how people would express their political views on Facebook," she says. "It was a form of deception where the researcher would present himself as someone different so he could look at the interactions."

On the surface, an IRB might ask if this would even qualify as human subjects research, she notes.

"One could argue, depending on the type of research, that the researcher could have just been looking at language," Buchanan says. "So maybe it's doing a content or discourse analysis and is not human subjects research."

And even if an IRB decides this is not human subjects research, what about the issue of deception, the researcher creating a fake persona to obtain information that was intended for a specific audience, she adds.

"The IRB was unsure if this fell into the realm of deception and how to evaluate it," Buchanan says. "However, the researcher could say, 'If you don't allow me to create this fake persona, then I won't be able to get the responses.'" ■

ETHICAL CASE STUDY

Weighing incentives in subject recruitment

How high should payments go?

For researchers and IRBs there is an ethical paradox in behavioral studies involving populations that are hard to engage.

On one hand, these populations likely need interventions and programs tested in like individuals as much or more than the general population.

On the other hand, they might have more obstacles to study enrollment, so recruiting participants might require incentives that raise red flags for IRBs.

Researchers who attempted to walk this line in one study — involving low income, urban parents of pre-schoolers — found that their recruitment incentives may have been too cautious, says **Deborah A. Gross**, DNSc, RN, FAAN, professor, Leonard and Helen Stulman Endowed Chair in Mental Health and Psychiatric Nursing at Johns Hopkins School of Nursing in Baltimore, MD. Gross received grant funding for the study by the NIH/National Institute for Nursing Research when she was on the faculty at Rush University College of Nursing in Chicago.

"In anticipation of problems around coercion, we made our incentives low," Gross says. "But now that we've collected data, I think we made it too low."

Finding the right balance is difficult.

"The IRB approved our incentive because we made it low enough to avoid undue influence, but I suspect it was so low it didn't work," she adds. "So how high is high enough, but not too high?"

Down to cases

The result is essentially a case study of how researchers and IRB members attempted to find the right balance between adequate incentives for recruitment and retention and appropriate participation fees. For example, if fees are too high they may lure participants into a study they might otherwise find counter to their family's best interest.

Study's purpose: Investigators wanted to study the success of an intervention program aimed at improving parenting among low-income parents of children between the ages of two and five years of age.

They targeted populations in the urban settings of Chicago, IL, focusing predominantly on minority parents whose incomes were low enough to meet eligibility requirements for subsidized child care services.

The target population included single parents and people who worked 30 hours or more at very low-wage jobs.

"This population is hard to engage because these are parents who have a lot on their plates," Gross says.

The goal was to teach parents the skills they would need to prevent later behavioral and social problems among their children.

Recruitment and retention methods: Researchers decided to recruit parents who attended day care centers that served low-income families.

The families were asked to participate in exchange for these incentives:

- Thirty dollars for each of four assessments, including assessments at baseline, post-intervention, six month follow-up, and one year follow-up;
- Free copies of four 15-minute videotaped free-play sessions with the parent and child;
- Free dinners at each two-hour intervention sessions;
- Free child care during intervention sessions;
- Discounts on child care center co-payments of 20% with a $5 minimum during the 12 weeks in which participants attended the intervention sessions; this incentive was added on for a separate study when the first study's incentives did not achieve desired enrollment;
- The intervention sessions were held at the child care center where participants' children already attended, and they were scheduled to start right at the time participant parents normally picked up their children, from 5:30 to 7:30 p.m. or from 6-8 p.m. weekdays.

Results of recruitment strategy: "After all the incentives we offered, we still found that relatively few parents enrolled in the study," Gross says.

When the child care center discounts were added to the incentive package, study enrollment improved by 15%, but this additional incentive did not improve attendance rates, she adds.

These kinds of results are unfortunate from a statistical standpoint and can result in unclear answers to the study questions.

