IRB ADVISOR

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INSIDE

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Experts: NIRB and IRBshare are alternatives to central IRBs

Models speed up review, reduce workload

IRBs continue to navigate many changes in how they are structured, whether these involve collaboration with other institutions or maintaining a solo mission.

As some IRBs and research institutions seek more efficient ways to achieve quality human research protection during multisite trials, new models have emerged. One of the newest is the National IRB Reliance Initiative (NIRI).

NIRI's IRB Reliance agreement — also called IRBrely — offers institutions and researchers a way to streamline IRB review processes and reduce administrative burden.[1,2]

The NIRI effort is consistent with National Institutes of Health (NIH) draft policy of Dec. 3, 2014, that promoted the use of one IRB in multisite clinical research studies. IRBrely was created by a committee of investigators from eight Clinical and Translational Science Award (CTSA) institutions with funding from the National Center for Advancing Clinical and Translational Science, says **Barbara Bierer**, MD, professor of medicine, pediatrics, at Brigham and Women's Hospital and Harvard Medical School in Boston. Bierer also is senior reliance advisor for NIRI.

> THE IDEA BEHIND IRBSHARE WAS THIS QUESTION: "HOW CAN WE GET MULTICENTER STUDIES STARTED UP QUICKLY TO REDUCE START-UP TIME?"

The group developed a draft agreement and standard operating procedures (SOPs) are being piloted in a national clinical trial centered at Duke University and involving institutions from New England to California, Bierer adds.

Another new model is IRBshare, a shared review model, which is a very

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different concept than the central IRB review, says **Julie A. Ozier**, MHL, CIP, director of the human research protection program at Vanderbilt University in Nashville, TN.

IRBshare is based on one alliance agreement with each site involved in a multisite study, Ozier says. "We have 54 sites across 28 states, and this was rolled out in the fall of 2012."

The national initiative brings together and builds on the successes of these existing reliance networks, she adds.

Specifically, the Harvard Catalyst IRB reliance model, started in 2008, provides systematic standards and shared cooperation among Harvard's 11 schools and 17 affiliated academic health centers, as well as additional signatories throughout New England.[1]

After the Boston Marathon bombing in April 2013, researchers found the Harvard Catalyst network very useful: Boston physicians were able to quickly study the outcome of blast-related ear injuries after the bombing because of rapid IRB approval from seven hospitals in an IRB reliance network, according to NIH's National Center for Advancing Translational Sciences (http://www.ncats.nih.gov/pubs/features/irb-reliance).

The idea behind IRBshare was this question: "How can we get multicenter studies started up quickly to reduce start-up time?" Ozier says.

"We also asked, 'Why don't IRBs talk to one another?'" she says. "If IRBs talked with one another about their determinations, they could help each other out."

IRBshare works this way: One IRB is the first to review a study. Once the protocol is reviewed and approved, all the documents are put into a portal, and all the other IRBs can choose to rely on that review, adding their own local context and local required language, Ozier explains.

For example, once an investigator agrees to use IRBshare, then a research site that is a member of IRBshare can agree to use IRBshare, Ozier adds.

"It's a tool to document who is relying on who and what document they're using to rely," she says.

"The caveat to IRBshare is that while they share the initial review and would share every other major review, continuing reviews, and major amendments, the local IRBs would all be responsible for this study at the local level," Ozier says. "So any kind of minor changes, such as a change in personnel, would be managed at the local site and wouldn't go back up the system for review because it's a local issue."

This way, local IRBs still have some control; they also review adverse events and noncompliance, Ozier adds. "They would give information to any coordinating center or sponsor, but not to other IRBs."

While there are central IRB models, commercial/independent IRBs, and IRBshare, the reliance model provides the most flexibility for research institutions, Bierer notes.

"It's not a central IRB, and it's not a designated IRB," Bierer explains. "But research sites can use one IRB for its initial review of a multisite study, as well as subsequent reviews and continuing reviews."

They also can choose not to defer their review to another IRB, she adds.

The difference between the reliance model and the central

IRB model is how the main IRB is designated and how the other IRBs choose to collaborate with that IRB, Bierer explains.

"In a central IRB there is a designated IRB of record," Bierer explains. "If you sign on to these protocols, you are required to go to the designated central IRB regardless of who the principal investigator is."

In the reliance model, there is flexibility in selecting the IRB that will do the review. Other collaborating IRBs can provide expertise related to their board's knowledge and experience, she says.

