IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Informed consent, standard of care debated at OHRP meeting

OHRP will issue new guidance

A late-August Office of Human Research Protections (OHRP) public meeting in Washington, D.C. brought debate from researchers, physicians, and patient advocates on the subject of standard of care research and how IRBs should assess risks in randomized trials.

The public meeting was convened in response to fallout from the 2010 Surfactant, Positive Pressure, and Oxygenation Randomized Trial (Support). The National Institutes of Health (NIH)-funded study included 23 research institutions under the coordination of the University of Alabama at Birmingham (UAB) and tested oxygen levels for nearly 1,300 premature infants. The study intended to find the optimal oxygen concentration for the premature infants. The infants receiving higher levels of oxygen developed retinopathy and other eye disease twice as much as the infants in lower oxygen levels. Those receiving lower oxygen levels had higher rates of brain damage and mortality.

Support study

UAB came under fire following the results of the Support study, with the main issue being whether parents were given adequate informed consent of the risks involved. OHRP sent UAB a determination letter in March of this year, stating that while there were no issues with the study design, OHRP found the oxygen saturation levels part of the Support study to be in violation of regulatory requirements of informed consent, neglecting to fully describe the risks of blindness, brain damage, and death for the randomized study, and required corrective action from the institution.[1]

Bioethics leaders across the country have been sharply divided by the OHRP determination. In the June 20, 2013, issue of the *New England Journal of Medicine*, 46 bioethics and pediatrics leaders published a letter to the editor in defense of the Support study, urging OHRP to withdraw its decision. "Although we acknowledge that the permission forms could have been improved, we disagree that the random assignment of infants to a high

oxygen-saturation level or a low oxygen-saturation level imposed additional risks that the investigators failed to disclose," according to the letter. "The OHRP should not sanction research institutions simply because it disagrees with their assessment of the risks of research but should do so only if it finds that an institution has failed to meet the terms of its federal-wide assurance, such as in the manner in which its institutional review board is constituted or operates."[2]

OHRP placed enforcement of the corrective action plan on hold pending the issuance of further guidance. The organization planned the public meeting as a way to determine the direction that human research protection programs should take when approving informed consent and determining how federal regulations should be applied to studies with one or more standard of care interventions in which subjects are randomized.

Consent form debate

The public meeting featured speakers on both sides of the Support trial issue. Each of the speaker had seven minutes for presentations before taking panel discussion questions.

"The most important take-home message for OHRP today is that the obvious deficiencies in the Support study consent process signal an urgent need to strengthen informed consent for human subjects research, not weaken it as some in the community are advocating," said **Michael Carome**, MD, director of the Health Research Group at watchdog organization Public Citizen in Washington, D.C. "Many critics of OHRP's actions have sought to blur the line between research and clinical care and appear to view the process of obtaining informed consent as an unnecessary impediment to conducting clinical trials and advancing medical knowledge."

"The fact that this meeting is occurring reflects the tremendous influence that NIH, which approved the SUPPORT study and spent nearly $20 million on it, has wielded in an effort to undermine OHRP's authority and reverse OHRP's findings," Carome said.

John Lantos, MD, gave a personal account of his twin grandsons born too premature to qualify for the Support study. One died within hours of birth, while the other survived but with severe retinopathy. Had the babies been enrolled in the study, Lantos said, the family would have been outraged at the outcome. But had they read a consent form filled with all potential risks and not enrolled and the babies had the same outcome, no federal regulators would have looked at the consent process.

"Consent forms should explain those real and likely possibilities and if they do not, they are not empowering people to make informed choices; they are scaring them into making uninformed ones," said Lantos, director of the Children's Mercy Bioethics Center at Children's Mercy Hospital in Kansas City.

When consent forms overstate the risks of research

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and don't say that research subjects might be better off than those not enrolled in the study, Lantos said, the forms are misleading and dangerous. "Misleading inaccuracies push patients away from safe, well-designed studies and towards treatments with unknown and often greater risks and babies die as a result," he said.

One bioethicist stated that the research system is no longer designed to reward those who are "ethically meticulous," saying those who are meticulous experience delays, lower enrollment, and perhaps failure to compete. "In short, the system is set up to allow these ethics problems to keep happening; it may even promote ethical short cuts and missteps," said **Alice Dreger**, PhD, bioethicist at Northwestern University in Evanston, IL. "If ethical shortcuts and missteps go unpunished, if OHRP fails to enforce findings of wrongdoing, what external incentive is there to be ethically meticulous other than the fear of lawsuits?"