The study might have recruited subjects from other venues, but investigators had determined that a childcare agency that they already used was the best suited for a variety of reasons.

"One, the mission of early childcare centers is to promote the health and well-being of children and their families, and I saw the parenting groups as contributing to this existing mission," Gross says.

"Second, we thought it would be convenient because their children already were there, and they had to pick up their children anyway," she adds. "So why not give them a night off of cooking dinner."

This reason had a lot of appeal on the face of it, she says.

"But what we have come to realize is that parents' work schedules vary, and for a number of reasons, parents don't come to these evening sessions," Gross says.

These reasons include the following:

• They can't leave their work early enough to attend the parenting group sessions.

• By the time the parenting sessions end, it's dark out and some parents are reluctant to take home public transportation after dark.

• Parents might have school-age children at home, and while they could bring them along for the free child care, they didn't have time to pick them up after work before heading to the child care center.

"We'll continue to look for the perfect venue, if there is such a thing," Gross says. "We'll have to offer different pathways."

These could include offering the intervention on the weekend at a different setting, since child care centers often are not licensed for use on the weekend.

IRB and researcher discussion of recruitment incentives: "The IRB has been fine with the research incentives," Gross says.

"We rationalized the $30 payments for completing the assessments as based on an hourly wage of $15 per hour for two hours," she explains.

"Where we have always struggled is with the notion that when you give an incentive for a discount or cash incentive, how much is enough to motivate behavior change without being coercive?" she adds.

This is an especially problematic concept when subjects are from low-income families.

"I am sure if we had offered parents $100 for every session they attended, we'd get a much better attendance," Gross says. "But then you have to ask yourself what these people are not doing in order to attend our sessions."

For example, one parent who repeatedly signed up for the study, but never attended a single group session was asked by one of the study investigators why she never attended. The woman responded that she wanted to become a better parent to her three-year-old, but she also had a 15-year-old at home. And if she wasn't home when her teenager came home from school then she was worried he would be recruited into gangs, Gross explains.

"Every day, parents are reprioritizing the demands on them, so you don't want to offer an incentive that would have them prioritize their demands in a way that's not healthy for their family or for them," she says.

"You can't just give them whatever the market would bear because you might encourage them to make unwise decisions," Gross says.

Another example would be if a parent left his or her job early to come to the group. But then this could jeopardize the parent's employment status.

"That's the quandary low-income parents face," she says.

"I think IRBs are in a tough spot when deciding these issues," Gross says. "They're at arms' length from the research, and they're trying to make wise decisions."

But there needs to be more research on what is the best price for incentives and the balance between an incentive that is high enough to achieve the necessary enrollment and low enough to prevent undue inducement, she explains.

"I don't think anybody has that answer," Gross says. "I would want IRBs to invest in studies that try to answer that question." ■

Feedback to subjects can be tricky but important

Internet has changed how we see personal data

As Americans become increasingly accustomed to learning more about their own health, it's becoming more common for research participants to expect to learn about their personal results during a study.

"In the genetics domain, we're seeing people getting more interested in getting information about themselves in direct-to-consumer testing," says **Stephanie Malia Fullerton**, DPhil, an assistant professor in the department of bioethics and humanities at the University of Washington School of Medicine in Seattle, WA.

"I think this is changing people's perceptions about access to their information," Fullerton says. "And with the rise in technology and the Internet, people are far more used to knowing and controlling their personal information."

Online social networking sites also have changed the public's perception of privacy.

"People in their 20s and 30s, who are very involved in social networking, have a very different sense of what they wish to make public or keep private about themselves," Fullerton says. "And they have a better sense about how to control their information."

There are parallels to this in patient care where people now can access their medical records and sometimes even correct them, Fullerton says.

"There is a greater expectation because of the changes in technology that people should be able to correct, access, and edit their medical information," she adds.

Against this backdrop are research and the tradition of keeping individual subject information from the individual subjects.

