IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

June 2013: Vol. 13, No. 6
Pages 61-72

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Consent form specialists assist investigators and board members

IC template also ensures compliance

Experts say IRBs spend much of their time discussing informed consent issues and nuances, and yet this is the area cited most often in recent regulatory letters sent to research institutions.

The Office for Human Research Protections (OHRP) of Rockville, MD, for example, has noted instances of risk and alternatives to a study's intervention being omitted or inadequately described in OHRP's recent letters of determination. These findings were sent to some of the largest research institutions in the country. *(See story on recent OHRP compliance letters, page 63.)*

So if even large institutions can run into noncompliance trouble, what types of practices might prevent an OHRP finding?

One possibility is to have experienced IRB staff, called consent form specialists, help investigators and IRB members with all informed consent issues.

Johns Hopkins University School of Medicine in Baltimore has three

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consent form specialists who each work with two IRBs, and a consent form manager. The institution has used this model for more than a decade, and it's worked well — helping to keep the institution compliant with informed consent regulatory requirements, says **Judith Carrithers**, JD, MPA, assistant dean for human research protection and the director of the human research protection program at Johns Hopkins University School of Medicine.

"If a specialist notices there are risks in the protocol that are different from those in the consent form, then they advise the board of these differences," Carrithers says.

"Our IRB chairs would say having the specialists was the single best change we ever made," she adds. "They are very helpful in smoothing the process out."

Consent form specialists also help investigators reformat their consent form language and use simpler words, trying to reduce the reading level to an average of around eighth grade, she notes.

The three consent specialists rotate to working with different IRBs every six months so they become accustomed to working with all of the boards, says **Victoria Hadhazy**, MA, CIP, consent form manager in the human research protection program at Johns Hopkins University School of Medicine.

"We attend board meetings, which last two to four hours, depending on the agenda, and we are there to ask and answer questions," Hadhazy says.

After IRB meetings, consent specialists spend up to two hours doing post-meeting work and additional documentation, she says.

"Our schedule is heavy and we're all good at time management," she says.

Hadhazy and the consent form specialists have significant research experience, including expertise in writing informed consent forms.

"We have two consent form specialists with master-level degrees, and a third with a European law degree," Hadhazy says. "We all work in the exact same way with a private drive on our computers where all consent forms are kept."

The specialists work interchangeably and determine by file name who has worked on a particular consent document, she adds.

Consent form specialists help the IRBs focus when discussing consent issues, and they bring disparities to their attention, Carrithers says.

"They confirm whether all of the required elements of informed consent are included," she adds.

The consent form specialists provide a structural review, ensuring the online application and consent form are consistent, Hadhazy says.

"We look at the document and put in our standard wording where needed and try to bring down the reading level," she explains. "We sometimes move text around to make sure the most serious risks are the first ones listed, leaving the more minor risks at the bottom of the section."

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

POSTMASTER: Send address changes to IRB Advisor, P.O. Box 105109, Atlanta, GA 30348.

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Editorial Questions

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The specialists also check the protocol to make sure that alternatives to the study intervention mentioned in the protocol are also mentioned in the consent form. The IRBs' scientific experts also check to make sure alternatives are listed, she adds.

"For every new application, we complete an elements review," Hadhazy says. "It's actually part of the electronic application now, and the consent form specialist fills it out for each consent form."

The consent form specialists list which essential elements and which additional elements are included in the consent form, and they point out if there's an additional element that is protocol-specific that should be listed but is not, she notes.

"Our consent form template, which investigators follow, is in a question-and-answer format, so when they are drafting their consent form all elements are available in that template," Hadhazy says.

The template is generally revised annually, and it has proven very helpful to researchers and the IRBs, Carrithers says.

The IRB office also provides investigators with a checklist that will help them prepare the consent form. The checklist refers directly to the eight required informed consent elements under 45 CFR 46.116 and the seven additional elements. It asks whether 18 items pertaining to the regulations are included on the consent form and whether an additional nine items related to additional elements of information be included when appropriate.