Other speakers expressed concern that there is no standard definition for the term "standard of care."

"Talking about standard of care studies is an inappropriate shortcut that obscures consideration of fundamental elements of ethical research," said **Lois Shepherd**, JD, a Peter A. Wallenborn, Jr. and Dolly F. Wallenborn Professor of Biomedical Ethics at University of Virginia School of Law. "First, it is not clear what the term standard of care intervention means, nor is there reason to assume so-called standard of care studies merit ethical treatment."

Jeffrey Drazen, MD, editor-in-chief of *NEJM*, said the definition may be clouded through recordkeeping. "Doctors who do things that are generally accepted by the community are a standard of care. Unfortunately, we don't often keep meticulous records about what standard of care is, which may lead to many arguments about it in an ex post facto sort of way," Drazen says.

Suggestions for IRBs

Elisa Hurley, MD, education director at Public Responsibility in Medicine & Research (PRIM&R) outlined six questions that PRIM&R recommended IRBs ask when considering protocols and informed consent involving randomized trials:

• Have the investigators established that the medical interventions being compared are within the accepted standard of care and that doubt exists regarding their relative effectiveness?

• How will potential subjects be informed of the risks, benefits, and potential harms of the interventions?

• How will potential subjects be informed that they are being asked to participate in a study comparing two interventions and that if they don't wish to participate, they will instead receive standard of care? "The key for us in the IRB should be to ensure that the investigator has set forth how subjects come to understand that they have this choice as regards the specific intervention being studied, between remaining in a therapeutic doctor-patient relationship and entering an investigator-subject relationship, in which case their physician won't routinely be making personalized clinical decisions about the use of interventions in their study," Hurley said.

• How will potential subjects be informed of any available alternatives to the interventions being offered in the study?

• What burdens and potential harms — beyond those inherent in the interventions being compared — are added by participation in the study?

• How will potential subjects be informed of any additional risks? "The IRB must determine whether investigators have thoroughly examined and identified the burdens and potential harm to potential subjects that are added by participation in this study, over and above the risks of receiving either intervention being compared, and that they have developed an adequate description of added risks for the informed consent process," Hurley said.

David Forster, JD, MA, CIP, vice president of compliance at WIRB-Copernicus Group, had this suggestion: "What I would like to propose is that there be guidance from the agencies that is consistent in how we classify and assess risks and benefits of research, all research, and how risks and benefits are presented to subjects in the consent form. But in evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research."

Drazen suggested convening a central IRB that could approve study design, define research questions, and define clinical equilibrium. "I think that there should be an IRB convened specifically with expertise to look at the question that is being asked. And once they have read and said yes, clinical equipoise exists and the method that you're using to address that question doesn't contain excess risk for the people in the population, it is well laid out."

There is no set timetable on when to expect new OHRP guidance. Sorting through the key issues and developing new guidance will not happen overnight, said **Wanda K. Jones**, DrPH, Principal

Deputy Assistant Secretary for Health, U.S. Department of Health and Human Services (HHS).

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Achieving accreditation through tough times

Seek help early and often

Every human subjects research protection program seeking accreditation expects the road to be long and difficult. Just add a few more years and unforeseen obstacles, and the experience might parallel what WellSpan Health in York, PA, dealt with before receiving an accreditation plaque in July 2013.

"We started the process seven years ago, and there have been many challenges in those seven years," says **Melissa Schlenker**, MS, CCRC, CIP, the IRB and clinical trials manager at WellSpan Health.

WellSpan Health's leaders decided to pursue accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) so the organization would be more attractive to pharmaceutical and device sponsors of clinical trials, she says.

"It would show our local community that we had their best interest in mind, and it would help us standardize our programs," Schlenker says.

Achieving these goals was not easy.

The IRB office's leadership changed twice; the organization downsized its overall staffing from 10 employees to four and its IRB staffing from four to two positions. The organization changed the office structure to merge quality improvement with the IRB office, which now is the population health management and research office, Schlenker says.