Some researchers and IRBs take the position that no personal information collected during a research study should be communicated to research subjects. Others say subjects are entitled to this information because it's about them.

"I think there's a middle way, and it's connected to benefits," Fullerton says.

"We have an obligation in the research domain to give people information that is so overwhelmingly important to them that it would be unfair to not communicate that information back," she says. "This is if the information would make a tangible difference in their health care."

However, this does not mean researchers are obligated to return genetic test results to patients or to communicate health issues that would not make a tangible difference in their health care.

"There are certain cases where you have an ethical duty to communicate information back, and you don't want to close that door completely," Fullerton says.

Making common sense of the issue

The key is for IRBs and researchers to use common sense: "If research information potentially could save someone's life, then not communicating it back to them would be untenable," Fullerton says.

For example, if a person is seen at a research visit and the person's blood pressure is dangerously high, then the clinic should refer the person immediately to a doctor or emergency room, she explains.

With genetics research, IRBs will need to consider a different situation. So far, nearly all of the genetic variance associated with disease risk is very common in populations and most only increase a person's lifetime risk of a disease by a very small amount, Fullerton says.

These two features make it difficult for IRBs and investigators to consider giving information back to participants, she adds.

"That information ultimately is not going to make a difference in someone's clinical care, and it's not supplemental to family history information, which is far more relevant than a genotype," she says. "So it's very unclear what to do with that information."

Occasionally there is the rare genetic finding that poses a true ethical dilemma. These are findings that would appear to be important for clinical care, although they are not in the category of life-threatening risk.

For example, a genetic researcher might accidentally discover a person who has a chromosomal abnormality that had not been detected, such as an extra X chromosome, Fullerton suggests.

"They've gone through their whole life believing they're one gender, although the extra X chromosome has various implications," she says. "This is clinically well-defined, and when people are diagnosed with this condition and found during routine clinical care they might be given testosterone supplements."

But this isn't a life-threatening condition, and someone could live a long life undiagnosed.

IRBs might consider making an exception for these types of circumstances and permitting investigators to give participants the results. But there are other ethical issues to consider.

One is that finding out this type of information could be disruptive to a person's identity and emotionally painful to the participant.

"Is this information that we researchers should be communicating back to the person who was identified or not?" Fullerton asks. "I don't know the answer, and so far, no one knows because it's a very difficult question."

Further research should be done to consider this ethical dilemma. Meanwhile, IRBs and investigators should make decisions on a case-by-case basis. If they decide to share sensitive information with participants, they should have a process that will ensure this communication is done appropriately.

"I believe it is inappropriate for IRBs to basically insist that researchers never return anything," Fullerton says. "I think what IRBs should be looking for in protocol applications is some plan from investigators for how they intend to manage clinically actionable, usually incidental research findings."

These plans might include a risk and benefits calculation, anticipation of unusual results, and steps that will be taken if results are to be communicated to research participants. Among these steps are processes for confirming results by a certified lab and referring participants to specialists, she adds. ■

Changing trials in midstream

Adaptive design an intriguing alternative

As concerns grow over the expense and slow progress of classic randomized clinical trials (RCTs), an intriguing alternative is gaining steam – adaptive design, in which trials change at various decision points in response to accumulated data.

Unlike a trial unexpectedly changed or stopped midway, these trials are designed with the expectation that there will be changes. For example, one might start with four different doses of a study drug, and two arms would stop enrolling new subjects after a predetermined point, based on data analysis. Or a trial could be designed to change inclusion criteria if enrollment does not meet targets.

In recent years, interest has increased in this approach, fueled by more sophisticated computer models that can help with the designs. The FDA earlier this year released draft guidance for the adaptive design of drug trials.

Proponents of adaptive design say the idea provides some human subjects protection benefits, allowing people to be moved out of ineffective arms more quickly rather than waiting until the end of a protocol. If a trial is speeded up, they say, fewer participants overall might be needed.