Here are some sample items from the informed consent checklist:

- a statement that the study involves research;
- a description of the reasonably foreseeable risks or discomforts to the participant;
- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;
- a statement that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled;
- a statement that the particular treatment or procedure may involve risks to the participant which are currently unforeseeable;
- anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent;
- and a statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant. ■

OHRP letters focus on informed consent issues

Thorough risk descriptions needed

The University of Alabama at Birmingham (UAB) was the most recent in a small list of institutions that received letters of determination from the Office for Human Research Protections (OHRP) of Rockville, MD, about allegations of noncompliance. UAB's letter was about the SUPPORT study, which randomized premature infants to lower or higher ranges of oxygen levels, and was conducted between 2004 and 2009.

OHRP's March 7, 2013, letter to **Richard B. Marchase**, PhD, vice president for research and economic development at UAB, states, "Based on the consent form template and UAB consent forms, we determine that the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death. (As discussed at the end of this letter, participating in the study did have an effect on which infants died, and on which developed blindness.)"

UAB's media office declined to comment on the letter and study because of pending litigation, but referred *IRB Advisor* to several letters and editorials, including a *New England Journal of Medicine* editorial that states, "Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice."[1]

OHRP's top priority is protecting human subjects in research studies, says **Ann M. Bradley**, press officer, in the Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services.

"OHRP is currently reviewing UAB's response to its determination letter and will provide further comment when it's appropriate to do so," Bradley says.

Another *NEJM* editorial, by David Magnus, PhD, and Arthur L. Caplan, PhD, said the

UAB trial is an example of how comparative effectiveness research can dramatically improve patient care while reducing costs. Prior to the UAB study of oxygen-saturation levels used in very premature infants, the standard of care varied, they write.[2]

The issues raised by OHRP with the study involve both the study's risk and the informed consent. SUPPORT investigators believed there was no additional risk to enrolling in the study since the infants would receive levels of oxygen equal to the prevailing standard of care, Magnus and Caplan write.

"Before the study began, there was insufficient evidence to know what oxygen level within the guideline-specified range was best," they say. "The first problem with the OHRP letter and a good deal of the public outrage that followed is the confusion of the risks of the clinical treatment with the risks of randomization."

The study's non-randomized case-control group fared worse than patients enrolled in the study, which would seem to negate the OHRP's claim that infants enrolled in the study were exposed to greater risk, Magnus and Caplan argue.

Because of these facts, OHRP is mistaken in its assumption that there is increased risk to being enrolled in the trial and, therefore, the investigators did not provide adequate informed consent about that risk, they say.

This kind of faulty logic "poses substantial risk to the conduct of valuable comparative effectiveness research," the writers conclude.

Additional examples

A review of recent OHRP letters of determination shows additional examples of allegations involving informed consent, risk, and communication of alternatives to research interventions. These include a letter to an Indian hospital in October 2012, in which OHRP alleges in its determination that "subjects were not adequately informed of the alternative procedures or courses of treatment regarding screening for breast cancer or cervical cancer," and that "subjects were not provided, in writing, with information about the possible alternative of seeking breast or cervical screening outside of the research, as required by HHS regulations at 45 CFR 46.116(a)(4)."

Two letters to U.S. universities, both dated in November 2012, discussed determinations involving inadequate informed consent. One allegation found that the informed consent failed to provide "a description of any reasonably foreseeable risks and discomforts," and the other letter alleged that the informed consent did not adequately disclose appropriate alternative procedures or courses of treatment that might be advantageous to the subject.

"Specifically, we noted that the informed consent documents of numerous protocols did not include appropriate information regarding the option of obtaining the research intervention outside of the research," OHRP says in the determination letter.

In each of these cases, OHRP noted the institution's cooperation with following corrective actions, but to IRB professionals the big question would be how to avoid noncompliance and prevent their institution from being on the receiving end of an OHRP letter of determination.