Despite having a smaller staff, the office had to create new standard operating procedures (SOPs), develop numerous tools including checklists, and prepare staff for accreditation survey interviews. Then two weeks before the survey was scheduled, Schlenker broke her ankle and was forced to remain homebound for three months.

The accident occurred right before the IRB office was going to hold mock accreditation interviews, notes **Tara Moore,** quality assurance (QA) specialist at WellSpan Health.

"AAHRPP had provided us with a list of people they would like to interview, including IRB members, researchers, research staff, and leadership," Moore says. "We had scheduled the mock interview for right before the site visit of Feb. 15. Then Melissa fell and broke her ankle the Monday before the mock interviews were going to start."

With help from others at WellSpan, Moore went ahead with the mock interviews.

"We work closely with research managers in other departments," Schlenker says. "And everyone rallied and said, 'Whatever you need to make it happen, we'll help.' Everyone understands the importance of accreditation, and they felt they were invested in our achieving accreditation."

Schlenker and Moore provide these descriptions of their institution's accreditation process, including how obstacles were overcome:

• **Improving SOPs.** When they started the accreditation process, the human subjects protection program had five standard operating procedures (SOPs). When they were done about five years later, there were 45 SOPs, Schlenker and Moore say.

The original SOPs were all-encompassing and general policies tied closely to federal regulations. These were enhanced and made more useful with definitions of words, references to regulations, and references to AAHRPP standards. The idea was to provide context, answering any questions about why a particular policy or procedure was necessary, Schlenker explains.

They reviewed SOPs other institutions were willing to share and adapted what would work and meet their own SOP goals.

"We sometimes pull out our policies and procedures to see if we're doing something right because rules and practices change over time," Schlenker says. "The SOPs need to stay current with changing regulations."

A core group reviewed the SOPs, providing feedback. Also, the IRB had access to a medical writer who reviewed the work for clarity and grammar, she adds.

• **Work with AAHRPP early on.** "At some point in your preparation you have to contact AAHRPP and tell them you're getting ready to submit an application," Schlenker says.

Schlenker and Moore took advantage of AAHRPP's consultation services and advice in the many months leading up to their scheduling a site visit.

"They read our SOPs and gave us critical feedback

that was helpful in making sure we met AAHRPP's expectations for that standard," Schlenker notes. "As time got closer to finalizing the application, I had more direct communication with them."

As the submission date drew near, Schlenker asked AAHRPP consultants to review all of the SOPs and checklists.

"I'd encourage people to take advantage of the access they have to an accreditation director because the information is quite helpful," she adds. "I would have reached out to AAHRPP a lot sooner, in hindsight."

• **Find outside help and resources.** Moore sought help from other institutions through the IRB Forum website.

"I asked if they would be willing to share tools and checklists, and then I'd adapt them to our needs and ask our biggest customers if these would work for them," Moore says.

"Just reach out to people and ask for information and guidance from others," Schlenker says. "People shouldn't be afraid to look to colleagues at other institutions for help."

Plus, there are resources available on AAHRPP's website, and AAHRPP staff are very friendly and accommodating, Schlenker says.

"They want to see you succeed, so don't be afraid to ask for help," she adds.

• **Use the self-assessment tool.** AAHRPP provides a self-assessment tool that institutions can use once they have revised SOPs and developed checklists and other tools, Schlenker notes.

"You take this self-evaluation form and go through it step by step, writing down SOPs and reference and where you address a specific standard, and that was very helpful," she adds. "It took us two days to go through all of our documents, and at the end we knew where we had holes in our policies and procedures."

With this information, they were able to add information to the SOPs or develop another checklist or reporting form, Schlenker adds.

Although Schlenker and Moore did not think to use the self-assessment tool early in the process, they say they now wish they had. "In hindsight, when we started writing SOPs, we should have referred to that self-assessment tool much sooner," Schlenker says. "We could have used the self-assessment tool to drive the writing of the SOPs."

The self-assessment tool explains the AAHRPP standards and the expectation for each standard.

"If we could have started with that as a reference, it probably would have made it easier to focus our SOPs and saved us a lot of time," Schlenker says.

• **Conduct mock interviews.** "I was given the list of possible questions that could be asked, including questions specifically to the institution officials, specific to research staff, and specific to IRB members," Moore says.