But it's still unclear whether there would be improvements to participants' safety as a result of increased use of adaptive trials, says **Marc K. Walton**, MD, PhD, associate director of the Office of Translational Science of the FDA's Center for Drug Evaluation and Research in Silver Spring, MD.

"We're not convinced there are ethical imperatives to use this approach," Walton says, noting that many decisions made in adaptive design studies are based on limited amounts of data. "So the true accuracy of those decisions really remains to be seen."

And Walton says moving participants from a seemingly less active dose of a study drug to a more active dose also raises the possibility that they're being moved to an unrecognized more toxic dose, which increases risk.

Complex studies

While FDA's guidance addressed the design of these type of trials, currently there is no planned guidance for IRBs on the topic from the Office for Human Research Protections, says Health and Human Services spokeswoman **Lt. Kate Migliaccio.**

And some of these trials come with a certain degree of technical complexity, since many rely on statistical models to determine what changes would be made during the course of a study as a result of data collection.

That leaves IRBs with the task of determining what potentially could happen in these trials and how to ensure that all the various possible outcomes provide as much protection to subjects as possible.

Walton says IRBs have plenty of experience handling changes to protocols. But in adaptive design, those changes are considered and planned for from the beginning. He says IRBs need to be sure that they understand the rules that would govern those changes, and the various circumstances that could result.

"They have to try to think of all the different ways the study could go," Walton says. "And they have to decide whether or not they're comfortable with the safety of the study participants for all of those different circumstances. Their task in that regard is similar to FDA's in terms of reviewing and approving the study from the design point of view before the study even gets started."

He says that the more complex adaptive design studies may require more careful and intricate consideration than more traditional designs. "So it may well be that IRBs find they require greater amounts of time to think through the proposed study."

Ensuring expertise

The category of adaptive designs as described in the FDA guidance is a broad one – Walton says it can include fairly straightforward approaches that IRBs are used to seeing (for example, changing eligibility criteria to boost enrollment or incorporating a group sequential stopping rule that halts the study when predetermined measures of efficacy or inefficacy have been achieved).

However, some of the newer designs can be much more complex, relying on intricate computations to evaluate that IRBs may be less familiar with, he says.

As a result, they may need to make sure they have adequate expertise on the board – or can consult with someone to provide that expertise – in order to answer any questions that arise.

Marjorie Speers, PhD, executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in

Washington DC, says that doesn't necessarily mean that an IRB needs to have a biostatistician on its board.

"But what the IRB does need then to do is to ensure that that study has been reviewed by a peer review process or by the sponsor or a scientific review committee that can attest that the statistical design of the study is appropriate, she says.

Once the study is under way, the question of whether IRBs should review individual changes isn't entirely clear.

Walton says it wouldn't be necessary for IRBs to have additional review of the protocol if an adaptation is made in accord with the initial design.

"Changes are planned for and are explicitly laid out in the design of the study from the very beginning, so I'm not sure that the IRB has to have additional review of that at the time that it occurs," he says. "After all, the criteria for making the changes are laid out.

"And the IRB won't have access to the data that was the basis of making the change. They'll only know that a modification occurred at the planned time and according to the prospective plan. They would not really have any new information as a basis for reevaluating the study."

Speers says adaptations that change the trial in any unanticipated way should still go back to the IRB for review.

"Unless you can predict what that change is going to be, and when it would occur, then yes, each change would have to go back to the IRB" she says.

For example, the trial's design may allow for options to increase or decrease sample size or to discontinue one arm of the study.

"You know that going in – the study will be designed in such a way that if the interim results look a certain way, then you might change it in a certain way," Speers says. "But when those results or those data are finally available and looked at, they might be different than what was predicted. So the IRB would need to look at those data in relationship to the change that's being proposed."

Not right for every study

Because of their complexity, adaptive design trials are not necessarily appropriate for every protocol, says **Daryl Pullman**, PhD, an associate professor of medical ethics at Memorial University of Newfoundland in St. John's who has written on the ethics of adaptive design.