"Regardless of the amount and type of risk to their research participants, all research team members have a duty to make sure everyone they approach to enroll understands what is involved when they choose to be part of the study," says **Megan A. Foradori**, RN, MSN, contractor with Henry M. Jackson Foundation for the Advancement of Military Medicine and research agenda project consultant for the TriService Nursing Research Program in Pittsburgh.

While Foradori says she is unable to comment on specifics of the OHRP letters of determination, she notes that IRBs should look favorably on research teams who can demonstrate that they have gone to great lengths to appropriately explain all factors related to participation.

For instance, in a low-risk study of kidney donor candidates' decision-making preferences, research nurses who enrolled patients provided a visual aid during informed consent, Foradori explains.

"It's a schematic of the arms of the study, what was involved at each step for the participant, and the information we would be collecting throughout," she says. "This not only demonstrated to the participants that we took extra steps to ensure their comprehension, but I believe it also exhibited to our IRB that each participant had a clear understanding of

the study protocol, our expectations, and their rights before they enrolled."

While any research organization that receives an OHRP letter of determination will work hard to answer the allegations and make any corrective actions necessary, this scenario is far from ideal. The best case would be to have policies, procedures, and practices in place that prevent that letter from being sent in the first place. IRBs can assist with this through best practice models, such as using protocol templates that guide investigators through informed consent forms, following regulatory requirements, and from having informed consent experts assist IRBs and investigators with creating and improving the documents.

"OHRP and others concerned with human subjects protections have long urged investigators and institutional review boards to simplify consent forms to focus on essential elements, namely, a description of the study purpose and procedures, the risks and benefits of study participation, and alternatives to research participation, that are required for an enlightened decision about whether to participate," Bradley says. "The Advanced Notice of Proposed Rulemaking now progressing through HHS would revise the regulations to provide greater specificity about how consent forms should be written and what information they should contain," Bradley adds. "The goal would be consent forms that are shorter, more readily understood, and less confusing, that contain all key information, and that can serve as an excellent aid to help someone make a good decision about whether to participate in a study."

Ensuring clearer, simpler informed consent documents is part of the IRB's role, Foradori notes.

"IRBs, I believe, should take a critical look at the information being provided to potential research participants in submitted protocols," Foradori says. "And, if there is any indication that there may be room for knowledge gaps, they should require that teams utilize additional tools/methods to clarify the research protocol and resubmit. "

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Community research requires compromise

Michigan BioTrust provides model

IRBs increasingly will have to adjust to collaborative approaches in research, including working with community partners and other stakeholders, experts say.

Biotechnology and its many privacy and confidentiality challenges have made community-based participatory research (CBPR) an important option for facilitating research strategies that stakeholders can trust.

For instance, the state of Michigan established the Michigan BioTrust for Health as a repository for the dried blood samples collected at newborn screenings. These samples are de-identified, labeled with a code and stored at the Michigan Neonatal Biobank for research. Before the samples could be used for research, it was necessary to establish guidelines and protocols.

The Michigan Department of Community Health (MDCH) IRB that was involved with the project felt strongly that obtaining informed consent from the newborns' families was the right thing to do, says **Harry McGee**, MPH, IRB chair at Michigan State University in East Lansing.

"It boiled down to in my own mind that you couldn't assume a parent would be OK with the government using their DNA for research," McGee explains. "IRB members felt the community, which is the entire state of Michigan, should have a voice in what was being done and could be done."

The MDCH already had five nonaffiliated members on its IRB, but the board decided additional community representation was needed. So they helped to form a 15-member community advisory board representing religious, community, and special interest groups.

"We felt risks to groups or communities should also be a consideration, so we sought the advice of that community board on issues that would not necessarily be a risk to an individual subject, but would be a more general risk to the community," McGee says.

"Blood was collected for screening, not for research, and the whole issue was whether or

not there should be a consent process if you're using that for research," McGee says. "The IRB felt strongly that even if consent was not required by the regulations that it was the right thing to do."

As the BioTrust was created, the IRB and community advisory board were intimately involved in making decisions about informed consent and other issues, he recalls.

"One of the important considerations involving the community advisory board is whether the research is in the interest of the population of Michigan," McGee says. "If it's going to be used for research it has to meet some potential benefit for the citizens of the state or groups within the state."