Moore gave the people who would be interviewed by accreditation surveyors an idea of what they would be asked, and then she reviewed answers and important information with them. As part of mock interviews, she asked them questions pertaining to their role at the institution.

"If they didn't know the answer, they would ask for help," she says. "I would help guide them."

Moore also advised staff and others who would be interviewed to be honest with the surveyor about any issues they had with the IRB.

"I told them if they don't feel comfortable telling me anything, then they can take it to that official," Moore says. "And they did: One of the suggestions from the surveyor's interview with researchers caused a change in our policy."

WellSpan Health has two IRBs, one that specializes in cancer studies and one for medical-surgical studies, she notes.

"Historically, that's how it's been," Moore says. "Occasionally there has been a need or request to have a cancer study reviewed by the med-surg board and vice-versa."

But investigators told AAHRPP officials that they would like to go to any IRB at any time, Moore says.

So the institution made a policy change in July 2013 that permits any study to be submitted to either IRB. While the two IRBs still specialize, there can be a consultant available to assist if they review a study outside of their specialty area, she adds.

• **Make lemonade out of problems that arise.** Several obstacles arose as the IRB office prepared for accreditation. Research directors and other staff came and went. The office was downsized even as the workload, because of accreditation preparation, increased.

Then Schlenker, who had been preparing for accreditation for several years, broke her ankle and had surgery two weeks before the scheduled site visit.

"I was out of the office for three months, but was available by telephone, and I spoke with site visitors over the phone," Schlenker says. "I worked four hours a day from home; I made the changes AAHRPP requested while I was on medical leave, so we met their deadline."

Soon after Schlenker returned to the office in May 2013, AAHRPP reviewed the application. By the end of June, WellSpan Health received word that it had achieved full accreditation.

"They requested that we monitor or audit some of the changes we had made as a result of the site visits," Schlenker says. "We need to follow-up on those items for seven months, doing some audits, and writing reports." ■

BEST PRACTICES SPOTLIGHT

IRB expert strategies for improving PI–IRB relations

Empathic responses build trust

IRBs should ask themselves: Are we gatekeepers? Or are we collaborators, navigators, and concierges?

Their answer partly depends on how investigators and research staff view the IRB's role and actions. And it depends on trust.

"Those of us with a lot of experience trying to run day-to-day operations for IRBs might think of our IRBs as a bureaucratic part of the university, and some IRB staff might think of themselves as gatekeepers," says **Suzanne M. Rivera**, PhD, MSW, assistant professor of bioethics and associate vice president for research at Case Western Reserve University in Cleveland.

However, it could be a mistake for an IRB to let investigators and others in the research community define the IRB in this way, she notes.

The status quo creates a revolving door relationship between the IRB and researchers, and it results in distrust, creating campus lore about how slowly the IRB handles protocols, Rivera explains.

"One bad experience with the IRB breeds a lifetime of distrust," she says.

"If we're interested in improving the way IRBs and investigators work together then it's important to think about how we all want the same thing — to promote high quality, professional research," Rivera says.

IRBs can do this by having empathy for the challenges researchers face. One strategy is to offer investigators alternative routes to achieving their goals when their initial proposals have problems, she adds.

"This creates a chain of events where investigators experience staff as navigators," Rivera says. "Investigators begin to see IRB staff as trained professionals with regulatory knowledge and helpful problem-solving skills, and so they trust IRB staff."

When IRB offices work collaboratively with researchers, the research community begins to see the IRB as adding value to its work and contributing in a way that makes projects more efficient and the process smoother, she adds.

Rivera, who has given many national talks on this subject, advises IRB staff to see themselves as assistants and not an obstacle to research. And she tells principal investigators about the pressures IRBs are under.

"I try to address both sides of the equation," Rivera says. "I want investigators to see IRB staff as professionals with a wealth of knowledge to offer, and I want the IRB staff to see that they can play a really important role in helping research get done."

The goal is to improve the often adversarial relationship between IRBs and investigators.

Here are some of Rivera's tips on how IRBs can improve their image in the research community:

• **Remind folks they are on the same team.** This strategy will help in one's workplace, as well as one's personal life, Rivera notes.

"If we're having an argument or disagreement, it's helpful to remind each other that we're all on the same team," she says. "Reframe it; it's not me against you. We all want the same thing, so reminding everyone of that can be very helpful."