He says they would tend to work better in situations where it's possible to see fairly immediate results from a treatment. While some argue that adaptive design is better suited to more innocuous trials, Pullman takes the opposite approach.

"My view is that in situations where perhaps there were life and death kind of consequences – where the information could be critical to making care decisions in terms of putting (subjects) on a treatment that is shown to be effective – then you should design your trial to ensure that more people get on the effective treatment more quickly, rather than waiting until the end (as would occur in an RCT)," Pullman says.

Walton says FDA doesn't expect a sudden flood of new complex adaptive design trials to be submitted for review.

"We expect that sponsors will consider these methods, and begin to use them in a cautious manner, as experience with them grows over time," he says. "So there will not likely be an overwhelming increase in evaluation burden immediately – rather, one that slowly over time develops as sponsors learn where and how the methods can be best applied."

To view the FDA's draft guidance for industry for adaptive design clinical trials for drugs and biologics visit this website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. ■

Adaptive design: Points to consider

Informed consent, therapeutic misconception

Adaptive design clinical trials raise many of the same issues in IRB review as do unplanned modifications to existing trials, says **Marjorie Speers, PhD,** executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in Washington DC.

"IRBs are faced every day with adaptive designs, because every day, they approve research studies and something will change in that study," she says.

But adaptive design does add a few wrinkles to some of the usual IRB issues:

Informed consent: Researchers and IRBs must decide how much to tell subjects about the potential changes that might occur during the study.

The informed consent for adaptive studies should

explain to participants that there will be examinations of data at set points in the study, approximately when those points will occur and what kinds of changes might result, says **Marc K. Walton**, MD, PhD, associate director of the Office of Translational Science of the FDA's Center for Drug Evaluation and Research in Silver Spring, MD.

"For example, (the informed consent) might state that two of the four dose groups will no longer have patients randomized to them, and only two of the dose levels will be continued for the assignment of new patients," he says.

Participants would need to be told if they were being enrolled after a decision point in an adaptive trial.

The complexity of some versions of adaptive design can lead to increased challenges in making consent understandable, says **Daryl Pullman**, PhD, an associate professor of medical ethics at Memorial University of Newfoundland in St. John's.

"Consent documents tend to be very long and technical already," Pullman says. "And I think they could become even longer and more technical if you're trying to explain all the intricacies of an adaptive design to potential research subjects. More description in those situations can actually undermine the informational content of it."

He says he doesn't believe it's necessary to reconsent subjects once the study is under way every time there's an adaptation.

Therapeutic misconception: Pullman also worries that the nature of an adaptive design — changing interventions as researchers know more about what seems to work — will make it more difficult for subjects to grasp the difference between treatment and research.

"Adaptive design tends to cloud that," he says. "I think it's going to become more difficult for clinicians to make that distinction."

The distinction might be especially difficult if the adaptive design calls for particular groups of subjects to be moved from one arm of a study to another.

Walton says that while it is possible to design an adaptive trial that could result in changing an already enrolled participant's treatment — increasing or decreasing a dose, discontinuing treatment to one arm of a trial, etc. — most designs he sees use interim data to change enrollment patterns for future patients.

"The adaptations that have been focused on in the (FDA) guidance document are on what happens to patients who are enrolled after the point of interim analysis, not changes to the management of patients already enrolled in the study," he says.

Computer simulations: One new tool that IRBs may find helpful in reviewing a proposed adaptive design is a computer-generated trial simulation, which runs through potential scenarios for adaptations proposed during the trial to see how they might play out. The FDA draft guidance on adaptive designs says such simulations can help evaluate various design options ahead of the trial.

"A report of the study simulations that were conducted will be extremely helpful to FDA in understanding what may occur during the study," Walton says. "And I think that IRBs will find that also to be very valuable to look at. It's a new kind of information that they are not currently familiar with seeing."