"One might have specific IRBs constituted for certain expertise, such as prisoner research or pediatric care," Bierer says.

Further, the collaborating IRBs are not required to rely on, but can exercise independent oversight for the trial, Bierer says.

"You might have a situation where an IRB would like special oversight of an investigator, or where the study population at one institution is likely to be very different from other sites," Bierer explains.

"In these situations, an IRB might want to perform a local review," she adds. "Although we feel like the number of times this is going to be true is very, very small, we want to allow for institutions to make an affirmative decision, rather than enforcing a universal requirement."

Since rolling out IRBshare, there has been more collaboration between the involved IRBs, Ozier notes.

When compared to a national average of about a month for IRB reviews, the IRBshare model is faster — about 17 days from submission to approval, Ozier says.

"It cuts in half the turnaround time for studies," she says.

Another benefit is that IRBshare promotes consistency because the IRBs do talk with one another. "Anytime they disagree, they talk," she says. "They either come into the alliance or agree to disagree; it's very transparent in that regard."

IRBshare also decreased analysis time in the pre-review process, Ozier says.

"It's an abbreviated protocol application," she says. "It's really just asking about the things locally that they're going to be doing, the local subjects' injuries, local HIPAA provisions, managing the drug locally, and those kinds of things."

Not all IRBs are satisfied with retaining some of the responsibility of local reviews, Ozier says.

"I think a lot of IRBs would like to just rely on and not have that added responsibility of the local reviews," she adds.

"They have signed on, and the feedback is great — but it's only part of the picture," she says. "They really are okay with giving up the responsibility and letting another IRB do the whole review for them."

Some IRBs like the central IRB model better, she adds.

"So we're creating a central IRB model within IRBshare," Ozier says. "We haven't rolled it out yet."

From an investigator's perspective, any type of shared review is a more efficient process.

"Investigators uniformly appreciate not having to go to individual IRBs," she says. "I haven't spoken to any investigator who has anything but appreciation for our easing the administrative burden of clinical research."

Also, the reliance agreement frees up full-board IRB review time.

"These multisite studies involve significant work for an IRB," Bierer says. "Substantively, this new system will be able to save time and money; it will streamline not only the initial review, but also study amendments and continuing reviews, and ensure coordination of communications regarding adverse events and others."

In some traditional multisite study reviews, the workload is substantial, she adds.

"Suppose you have five IRBs reviewing the same protocol. One IRB reviews it and approves it, but the second IRB reviews it and makes a slight change to the informed consent. The first IRB has to re-review the changed document and approve the change," Bierer explains. "You could go back and forth amongst these IRBs multiple times before you have an aligned IRB approval on a study."

The difference between the reliance model and the central IRB model is in how the main IRB is designated and how the other IRBs choose to collaborate with that IRB.

Bierer sees the national IRB reliance effort as the next step toward harmonization of workflow approaches, definitions, and education of human research protection staff.

"The foundation of the National IRB Reliance Initiative is building trust and coordination," she says. "We would like to stand for something that works for the nation."

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Here's a quick look at the national IRB reliance agreement

Key features may help speed review process

A national IRB model was developed to make the IRB review process more efficient and to offer research organizations an alternative to the central IRB model.

IRBrely was adapted by the National IRB Reliance Initiative (NIRI) from regional IRB reliance efforts led by a number of CTSA sites, including those based at Harvard University in Boston, Case Western Reserve University of Cleveland, the University of Wisconsin-Madison, and the University of California system, says **Barbara Bierer**, MD, professor of medicine, pediatrics, at Brigham and Women's Hospital and Harvard Medical School in Boston. Bierer also is senior reliance advisor for NIRI.

The Ohio IRB Reliant model covers the state of Ohio with eight institutions. The Greater Plains IRB Consortium, which includes the University of Wisconsin-Madison, spans seven states and 10 institutions. The University of California model spans the 10 UC campuses and Lawrence Berkeley National Laboratory.

Key features of the national IRB reliance agreement include:

1. Investigators request single site review for a multisite study, utilizing the IRB reliance network. Informatics support with a Web-based system under development support reliance both to join the National IRB Reliance Initiative, as well as to rely on another institution for any given study protocol, Bierer says.