IRBs can promote a team atmosphere by inviting investigators to talk with them about what works and doesn't work in the IRB office, Rivera suggests.

"Create a sounding board and invite investigators to speak with the committee," she says.

"When an investigator is taking a particularly adversarial stand to the IRB, I approach him and ask if he'd consider being a member," she says. "Some of his animosity is coming from a lack of knowing."

Having former opponents serve on the IRB can turn staunch critics into passionate advocates once they have an opportunity to serve and see how everyone can work together, Rivera notes.

Occasionally a conflict between IRB staff and an investigator can escalate, and this is when research program leadership or an IRB chair might step in to bring about a resolution.

"By meeting with the investigator, listening actively and with an open mind, I've been able to offer a third-path solution that meets the

investigator's needs and doesn't cause IRB staff to break rules or compromise a principle," Rivera says. "IRB staff is overworked and under-resourced, and sometimes there isn't time to take a moment to think creatively about an alternative solution because people are trying to keep their heads above water."

• **Don't take it personally.** "Don't take it personally because if we take it personally whenever someone is getting difficult with us, it's easy to get burned out on this job," Rivera says. "It could be you're the fifth person they've called, so remind yourself that everything is not about you; the person could be having a bad day for a hundred different reasons."

Occasionally, someone will criticize, complain, or even yell at an IRB staff professional. It happens, and IRB staff should learn how to handle these conflicts without taking them personally.

"What is essential is to be professional; professionalism is mandatory at all times," Rivera says. "Use professional, accurate and timely goals for providing service."

If an IRB client is abusive, the office leadership should put an end to it.

"It's not appropriate to be abused, so if anyone is screaming at the staff, using foul language, or threatening to have them fired, then it's not okay," Rivera says.

The key is to prevent unnecessary conflict by being respectful and making sure that whatever the IRB is requiring is logical and makes sense, she notes.

An IRB that reviews its website and looks for ways to make its requirements clear and easy to navigate can help reduce unnecessary acrimony and frustration among researchers and other clients, she adds.

"You should have a very clear and easy-to-navigate website that includes all of the steps for an IRB application," Rivera says. "And hold office hours once a week where principal investigators can bring in draft protocols and get assistance with them before entering them in the online review system."

• **Choose your words carefully.** IRB staff need to maintain a calm, dispassionate demeanor when explaining an IRB's actions, Rivera says.

"Avoid a power struggle and don't be hostile," she says. "Don't let your own emotions escalate."

Also, IRB professionals delivering bad news

Emails are OK, except when written casually

Take a professional approach

IRB staff should learn how to write professional emails, which mirror hard copy letters of previous generations, an expert advises.

"I've actually put together a cheat sheet for my staff about email principles," says **Suzanne M. Rivera**, PhD, MSW, assistant professor of bioethics and associate vice president for research at Case Western Reserve University in Cleveland.

Rivera counsels her IRB staff to use emails sparingly when communicating with researchers. For instance, if a face-to-face meeting or phone call would be a better way to resolve a problem, then take the time for these.

"Emails can be a good thing, but if it takes three or four times back and forth to be understood then you really should get out of the chair and go see the person," she says.

Here are Rivera's email tips:

• Never send an email when you are angry. Save as a draft and look again in a few hours (or the next day).

• Treat your emails like a postcard — assume anyone might read them.

• Avoid sarcasm and humor when conveying important information. Email is not a good medium for joking.

• Put yourself in the other person's shoes.

• When in doubt, remember the "Golden Rule."

Also, here is a list of email errors to avoid:

• lack of a proper salutation;

• lack of a "kiss" [keep it simple stupid] introduction sentence;

• imprecise use of language/confusing prose;

• incorrect grammar, punctuation;

• overly familiar tone;

• "yelling" your message (ALL CAPS);

• sloppy forwards;

• disrespectful use of quotation marks;

• lack of a "kiss" concluding sentence;

• spelling errors;

• sloppy copies;

• unhelpful subject lines;

• using email when face-to-face or phone contact would be better. ■

should reframe the news in terms of what is possible, she suggests.

Instead of sending out a quick email saying the request is denied, IRBs should speak with investigators face-to-face and offer suggestions for what might work, Rivera says.