The Michigan BioTrust's consent policies are clearly outlined on its website at www.michigan.gov/mdch. *(See story on Michigan BioTrust's consent policy, below.)*

While collaborations between IRBs and community boards can result in fair decisions that consider the public health risks and benefits of research, they can also make the IRB process more complex.

"Collaborations are messy," says **James Edwards**, PhD, MSW, executive director of the Johnson Center, Grand Valley State University in Grand Rapids.

Community-based research requires IRBs to deal with multiple stakeholders, including funders and directors of agencies. Plus these community partners expect immediate responses to their questions and prompt study reviews, which can be challenging, Edwards notes.

IRBs also have to deal with flexibility, which is inherent in CBPR.

"We might have an initial design of capturing this information, and then we find out early on that what we anticipated is not going to happen the way we thought," Edwards says.

For example, investigators involved in a community-based research project were collecting data from the state about child welfare recipients and their children. State officials repeatedly assured them that they would receive the necessary information. Suddenly, the state changed its mind and said the data could not be released, Edwards recalls.

Researchers had to change the study design

Michigan BioTrust consent options

Its policies provide best practice model

The Michigan BioTrust for Health, which is part of the Michigan Department of Community Health, has for decades collected and stored dried blood spots following newborn screening.

When the agency decided to make these de-identified samples available for research, the department sought community input on how best to make this happen. The result was a requirement that all samples used for research would need prior informed consent.

"In Michigan we have specifically created a bio repository for those newborn screening bloods to include research," says **Harry McGee**, MPH, IRB chair at Michigan State University in East Lansing.

Here's how the BioTrust's informed consent process works:

• Blood samples taken from births after May 1, 2010, were subject to the new parental consent process at hospitals. Hospitals and midwives give new parents an option of signing a consent form after delivery if they want their child's remaining blood spot samples made available for future medical research. Parents can change their mind later.

"The informed consent process takes place at the time of birth when the mother is approached with information about the BioTrust," McGee explains. "She is offered a consent form that says she has the choice of allowing or not allowing the blood that is already going to be stored for newborn screening purposes to also be used for research that would take place without the identity of the child or mother being revealed to the researcher."

• People born between July 1984 and April 30, 2010, who do not want their stored blood spots used for future research can fill out a form to request that the sample be saved but not used for research or they can request the sample be destroyed.

• Samples prior to July 1984 were destroyed, but all samples collected since then will be saved indefinitely.

"It's stored for immediate newborn screening purposes and stored in the long term for the personal use of the child or family," McGee says.

For example, the stored samples could be used for forensic purposes, he adds. ■

and meet with child welfare recipients and their families to obtain additional information and informed consent, he adds.

When funders are involved in community-based research, it can pose ethical challenges for researchers and IRBs, Edwards notes.

"IRBs are good about asking who is funding the research and where the support is coming from, but does the funder have a role in the research?" he says. "More and more we're seeing when we're doing this type of [community-based] research that community foundations and private funders want to be at the table to help in the design of the study and stay involved in the research process."

Informing the community

The funders might be at the table as both a funder and as a stakeholder, and the IRB's and research institution's job is to balance those roles and try to protect the principal investigator from any potential bias and conflict of interest based on that involvement, Edwards says.

One strategy is for research institutions to have staff serve as a buffer between the investigators and community boards or funders by attending the meetings in place of the investigator, he notes.

"We highlight in our application those relationships and how they're handled," Edwards says.

Another issue that often comes up with CBPR involves informing the community about informed consent.

"This is the piece we all struggle with," Edwards says. "We typically end up with an education process in the community."

For example, a community-based organization might approach researchers, asking them to study the organization's ongoing program to evaluate its work for potential results that are generalizable. The organization has its own consent form, and although the people receiving the organization's program benefits will not see anything change, they still will need to sign a separate research consent form, he explains.