2. Sign on to the National IRB Reliance Agreement through a Joinder Agreement.

3. Delineated role responsibility for the following:

• Reviewing IRB: responsible for review and follow-up; ensures enrollment at each site commences only after all local institutional training and approvals have occurred; reports relevant unanticipated problems, adverse events, and deviations to participating institutions;

• relying on institution and relying on IRB remain responsible for study training, managing conflicts of interest, and ensuring compliance with the reviewing IRB mandates;

• chain of responsibility and communication through a lead study team via the overall PI responsible for research conducted at all sites; primary employer of the overall principal investigator is the presumed or default reviewing IRB, Bierer says.

4. IRB reliance is not mandated, but is determined on a study-by-study basis; if a study is deemed appropriate for IRB reliance, a study-specific authorization agreement need not be executed as the National IRB Reliance Agreement Network Joinder serves as the authorization agreement, Bierer adds.

Establishing an IRB reliance agreement may take time and effort, but it will make the IRB review process faster for multisite trials, Bierer notes. ■

AAHRPP findings reveal issues IRBs need to address

Defining research is biggest problem

Each year, human subjects protection programs worldwide prepare for accreditation, making changes and improving processes. But which problems crop up most frequently?

"Depending on guidance changes, it goes in spurts of which items are the hot button issues," says **Sarah H. Kiskaddon**, JD, MA, director, global business development and public affairs at the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC. Kiskaddon and Candice Yekel, MA, of Pennsylvania State University, spoke about the top 10 findings from 2014 AAHRPP applications and site visits at the 2015 annual AAHRPP Conference, held May 19-21, 2015, in Chicago.

Kiskaddon reviews the most common findings each year and has found a shift in where problems appear: Previously, AAHRPP site visitors found more problems during site visits; now, there is more

emphasis on correcting policies and procedures early in the step 1 review process.

"We're doing a little different process," Kiskaddon says. "The policies are revised more in the step 1 reviews and are very good before we go to the site visit." *(For site visit issues, see page 78.)*

This is why AAHRPP now identifies more issues with the P&Ps and fewer during the site visits.

"When we're doing site visits, we verify that the site is following its P&Ps, and because the first part is more rigorous, we don't waste anybody's time at the site visit," Kiskaddon says. "I think this is more efficient."

Here are the most common issues found during reviews of P&Ps and standard operating procedures (SOPs) by the Council on Accreditation in 2014:

• Element I.1.A – What activities are overseen by HRPP. "This has to do with defining what is research and what has to go to the IRB for review," Kiskaddon notes.

Research organizations need to research in relation to quality improvement and other activities in their P&Ps so it's clear to faculty and researchers when they have to seek IRB approval for a project, she adds.

"Eighty-one percent of organizations need some tweaking of the definitions of systematic investigation and generalizable knowledge," Kiskaddon says.

Specifically, P&Ps should provide examples for researchers of the kind of research that meets the definition and needs to be reviewed by the IRB.

• Element I.7.A – Confirm test articles have regulatory approval. "The HRPP needs to confirm that test articles have regulatory approval," Kiskaddon says. "Confirm the IND number or verify that there is no need for an IND."

About 71% of organizations' step 1 application materials required an addition or revision to satisfy this element.

"Occasionally we find that IRBs accept whatever is told to them and do not check to see if the study needs an IND," Kiskaddon explains. "An IND number should match the number on the investigator's brochure, protocol, and application form."

Also, IRBs should ask to see correspondence from the Food and Drug Administration (FDA) if there is no IND, she adds.

"They shouldn't rely entirely on investigators that say, 'I've been told I don't need an IND,'" she says. "IRBs should look into it."

• Element II.2.D – Conducting a review by convened IRB/Ethics Committee. "We require IRBs to have someone with the general perspective of research participants, which exceeds the federal requirement of having an unaffiliated member," Kiskaddon says. "We say that you should have someone on your IRB who recognizes the general perspective of research participants."

For example, an IRB could have on their board a parent of a child who was enrolled in a lot of clinical trials due to a chronic illness, she suggests.

"It has to be someone with the perspective of the research participant," she adds. "Another requirement is a standard for attendance of unaffiliated members at convened meetings."

The regulations are silent on their attendance, but AAHRPP says organizations should have a minimum requirement for attendance and track it, Kiskaddon says.

"For example, you might say that if they miss two meetings in a row they will be approached for discussion and replaced if needed," she adds.

About 66% of IRBs seeking accreditation in 2014 had problems with this standard.