"Be constructive and helpful rather than [just] sending an email," she says.

This approach especially applies to emails and any communication that is not face-to-face, she adds. *(See tips on writing professional emails, page 115.)*

"A lot of IRBs do their work by email, and it's a tricky medium," Rivera says. "People use it more informally than a business letter."

Rivera suggests IRB staff treat an email as they would a typewritten letter by always using a salutation, making sure it's accurate, and by avoiding sarcasm or humor, which can be misunderstood too easily.

• **Be clear about expectations.** IRBs can facilitate positive behavior by setting clear, logical rules prospectively, Rivera says.

"How can people know your expectations unless you've laid them out?" she says. "So avoid taking capricious actions or using what seems like a good idea at the time approach."

Investigators need to have a confident sense of who the IRB is and how it would respond to a particular modification or request, she notes.

So IRBs should avoid inconsistency, which results in investigators thinking that one time they brought the IRB a modification that was approved, and then the next time a similar situation was denied.

"Maybe there's a good reason for the different answers, but the way to head off these concerns is to set clear, logical rules up front and be transparent about them by having them on the website," Rivera says.

"Anticipate and minimize obstacles to compliance," she suggests.

For example, if an IRB knows its clients work between 9 a.m. and 5 p.m., then it would be helpful to make the IRB deadline between 5:30 p.m. and 6 p.m., giving them a little time to make it to the IRB office to drop off anything, she says.

"Or in case they are kicked off the online review system, have a drop box available," Rivera adds. "Maybe you could send a courier over to the satellite office so they don't have to come to the main campus to drop off materials."

The key is to anticipate obstacles and minimize them.

"This reduces criticism that you are throwing up obstacles, and you are showing that you are making it easy as possible to color within the lines," Rivera explains. "Researchers will feel invested in the process, and it will make more sense to them." ■

Improve IC process by taking a subject's view

Subject advocate offers advice

IRBs and researchers could improve the informed consent (IC) process by looking at research participants from a different perspective, an expert says.

Research participants are part of a community that might view research distrustfully or who may not understand the benefits of research to society or know enough about their own rights in a study, says **Corey Zolondek**, PhD, research subject advocate at Wayne State University in Detroit.

"We need to make informed consent as understandable as possible and make sure the forms are written in a way that covers all of the regulations, but also be relatable and understandable to participants in research," Zolondek says.

Research participants should be fully informed about their legal rights, and all risks and benefits need to be clearly disclosed and explained, he adds.

And this process begins with recruitment.

Zolondek was involved with a panel of former research participants who said there were right and wrong ways of being asked to participate in a study.

For instance, one former participant discussed how the physician who presented the study did not make it clear whether interventions being discussed were standard of care or research, he recalls.

"So she went into the study and came to understand through the consent process that it was research, but during the recruitment it should have been clear that it was a research project," Zolondek adds.

"During the recruitment process, a study should be explained well enough that someone knows whether or not she wants to go to the next step of signing up for a study," he says. "Any recruitment materials, be it an advertisement or

telephone recruitment, should present enough information to potential participants."

Zolondek's role at Wayne State University is to handle questions and concerns participants might have about a study, especially when they involve confidentiality or privacy and the informed consent process, he says.

"Also, I discuss why research is important," he adds. "Being a person with a scientific background, I do understand that participating in research leads to significant benefits."

These types of concepts should be covered in the informed consent process, but among some populations it may be difficult to communicate without the help of someone who knows that community well, he notes.

"Especially in Detroit with a large minority population, there's a lot of distrust of research and it's difficult to communicate how it can have a benefit to the community," Zolondek says.

When holding a seminar on how to improve informed consent in a community, a researcher told Zolondek about a study where the consent process involved very little discussion between the person giving the consent and the participants. The study involved a medical intervention, and the principal investigator was concerned that participants were not presented information adequately, he says.

"They wanted better ways to present information to participants, so I suggested they take the technical language and find simpler ways of explaining it during the consent process," Zolondek says.

The informed consent form explained everything well with definitions in parentheses, but the people administering IC were not as knowledgeable about the study as they should have been, he adds.

"I suggested that they train individuals giving consent to participants until they understood the study well and could explain it without having to reference the consent form," he says. "The consenters should be knowledgeable enough to address any of the participants' questions."