He says FDA hopes that simulation reports will be sufficiently understandable to people who are not statistical experts, but IRBs still might want to seek outside help when evaluating some of the more complicated studies.

"It might be that in some of these really complex ones, they'll want somebody who has some specialized statistical expertise to help advise them on whether or not the simulations have adequately assessed what might happen," Walton says. "We are hoping that the simulation report itself will be understandable to people without deep statistical expertise." ■

Framework developed for engaging community

Negotiate the details beforehand

With the creation of the Clinical and Translational Science Awards (CTSA) program, the goal of involving the community in research has drawn more support and interest.

Community engagement is a key strategic goal of the Clinical and Translational Science Awards program, and committees have been formed to develop road maps and best practices for institutions that want to partner with their communities to help increase knowledge that will promote health.

One such effort convened stakeholders — researchers, ethicists, IRB members, community partners and others — to discuss the challenges of community-engaged research (CEnR) and develop

a framework for thinking about human subjects protection issues that it raises.

Lainie Friedman Ross, MD, PhD, a professor of pediatrics and clinical medical ethics at the University of Chicago, says her work with the CTSA prompted her interest in developing a more formal means of identifying and addressing ethical issues in CEnR.

"We applied for (funding from the CTSA) proposing that we would involve individuals in community-engaged research, the community partners as well as people who did different components of human subjects protection," Ross says.

Her team identified 25 stakeholders and held two meetings with them.

"We asked them to tell us about community-engaged research, tell us about the obstacles, tell us about what you see as the human subjects protection concerns," she says. "Having listened to them, we then again reviewed the entire literature and came up with a novel framework."

The framework, outlined in papers published recently in the *Journal of Empirical Research on Human Research Ethics*, lays out structures for developing research/community partnerships, for identifying risks to both individuals and their communities and for fulfilling the federally regulated key functions of human subjects protection in a community research context.[1,2]

Negotiating a relationship

Ross and her colleagues note that partnerships between researchers and communities need to be negotiated in advance of the project. A memorandum of understanding created from this negotiation might address such issues as control of and access to the data collected, intellectual property rights, returning of research results and the authority that a group such as a community advisory board (CAB) would have regarding data monitoring or even stopping a research project over human subjects protection concerns.

She says that in this process, communities may be better served by CABs than by creating their own IRBs to oversee the research.

"There was a lot of community push (in stakeholder discussions) to form their own IRBs," she says. "I thought it made much more sense for the community to create advisory boards that had greater flexibility and weren't held to specific membership, specific rules, what they can and cannot consider, and those sorts of things."

Whatever the structure, it's important for the relationship to be bi-directional — considering each issue from the perspective of both the research enterprise and the community needs and expectations, Ross says.

"For example, just like the university has conflicts of interest, so do the communities," she says.

Determining risk

Ross says CEnR may require IRBs to adjust their usual ways of considering risk. She and her colleagues lay out three different levels at which community research may introduce risk:

- An individual level, with the possibility of physical or psychosocial risk to a subject based on his or her participation (example: an adverse effect from a medication, or becoming upset by research findings that indicate a health problem);
- An individual risk based on association with a group, regardless of whether the person participates in the research (example: an individual who belongs to a certain ethnic group is stigmatized by research findings that draw conclusions about that group);
- A group risk, if a community organization makes a decision to participate in research (example: conflict arises in an organization over a decision to participate in research or as a result of findings disseminated afterward).

Ross notes that IRBs are constrained by the federal regulations from considering long-term policy issues that may result from proposed research.

"That doesn't prevent them from acknowledging that there are community and group risks," she says. "They can consider the tension of what risks happen when some individuals agree to participate in research and some individuals don't.

"That's not to say that they shouldn't permit the research to go on. I just think that an appropriate review requires that you think about those additional risks."