"We say to the organization that their consent form might be fine for their program, but it's not fine for the research we're conducting," Edwards says. "So we have to reconsent people and offer them the option of not signing the consent and still participating in the program." ■

FDA's draft guidance clarifies IRB roles

New PIs should be well vetted

The Food and Drug Administration (FDA) has received many lengthy comments expressing concern about its recent draft guidance for IRBs, investigators, and sponsors regarding assessing the qualifications of investigators.

The November 2012 draft guidance suggests that IRBs review the qualifications of clinical investigators who conduct FDA-regulated research. IRBs have a role in reviewing an investigator's qualifications, the 10-page guidance asserts.

This assessment could be simple and straightforward or more involved, depending on the research and the IRB's relationship with the investigator, the FDA says.

IRBs also must review the adequacy of the research site, the guidance states.

"FDA's regulations require that before an IRB can approve research covered by the regulations, the IRB must be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice," the draft guidance says.

Shared responsibility

An example from the FDA is of a proposed clinical trial involving medical procedures. "The IRB's role is to assess the adequacy of the facility's staff and equipment, including the availability of emergency or specialized care if the need should arise," the guidance says.

The guidance should encourage IRBs to work in consultation with study sponsors in reviewing evaluations of research sites, but should not be required to replicate their efforts, which is how the draft document is being interpreted, writes **Mark Lacy**, public policy committee chair of the Society for Clinical Research Sites (SCRS) of Rockville, MD.

Shared responsibility "would help to avoid duplication of effort and the creation of new regulatory burdens and inefficiencies, which would detract from the protection of human

subjects," Lacy writes in a Jan. 22, 2013, letter.

"Finally, we would urge the agency to avoid releasing a guidance that potentially creates confusion by failing to distinguish between investigator-initiated and commercially sponsored research," he adds.

The FDA's guidance might not change much for IRBs, notes **Harry McGee**, MPH, IRB chair at Michigan State University in East Lansing.

"I think the FDA is just emphasizing that you need to be more careful about it," he says. "At Michigan State, in most cases, we are well familiar with the researchers, and a lot of the research that is being done is from the same researchers and we have their track record."

The FDA's guidance mainly will impact IRBs when they're dealing with a new investigator and research site, he adds.

"We'd look at the investigator's curriculum vitae, talk to the chair of their department, and we'd talk with someone in the field and ask if they know this person and their work," McGee explains.

Questions raised

One of the questions raised in response to the draft guidance involved how the assessment would occur if multiple IRBs are reviewing the same protocol.

"What are the responsibilities for each of the IRBs reviewing the studies, particularly those with peripheral roles on the protocol?" asks **Jody L. Ference**, MS, CIP, CCRA, CIM, director, human subjects protection branch of the Walter Reed Army Institute of Research in Silver Spring, MD.

The guidance also does not specify what type of documentation is sufficient for assessing a site, Ference notes.

"Is documentation of a Federalwide Assurance (FWA) for an institution enough?" Ference writes in the Jan. 17, 2013, letter to the FDA.

"For intervention studies, would it be sufficient and proper for the sponsor to provide a letter stating that a site is appropriate for conducting the specific type of research intended?" Ference asks.

When an IRB is not familiar with the research site or institution, it should gather additional information and engage in a more involved assessment, the FDA states. ■

University creates new model for shared review

IRBshare seeks to simplify the process

In June 2011, representatives from various IRBs and federal regulatory bodies met to discuss the development of a new model to improve the multisite study model. Lead by researchers from Vanderbilt University in Nashville, the team developed IRBshare to streamline the multisite review process and reduce headaches for IRB members.

IRBshare is a Web portal for shared multisite study review. Participating institutions can upload IRB-approved shared review documents and view those of other members, such as redacted meeting minutes, protocol, approved consent documents, and IRB applications. Local IRB forms and submission processes remain the same. The Federal Drug Administration (FDA)- and Office of Human Research Protections (OHRP)-approved IRBshare model, says **Emily Sheffer**, brings simplicity to multisite studies, improves IRB efficiency for multisite studies, and saves money by reducing the manpower needed to get a study approved.