One concern that participants might have is what will happen if the person is injured.

"Who pays if an injury occurs?" Zolondek says. "This should be clear."

The informed consent process should make it clear who will pay for medical treatment in the case of an injury.

"A lot of studies have standard of care elements related to the study, and participants are expected to have insurance cover that aspect," Zolondek says. "Going into a study it may not be clear what the participant will pay versus what researchers or sponsors pay."

When researchers and IRBs review informed consent forms and the IC process, they might ask themselves what they would want to know more about if they were the ones participating in the study. If they present information clearly and accurately, there will be fewer opportunities for participants to misunderstand a concept, such as standard of care versus a treatment intervention strictly for research or what it means if the patient withdraws from the study, Zolondek notes.

For example, in some studies the participant might not be permitted to stop taking the intervention medication overnight because of health problems if the medication is not dosed down. This kind of information should be presented to participants during the IC process, Zolondek says.

"Present information to participants even if they do not have direct questions about it," he adds. ■

Citizen science: a new frontier for IRB review

How IRBs can approach citizen science studies

While private companies that conduct human subject research do not fall within the definition of regulated research, the decision whether to entirely forgo approval is not always clear. Though some "citizen science" research can be as simple as gathering data from surveys, some can involve a person's self-reported health data — and can raise concern in the research world.

Citizen science is the concept of conducing scientific research, usually by amateur or nonprofessional scientists, by way of crowdsourcing. Though not a new concept, it has gained some public interest in recent months, particularly in the research and IRB worlds through start-up company uBiome. The California company created a crowdfunding program to raise money to develop kits to sample a person's microbiome to learn more about the "good" and "bad" bacteria in the person's body and how it correlates with the microbiomes of other contributors. For a fee, a person can

pre-order a kit, take a swab from his or her gut, mouth, nose, genitals, or skin, and send the sample back to uBiome for analysis and correlation.

Controversy arose among the research ethics community about the project: While uBiome is not required to seek IRB approval, does the company have a moral obligation to gain IRB approval, since health-related human subject research will be conducted? Are consent forms thorough, understandable and reviewed? How will participants' biological information be used — and how will it be kept private?

"There were a series of questions [about the project], but the primary question is one I would take as a derivative of the therapeutic misconception issue — when does a person go from being a client to being a subject?" says **Erica Heath**, director, regulatory affairs, Ethical & Independent Review Services, the IRB that approved the uBiome study. "Where is the differentiation, if there is one? This crowdsourcing for funding is a new idea in research, and it seemed to be nowhere close to as crisp as you might get in medicine."

"We wanted to do this in a way that is thoughtful, and take good care of our participants," says **Jessica Richman**, CEO of uBiome. "We're all from academic backgrounds and we wanted to get approval. We want to do this ethically, but what is practically, morally, and structurally the right way to do this?"

Richman says they spoke to a few different IRBs before finding one to work with them and "hold our hand" through the approval process. "It was a little hard to find someone to work with us," she says. "They've never seen this situation before and didn't know how to approach it."

Defining research

When the uBiome team first met with Heath and E&I Review for IRB consultations, Heath helped them outline what the research is and what they are trying to accomplish, and the obligations that come with the research, elements of consent forms, and the consent process. "It's that way with everybody who is a novice, and we get novices a lot," Heath says. "It's a teaching and learning environment. How do you write something simple and understandable? It goes back to defining what the research is — the research will define consent."

Heath began with the decision tree charts from the Office of Human Research Protections (OHRP), taking Richman and the uBiome team step by step through the decision tree to determine whether the project is research involving human subjects, if any exemptions apply to the research, any privacy and consent form issues, and if expedited review applies. "With each of those came more duties," Heath says. "The first issue we talked about a lot was research and what it was they would be doing. Once we get beyond that, what are the obligations that come along with doing research? We went over the consent process and the elements of consent and how to get them across formats. Defining the research went a long way toward creating what she [Richman] sent to the board," Heath says.

Client vs. participant

The next issue, Heath says, is to identify what a participant will get out of the study once he or she becomes a research subject as opposed to being a client. "It's unlike an investigational drug, where you get that drug," she says. "What are you getting here, and what are the risks of transition [from client to subject]? If you're just getting your own report back, that's one thing. If this is a long association study and can be compared to association studies, there are risks of incidental findings and such."