• Element I.6.B – Managing individual conflict of interest. This requirement was a problem for 62.7% of accreditation applicants. It also was a problem at the site visit for 30.4% of organizations.

Typically, the problem was they didn't track the regulations closely enough or didn't have a policy for requiring conflict of interest information, Kiskaddon says.

"We require you to define the process, have a disclosure form and do education around it, and if there is a disclosure, you manage it in some way, and it always goes to the IRB for final approval of the management plan," she explains.

Problems that occur include IRBs having a policy that needs tweaking or having a separate COI committee that develops a management plan, but does not close the loop by sending it to the IRB for final approval, Kiskaddon says.

During site visit reports, IRBs sometimes were not presented with management plans, or members had insufficient knowledge of the COI policies and procedures.

• Element II.4.A – Additional protections for vulnerable participants. IRBs should follow written P&Ps for determining risks to vulnerable subjects. Problems with this standard were common — 62.7% of application materials. They had problems with subpart requirements and requirements of other sponsoring agencies and with describing additional safeguards and protocol-specific findings.

"For example, organizations need to justify their determination with a subpart D determination,

and this has to be documented in the minutes of the meeting," Kiskaddon says. "Sometimes, we find inconsistent application of those procedures; they may be doing it and not documenting it."

• **Element I.5.D – Allegations and findings of non-compliance.** Organizations need clear P&Ps for addressing allegations of noncompliance, Kiskaddon says.

"Sixty-one percent of organizations have to make some changes," she adds. "They might need to revise their policies and procedures or make sure they record what actions the IRB takes."

For instance, the IRB might have a discussion about an issue of noncompliance without documentation of whether it's determined to be serious or continuing, she explains.

"They also need a process to review it and a timeframe for reporting it and what actions they take, if needed," Kiskaddon says. "What we require is that you define all the terms, identify who's responsible for making those determinations, when and to whom to report it, how you manage it, and how you document the determination."

• **Element I.1.D – SOPs made available to the research community.** An IRB's policies and procedures should be made available to researchers, sponsors, and staff, Kiskaddon says.

"Develop a method for disseminating SOPs and know what your policies and procedures are," she adds. "If things change, describe the method of disseminating the change; for example, describe whether it's on the website."

AAHRPP has found that 59.3% of organizations had to make some change in how they disseminate their revised SOPs.

AAHRPP tries to keep its extra-regulatory requirements to a minimum, but these are the ones that are well-represented in the list of top problems found during the accreditation process, Kiskaddon notes.

"These include things like quality improvement plans, evaluating IRB members, and contract provisions," she explains. "These are things you don't have to do by law, but you're doing them for AAHRPP accreditation, and they're new policies that we tweak a little." ■

Top IRB findings during accreditation site visits

These findings are less frequent

IRBs and human subjects research protection programs continue to have some concerns discovered during site visits in the accreditation process, but these in recent years have impacted fewer programs than have problems found with policies and procedures.

Typically, organizations have to do more work on their policies than on their site visits, and most issues are resolved before the site visit, says **Sarah H. Kiskaddon**, JD, MA, director, global business development and public affairs at the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC.

The following are the top issues discovered in 2014 during draft site visit reports:

• **Element II.1.B – Qualified leadership.** This element relates to draft site visit reports and pertains to the IRB having qualified members, staff, and leaders.

"IRB membership should be periodically reviewed and adjusted as appropriate," Kiskaddon says. "We found that 47.8% of draft site visit reports had an observation with this element."

For example, they found some issues on the evaluation of the IRB membership and leadership, she adds.

"You have to look at the overall membership periodically, as well as the ethics committee chairs and staff and members," Kiskaddon says. "They also need to provide feedback to those IRB members."

AAHRPP found that sometimes periodic feedback did not occur, or the IRB members did not remember ever being evaluated, she explains.

"Also, it's clear that more evaluation is needed if the members are not knowledgeable about things like the Belmont Report or the federal regulations," she says. "Either of those findings can trigger an observation with this element."

This element also pertains to IRBs having the right composition of members. For instance, if an IRB reviews a lot of oncology research, then the board should have at least one oncologist member, Kiskaddon adds.

• **Element I.6.A – Financial conflicts of interest.** Organizations have to follow written P&Ps to identify, manage, and minimize or eliminate financial conflicts of interest.

"You have to have a policy that relates to the organization as a whole or to senior leadership that might have a financial stake in research," Kiskaddon

says. "If an institution has a patent on research that's being conducted there, then the IRB or conflict of interest committee needs to know that the organization has the patent and that the university as a whole will benefit from the research."