A variety of actors

While acknowledging the important role of IRBs in helping to ensure the protection of individuals and communities in research, Ross says it's important to realize that there are many other entities that can share that responsibility, from investigators themselves to CABs and research advocates.

One of her papers outlines the various ways in which these actors can contribute to key functions of human subjects protection.

"We have to be careful of what we ask of IRBs. They're already overworked, there's already con-

cern about IRB mission spread," Ross says. "And to some extent, we need to think about human subjects protections more broadly. It's not just about IRBs."

Ross says that the current model of community research – one that tends to group people based on geographic location or race and ethnicity may give way to a model more focused on genomic identity.

"Hopefully, at some point, we're going to get rid of using race as a surrogate marker," she says. "We're going to be able to look at genotypes and understand, for example, why some people digest drugs differently than others.

"So we'll get rid of some of our large and inaccurate group classifications and we'll be able to group people more technically accurately for the purpose of health care."

She notes that groups of people with similar types of genomic conditions are now organizing via the Internet to seek out research as a community, which will bring its own advantages – and complications.

"It's something to think about – how that kind of community social network will change how we think about doing research and IRBs and everything else," Ross says.

REFERENCES

1. Ross LF, Loup A, Nelson RM, et al. Human Subjects Protections in Community-Engaged Research: A Research Ethics Framework. *J Empir Res Hum Res Ethics*. 2010; 5:5-17.
2. Ross LF, Loup A, Nelson RM, et al. The Challenges of Collaboration for Academic and Community Partners in a Research Partnership: Points to Consider. *J Empir Res Hum Res Ethics*. 2010; 5:19-31. ■

AHRQ clarifies grant application rules

The Agency for Healthcare Research and Quality (AHRQ) has issued a notice about its expectations with the completion of grants awarded from the funding provided by the American Reinvestment and Recovery Act (ARRA). Among the key points:

1. To reaffirm to AHRQ grantees that the primary goals of all AHRQ Recovery Act awards are to create U.S. jobs and accelerate the pace of health services research;

2. To remind project directors/principal investigators (PD/PIs) and grantee institutions that AHRQ fully expects Recovery Act grantees to expend project funds in a timely and expeditious manner in accordance with the expected pace of research;

3. To remind grantees that all Recovery Act expenditures remain subject to terms and conditions on the Notice of Award, including the AHRQ-HHS Standard Terms and Conditions for ARRA Awards (see http://www.ahrq.gov/fund/arraterms.htm) and all referenced regulations and OMB Circulars. ■

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

■ Fully-accredited IRB offers best practice tips

■ What stipulations should IRBs make for emergency research?

■ New research oversight rules revealed

■ University takes unique approach to biobank

■ Investigators surveyed about community engagement in NIH studies

CNE/CME QUESTIONS

1. Which of the following is a question IRBs could ask about a protocol involving Internet research?
A. Is it possible to have an equitable or fair representation in subject pool when most subject selection is based on type of site?
B. How does the researcher enter the research space to begin recruiting?
C. What if some people in a community agree to consent to the study, but others do not?
D. All of the above

2. How should IRBs handle protocols where participants might expect or desire to learn personal study results?
A. Have investigators place strong language in the informed consent that explains that no personal research results will be divulged under any circumstances
B. Ask investigators to return all red flag research results to the IRB so the IRB can determine whether or not those should be reported back to participants
C. Have a plan developed that includes a risk and benefits calculation, anticipation of unusual results, and steps to take if results are to be communicated to research participants
D. All of the above

3. Adaptive design clinical trials:
A. provide greater protection to research subjects because they allow for moving participants to more successful treatment arms.
B. provide less protection to subjects because changes in a trial would be based on limited amounts of data.
C. have not yet been established as providing greater or lesser protections to subjects.

4. An IRB may not consider the potential risks to a community of a proposed research study in its review.
A. True
B. False

Answers: 1. D; 2. C; 3. C; 4: B.