E&I Review Services was very focused on potential social and psychological risks of the uBiome project, Richman says. Those risks include subjects finding out a result about themselves they wouldn't like; subjects getting a result they may not like but isn't a health risk; or other people finding out something about the subject. There was not much concern about physical risks, she says. "The test is not diagnostic; we can't tell you whether you have a disease," Richman explains. "The main concerns were mostly risks involving information."

There is also a question, Heath says, of reliability of the data associations, and whether there will be enough data to make the study statistically meaningful. "When you start with no data points and you have participants wanting information to interpret their personal results, when is the data enough to be meaningful? This is a statistical question that bedevils scientists."

One of the concerns with the uBiome project is the fee involved, as research subjects typically do not pay to take part in a study. "It's pretty rare, though not unheard of, to have subjects pay for study participation," Heath says. She cites costs of smoking cessation plans, though participants earn money back through completion. "The next issue was, once a client becomes a subject, what is it they are getting out of the study by being a subject as opposed to being a client?" For example, a subject in a pharmaceutical or therapeutic study receives the experimental drug or control treatment. "Part of the distinction between client and subject was when you make that distinction, you can see what the difference is," Heath says.

Privacy concerns also topped the list. Richman says uBiome focused on privacy from the beginning, and participants can opt out of the data correlation if they desire. "No one else knows your data," she says. "You can have it correlate with other people in the dataset anonymously if you want, and you can opt in to the research study with the IRB." The data correlation will be done by uBiome.

"In any genetic study or association study, you have to look at it in two ways — what is private about it and what harm the data could do, and how is it being protected," Heath says. "Both of those aspects are looked at. What's there and how harmful is it, or could it be? How is it being protected?"

How IRBs can approach

As these types of crowdfunded citizen science studies are relatively new, IRBs may have questions on how to proceed if approached for review. Currently, IRBs have little to no experience with citizen scientists, Heath says. "The citizen scientist job descriptions range from data gatherers to amateur investigators. uBiome was asked to define and separate their more rigorous studies from these amateur studies over which control was not yet defined," she says. "This could well be an IRB topic for the next decade."

To begin looking at the review process, "I would hope any IRB would start off with definitions and work through what it is they [the researchers] are doing, what's generalizable about it, how it becomes research, who the subjects are, and what they're doing," Heath says. "Then you can work through the determinations and consent issues. This is generally a good approach. Again, with different clients you'll find stopping points at different places, but the approach is a failsafe."

"We [IRBs] have been through all kinds of new things. We've seen genetics research, stem cell research, genome sequencing," Heath says. "This is another new thing on the horizon. It's fun to watch. That's what IRBs are all about — if these were all easy, we wouldn't need IRBs." ■

CNE/CME OBJECTIVES & INSTRUCTIONS

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 continuing education program and earn credit for this activity by following these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

COMING IN FUTURE MONTHS

- Organization expands international research on a shoestring budget
- Navigation tips when downsizing IRB
- Best practices in handling IC in international studies revealed
- Research program ups efficiency by consolidating

CNE/CME QUESTIONS

1. Which of the following was not an OHRP determination from the Support study?
   A. Consent forms did not fully describe reasonably foreseeable risks
   B. Study design violated federal regulations
   C. Corrective action was required
   D. None of the above

2. When an organization seeks accreditation through the Association for the Accreditation of Human Research Protection Programs (AAHRPP), it's a good idea to take which of the following steps in preparation?
   A. Contact AAHRPP early to seek consultation and advice
   B. Improve institution's tools and resources by asking for help from outside organizations
   C. Use AAHRPP's self-assessment tool to provide great focus on one's standard operating procedures (SOPs) and improvements
   D. All of the above

3. According to an expert on improving IRB and investigator relations, the following is a list of email mistakes. Which of these is not a mistake?
   A. Lack of a proper salutation
   B. Incorrect grammar, punctuation
   C. Treating emails like a postcard
   D. Using all caps

4. Which of the following should be explained clearly and simply to research participants during the informed consent process?
   A. Technical language should be simplified and defined
   B. Explain who pays if person is injured
   C. Make it clear how standard of care and the study intervention are different and which is which
   D. All of the above