Also, this issue will need to be managed in some way, she adds.

Just a few years ago, most institutions did not have a policy on financial COIs regarding organizations, but now they do, she notes.

Some institutions will send research with an organizational COI to an independent IRB. This isn't a requirement, but institutions do need to have a plan that the IRB knows about, Kiskaddon adds.

• Element II.5.B – Follow legal and regulatory requirements. "This has to do with documentation," Kiskaddon says. "The IRB has to document discussions and decisions relative to the approval of the research."

This element impacted 34.8% of sites visited. The chief problems were poorly-documented minutes and documentation issues.

"For example, decisions related to regulatory requirements are not documented," Kiskaddon says. "These could be related to protocol specific findings."

An IRB might have a long discussion at its meeting about whether a skin biopsy is above minimal risk, but then there is no documentation in the minutes about what the board concluded, she explains.

"You have to make those determinations and put those in the minutes," she adds.

• Element I.4.B. – Outreach activities. "Outreach activities to the community have to be evaluated regularly for improvement," Kiskaddon says.

The 21.7% of organizations that had observations on this element on the draft site visit report typically lacked evaluation of outreach effectiveness, she notes.

"They might do things on a website that is accessible to the community, but no one evaluates whether people use the website and whether revisions are made when things change," Kiskaddon explains. "Either there is no process or no one is documenting that it's being followed."

• Element I.5.A – Audits or surveys to assess compliance. Organizations need to conduct audits or surveys to assess compliance with organizational P&Ps, laws, regulations, codes, and guidance. Of the draft site visit reports in 2014, 21.7% had problems with this element.

"We require that quality assurance and quality improvement measures be done periodically," Kiskaddon says.

"You should pick out what you want to check on — for example, the IRB minutes — and measure it," she says. "If you find they are missing information and not complying, then do some intervention and check it again."

IRBs also may want to ensure that they are accessible to researchers who might have questions; they may want to do a survey of the research community to see what their weaknesses and strengths are and then make improvements and measure it again, she adds.

"IRBs need to distinguish between compliance and quality improvement," Kiskaddon says. "They should have sufficient goals and measures of compliance."

AAHRPP's feedback from accredited programs has been that this element has made the biggest difference in their operations, Kiskaddon notes.

"They say this standard, which requires them to make improvements as well as to measure compliance every year, makes a difference in the long run," she says.

• Element I.5.B – Audits or surveys to assess quality. This element also was an issue for 21% of organizations with site visits. It's different from Element I.5.A in that it looks at quality improvement rather than compliance, Kiskaddon says.

For instance, an organization might find a weakness in its human research protection program and collect data, but when AAHRPP visits, the organization has not completed its quality improvement process, she says.

"The need to do a quality improvement process and not just collect data," she adds.

• Element I.8.B – Agreements with sponsors. "This is one of the hardest standards," Kiskaddon notes.

"In studies whose sponsors conduct site monitoring visits, they have to have a written agreement with the sponsor," Kiskaddon says. "We look through clinical trial agreements and find that many sponsors monitor onsite, but if they find something that impacts the participant, they need to notify the IRB or organization in some way."

IRBs must have P&Ps that outline how this notification will take place.

For example, a drug company might audit a research site, finding that 10% of visits were missing blood pressure measurements, Kiskaddon says.

"This could be a safety measurement, and if it's not done then the sponsor might find that out, so we are now obligating the sponsor to report that back to the site," she adds.

In all, 21.7% of draft site visit reports had observations with this element. "Organizations won't be accredited unless they can correct this," Kiskaddon says.

• Element I.8.C – Data safety monitoring boards. This element is similar to I.8.B, but pertains to the sponsor's responsibility to conduct data and safety monitoring. Organizations should have an agreement with sponsors

that provides for the investigator or IRB to receive DSMB reports and to ensure participants' safety.

"Findings from the DSMBs should go to the researchers or the IRB," Kiskaddon says. "About 21% lacked sufficient contractual provision that required the sponsor to send DSMB reports to researchers or IRBs when appropriate."

• **Element I.8.E – Disclosing results agreement.** With this element, AAHRPP requires that institutions have a written agreement with sponsors that the IRB will be notified with the results of a study in order to inform participants. It pertains to studies in which participant safety could be directly affected by study results after the study ends.