"With IRBshare, IRB members can talk to one another and are now connecting with each other and relying on each other in a very open way," says Sheffer, project manager for IRBshare at Vanderbilt University. "They're reviewing other IRB approved documents and are able to communicate and consult with one another. The hope is that it will enhance communication and cooperation and result in more efficient and consistent IRB determinations."

The IRBshare model was born of experiences with multisite studies, where every site's IRB must review the same protocol. "When this many [reviews] happen, different IRBs may find different things wrong with the exact same protocol. It's not the most practical model," Sheffer says. "The current regulations are not designed for multisite review."

Gordon Bernard, MD, vice chancellor for research at Vanderbilt University, received a R13 conference grant from the National Institutes of Health (NIH) to develop the model. In June 2011, representatives from 37 Clinical Translational Science Award (CTSA) sites, OHRP, the Association for the Accreditation of Human Reasearch Protection Programs (AAHRPP), and independent IRBs met to discuss options to form

the new multisite research agreement. "The idea behind this grant was to bring together multiple stakeholders and industry folks and IRB personnel to talk about what they need to get multisite studies off the ground," Sheffer says.

After outlining the goals for the IRBshare model, the team decided to start small and establish the process only for initial study review. "We wanted to start small and think about what the biggest concern is, and we targeted initial study review."

In his presentation at the 2013 AAHRPP conference in Miami in April, Bernard outlined some of the goals of IRBshare:

—reduced administrative costs;

—faster review cycle time;

—faster study initiation;

—increased number of IRB approvals;

—fewer differences in number and type of changes requested for study documents;

—increased partnership satisfaction levels;

—learning from collaborations.

IRBshare is open to all organizations with a Federalwide Assurance with OHRP and has its own master agreement, the IRBshare Master Agreement (IMA), which establishes the temporary reliance required to conduct a joint review of a multi-site study. The IMA is the same for every IRB and does not make changes for individual institutions. Reliance is only for initial study review and local sites become the IRBs of record again. "The idea for the master agreement was to have one single agreement instead of a separate agreement for every study," Sheffer says. "The local IRB is going to maintain control of the study."

Once they are part of the system, participating institutions can take one of two paths for review: the shared review process or the traditional review path. In a shared review, an IRB will access the shared full board review in the system and rely on one single full board review of their choice via a subcommittee review (an IRB chair or designated IRB member) of the shared documents and an administrative review of local context issues. With traditional review path, a full board review can still be used if the subcommittee has any questions or concerns with the initial review.

Full board review documents are shared and can be viewed by all IRBshare members. Once a review is shared, anyone who is part of IRBshare can view it — users cannot select who can and cannot rely on the review.

When users log on to IRBshare, there is a user-specific dashboard screen that shows what projects the user is following, how many projects are registered at the user's site, and how many users are at the site. Users can also search for projects or create new one.

From there, the IRBshare project page is organized around the types of reviews completed by each institution (full board review, shared review, and undecided). For full board review sites, the documents uploaded by the local IRB are listed. The required documents include the study protocol, IRB determination letter, meeting notes, IRB application, and consent forms. Users can also upload any other documents that show that the study was approved without contingencies.

Member sites that are not currently part of a study can view any uploaded documents. An unexpected benefit, Sheffer says, is that IRBs can learn from other institutions' documents and adapt them to meet the needs of their IRB. For example, an IRB user at an institution not taking part in a study in IRBshare was able to log in, review another site's meeting minutes, and modify its own meeting minutes template for an AAHRPP application. "People are reviewing how others are documenting things and adapting their processes if they find better ones," Sheffer says.

So far, IRBshare, still in the pilot phase until more evaluative data are available, has 25 participating institutions and four studies. One institution, Duke University in Durham, NC, has completed a shared review, relying upon the review of Vanderbilt. "They thought the process was really easy and had no problems with the shared review," Sheffer says. The study was reviewed and received IRB approval in one day.