Draft site visit reports found that 21.7% of sites had concerns with this element, including problems with the contract and the process.

"Sponsors have resisted this over the years, but are conforming more and more now," Kiskaddon says. "They continue to analyze data up until they publish it, and during the analysis phase of study, you need a process to notify an organization if you find some information that affects the health or welfare of study subjects." ■

Dig deep when analyzing risks and benefits

Revisit language related to risk

When IRBs and investigators deal with risks, they should identify reasonably foreseeable risks and have reasonable precautions to prevent harm from happening.

Risks are the cornerstone of human subjects protection laws.

In fact, when you distill federal regulations regarding human research subject protection, it can be described with just three sentences, says **Ernest Prentice**, PhD, associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha. Prentice is the former chair of the Secretary's Advisory Committee on Human Research Protection (SACHRP) for the U.S. Department of Health and Human Services.

"One would be that the risks to subjects are minimized; two, that the risks to subjects are reasonable, and three, that there is adequate provision for monitoring the safety of subjects," Prentice says.

So if an IRB plans to revisit policies and procedures (P&Ps) regarding protocol review, they might want to revise or at least revisit their language related to risk.

"The common interpretation of a risk is that it's a potential harm," Prentice says. "But you need to look at it more narrowly."

For instance, every medication has a list of side effects, and each of those is a potential harm, he says.

"Those side effects are all going to occur, and every time you pick up a prescription, you get an insert that lists all of those risks," he adds.

From a research perspective, the risks described should be reasonably foreseeable, which might not mean they are possibilities, but that they are likely to occur in at least some participants, Prentice explains.

The IRB's role is to make certain investigators have minimized those risks as much as possible, he adds.

"Take a procedure like venipuncture, which everyone has had at one time or another," Prentice says. "What are the known potential harms? One, it will hurt; it's painful. The second risk — depending on the size of the needle and difficulty of the phlebotomist — is that you might get some bruising."

Other risks are rare, such as obtaining an infection or fainting from the procedure, he says. "Someone could faint. Someone could faint, fall out of a chair, crack his head, and suffer a concussion."

While that scenario is possible, is it something that needs to be listed on the research informed consent form, Prentice says. *(See story with examples of risk scenarios, page 81.)*

"We don't put that stuff in there because in a research context, we have to narrow down our considerations of risks to those that are reasonably foreseeable," he adds.

Risks also are situational and population-dependent.

"Some subjects are more vulnerable to a risk occurring than others," Prentice says. "For instance, the risk of infection with a simple venipuncture: If you're immunocompromised, there's a greater chance of infection. And hemophiliacs have a greater chance of bleeding and bruising from the procedure."

People who are elderly and frail are at greater physical risk in medical studies, he adds.

"When an IRB reviews risks, they have to look at not only the intervention, but the risk susceptibility of the subject population," Prentice explains.

Also, when IRBs analyze risk, the questions they should always have in mind are: What can we do to minimize risk? What kind of precautions can we put in place to safeguard subjects?

"If you want to totally eliminate risk, then don't approve the research project,"

Prentice says. "But we're not going to do that, so what we have to do instead is come up with reasonable precautions."

The following are ways to develop reasonable precautions:

• **Investigators start by thinking about subject safety.** Investigators are the first to ask: What do I need to do to minimize risk?

"For example, and the regulations speak to this, can I go ahead and utilize an already scheduled clinical procedure and use data from that procedure?" Prentice suggests. "So if a subject is going to have a CT scan, can I use that CT scan, which is done for clinical purposes, rather than have another one done for research purposes?"

Subject safety should be a consideration when schedule procedures that might be duplicates of procedures conducted for clinical purposes, he adds. "Any time you can use information from a procedure already done for clinical purposes, do it."

• **Assess the monitoring plan.** IRBs and human research protection programs (HRPPs) need to ask what sort of monitoring is necessary and what sort of follow-up procedures are necessary, Prentice says.

"If a subject experiences a certain level of symptoms, then maybe he should be withdrawn from research before he suffers irreversible harm," he says.

IRBs monitor and analyze risk, but it's up to investigators to list and clearly describe the known, reasonably foreseeable risks, Prentice says.

"I would not suggest they put in 10 pages of risks, which has become a problem with consent forms these days," he says.

• **Identify, define reasonably foreseeable risks.** "Take reasonable precautions to prevent harm from happening," Prentice says. "By reasonable precautions, you decide what's reasonable, and if it's not reasonable, then we shut down the research."