Sheffer says the team is reaching out to principal investigators and study teams as well as other IRBs. "Because this is a multiparty agreement, it's hard to get through the institutions. We're letting the investigators know they can also use IRBShare." One institution, according to Bernard, reduced paperwork for PIs by creating an abbreviated IRB application for locally submitted studies after the full board approval was uploaded to IRBshare. The PIs would then submit the shorter application, consent form, and cover letter.

"We have 25 members, and a lot already collaborate. We're contacting other sites to say they can use it — there's a process of educating and recruiting that needs to happen," Sheffer says.

While the IRBshare team continues outreach to more institutions to participate, Sheffer acknowledges the model is not for everyone. "Not everyone is quite ready for this type of system yet," Sheffer says. "Joint review models create

reluctance around issues of liability, accountability, responsibility, control, and quality, and those will be things we continue to work on."

Institutions have different concerns with joining IRBshare, such as having only one IRB member review and approve a study. "Sites have been really creative with coming up with solutions," Sheffer says. "They know they can always kick it [a study] back to the full board for review if they're not comfortable with shared review. They're getting used to it and understand that it's a thorough review of a study that has already been reviewed. Processes don't change very much for the local site. They can conduct local context review, then instead of waiting to get to full board, have the IRB chair or any IRB members do any of the shared review."

Sheffer says other IRBs have expressed interest in signing the master agreement if IRBshare includes continuing review and amendments — something that Sheffer says is on the horizon. IRBshare has already received verbal regulatory support for continuing review, and the team is working out ways to integrate it into the system and the master agreement. "We've heard from people who say they'll join when we get continuing reviews in place," she says. "We already started meeting with the system developer to make changes in the system as we work through kinks and nuances of regulatory piece. The biggest piece is making sure regulatory experts are on board. We need time to review and make sure things meet their standards." ■

Central vs. local IRB for multisite research

University study compares efficiency of both

The research oversight system, says a University of North Carolina at Chapel Hill researcher, has not evolved to keep up with the volume and complexity of the research it oversees. In the 1970s and 1980s, the research community consisted of a handful of single-site, single-researcher studies. Now, phase 3 studies can consist of thousands of subjects at hundreds of sites.

"Multicenter research is essentially a take-it-or-leave-it proposition for individual sites by the time we get our hands on it," says **Daniel Nelson**, MS, CIP, director of the Office of Human Research Ethics and professor of social medicine and pediatrics at UNC-Chapel Hill. "It is predicated on local review of single sites."

The premise is that the protocol will be performed identically at all research sites. If one site finds major issues with the protocol, that site will likely be excluded altogether, Nelson says. There are few effective means to modify the underlying protocol, he says, and local IRBs "are left tinkering around the edges with the things they can control."

"The net result is ineffective oversight of study-wide issues by a patchwork quilt of independent sites," Nelson says. "It's broadly accepted that redundant IRB review by dozens of local IRBs is not commensurate value added."

UNC-Chapel Hill is considering a policy change to address some of these issues. Nelson and colleagues conducted a randomized, controlled study to compare the use and efficiency of a central IRB versus a local IRB for approving multisite research. The aims of the UNC-Chapel Hill pilot project were to test a model that allows reliance on any central IRB involved with a multicenter clinical trial, Nelson says. The sample involved 43 consecutive industry-sponsored multisite trials, and UNC investigators and IRB members and staff were all blinded to the status of the individual studies. The studies were reviewed by the UNC Biomedical IRB, then randomized. Experimental investigators were given permission to register with the central IRB for that study.

To be eligible for the study, central or independent IRBs had to be accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP), be in good standing with the Office of Human Research Protections (OHRP) and the Food and Drug Administration (FDA), and be willing to establish a master service agreement with UNC.

During the study, UNC-Chapel Hill collected data on the effect on the local IRB workload; administrative issues with dealing with multiple central IRBs; researcher satisfaction and feedback; turnaround time; and contingencies identified by the local IRB on studies already reviewed or approved by central IRBs. In all, 20 central/independent IRBs were eligible for the pilot study. UNC executed agreements with 13 IRBs, and in the end eight IRBs were used.

Over a six-month period, 43 studies that had 32 sponsors and eight central IRBs were reviewed. Researchers found a potential time savings of around 20 days per trial, provided standing agreements were already in place. They also found that of the 260-300 full trial reviews at IRB meetings, one-third of initial reviews conducted by the Biomedical IRB are potentially eligible for outsourcing. Eighty-five percent of study researchers

felt that reliance on a central IRB would ultimately speed up the process, and any problems encountered would resolve as the model as more experience with the model is gained.

"Our desire to explore an alternative to the traditional 'sole provider' arrangement was well founded," Nelson concludes. ■

FDA: Obtain IND for *C. diff* treatment

Fecal transplants considered biologic therapy

The Food and Drug Administration (FDA) has now said that clinicians wishing to perform a fecal transplant for treatment of *Clostridium difficile* will have to obtain an investigational new drug (IND) application.

The fecal microbiota for transplantation, or FMT, therapy involves taking the fecal matter of a healthy person and transplanting it into the gut of an infected patient in order to combat the highly resistant bacteria. The transplanted fecal matter then establishes a healthy colony of bacteria to prevent *C. difficile* from taking hold in the gut. The experimental procedure is mainly used on patients with recurring *C. difficile* infections for whom conventional treatments have failed.[1]

The FDA held a public forum on FMT therapy at the beginning of May at the National Institutes of Health in Bethesda, MD. The agency says it considers FMT to be a biologic, which requires researchers to obtain an IND for the treatment. "Published data from case studies and metaanalyses suggest that the use of fecal microbiota to restore gut flora may be an effective therapy in the management of refractory *C. difficile* infection," the FDA says on its website. "However, the efficacy of this intervention has not yet been demonstrated in controlled clinical trials. Such controlled trials are needed to demonstrate the safety and effectiveness of FMT products for *C. difficile* infection refractory to conventional therapy."

The use of FMT therapy to treat recurring *C.difficile* infections has shown promise. A study presented at the 2011 Annual Meeting of the American College of Gastroenterology showed a primary *C. difficile* cure rate in 91% of patients who received the transplant, and a 98% cure rate in those who were given single-course vancomycin after transplant.[1] A Brown University Alpert School of Medicine study showed 92% cure rate in FMT therapy through colonoscopy.[2]

Researchers will have an emergency number for the FDA to obtain an IND for patients in dire need of the procedure.

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1. Brandt LJ. Fecal transplantation for the treatment of Clostridium difficile infection. *Gastroenterol Hepatol* (N Y). 2012 March; 8(3): 191–194.
2. Kelly CR, et al. Fecal microbiota transplantation for relapsing Clostridium difficile infection in 26 patients: methodology and results. *J Clin Gastroenterol*. 2012 Feb;46(2):145-9. doi: 10.1097/MCG.0b013e318234570b. ■

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

- Best strategies in making secondary data public
- Is it still possible to guarantee privacy of subjects?
- What are the limits of re-identification?
- Exploring IRB flexibility in the regulations

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CNE/CME QUESTIONS

1. According to the Johns Hopkins University School Of Medicine IRB, which of the following are included on a checklist for informed consent?
   A. a statement that the study involves research
   B. a description of the reasonably foreseeable risks or discomforts to the participant
   C. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant
   D. All of the above

2. From an IRB's perspective, which of the following is not a potential problem with community-based participatory research?
   A. community-based organizations often want fast answers and responses
   B. community-based organizations, including those that have sponsor members, increasingly want to be involved in study design and ongoing processes
   C. community-based organizations can be hijacked by people who are members of a polarizing group
   D. community-based organizations often require additional education about research informed consent and the differences between program evaluations and human subjects research

3. In the FDA's November 2012 draft guidance on assessing investigators' qualifications, the FDA states that before an IRB can approve research, it must ascertain what?
   A. that an investigator's curriculum vitae is thorough and honest
   B. that an investigator does not hold stock in a sponsor company
   C. the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice
   D. All of the above

4. When an institution becomes a part of IRBshare, it may submit changes to the IRBshare master agreement.
   A. True
   B. False