Investigators decide which risks are reasonable, and IRBs decide whether the principal investigator's description of risks is reasonable, he says.

"If subjects are more vulnerable, including elderly people, people who are chronically ill, including people with terminal cancer, then look at all these things and make an assessment of the risk," Prentice says.

• **Consider potential benefits.** Benefits in research are anything with a positive value, Prentice notes.

"It's something that may accrue to directly benefit the subject, or perhaps it will only benefit society in terms of advancement of knowledge," he says. "All research must have benefit to society, but not all will have benefit to the subject."

For example, Phase I in clinical trials involves toxicity testing, and there's typically no prospect of therapeutic benefit to subjects, Prentice says.

"IRBs have to factor that in," he says. "Does the investigator think there's any prospect of direct subject benefit and, if so, is it worth it? Or, if not, why is the investigator doing research in the first place? How will it advance knowledge?"

A flawed experimental design won't yield usable data, so it would be unethical to conduct it, Prentice says.

"The principle investigator has to make sure the experimental design is sound, and the IRB has to say, 'Yes, right design, and if it's carried out according to the protocol, it could potentially result in advancement of knowledge,'" Prentice adds.

• **Think about risk-benefit equation.** "We have reasonable precautions placed in the protocol to reduce the possibility of any subject experiencing harm," he says. "We've examined the anticipated benefit to society, and now it's time to look at the risk-benefit relationship."

IRBs might consider the possibility of risks outweighing benefits and whether it's ethical to do research where this occurs, Prentice says.

In situations in which there is the possibility of subjects experiencing direct benefit from research, then IRBs might find it acceptable to have a higher level of risk. They will make this assessment as they consider the risk-benefit equation, he explains. ■

Here are a few risk-benefit examples

Wading into gray area

As IRBs debate and consider how to assess risks and benefits in research, here are a couple of examples of cases where IRBs made controversial and sometimes opposing decisions:

• **Smallpox vaccine trials:** After the Sept. 11, 2001, terrorist attacks in the U.S., some worried about terrorists developing bioweapons such as smallpox, says **Ernest Prentice**, PhD, associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha. Prentice is the former chair of SACHRP.

"There was concern about whether or not we'd be exposed to

smallpox," Prentice explains. "There was a limited stock of the vaccine, which was not enough to inoculate everyone, so the idea was to dilute the vaccine and give it to kids to see if produced an immunological response."

The federal government pulled Dryvax, the smallpox vaccine used previously, from freeze-dried storage stockpiles. The National Institutes of Health (NIH) coordinated a multisite trial of diluting the vaccine in adults and wanted to develop a study at three institutions for dilution vaccine in children. The goal was to inoculate young children, ages two to five, to assess its safety.[1,2]

IRBs had to assess the potential risk of a terrorist getting hold of smallpox, which had been eradicated worldwide but was available in a handful of laboratories. Then they had to determine the risk to individual children receiving the vaccine and weigh that against the potential societal and individual benefit provided by a vaccine to a dangerous disease that no longer exists, yet could possibly appear again.

Two IRBs that reviewed the pediatric smallpox vaccine protocols approved them. A third IRB voted against it, and the study had to go to the Office for Human Research Protections (OHRP) for review.[1]

"This shows that IRBs can come to different conclusions," Prentice notes.

A panel of 10 reviewers considered risks and benefits of the vaccine. Before the smallpox vaccine was discontinued in 1971, it was routinely given to children from ages 1 and up. It also was considered to be the vaccine with the most severe adverse side effects, including the common side effect of fever and pain and less common reactions of vaccinia rash and widespread blotchy macular rashes. Some children had rare adverse effects, such as Stevens Johnson Syndrome, encephalitis, and death.[1,2]

The panel of 10 reviewers was concerned that the risk was understated and not reflected in the consent form or protocol. They also felt the potential benefit to the individuals was overstated.[1]

Reviewers also questioned the adequacy of the safety monitoring plan and said there was not an adequate discussion of alternatives to families.[1]

THE PANEL OF 10 REVIEWERS WERE CONCERNED THAT THE RISK WAS UNDERSTATED AND NOT REFLECTED IN THE CONSENT FORM OR PROTOCOL.

The reviewers rejected the research under 45 CFR 46.405, but felt it could be approved under 45 CFR 46.407, which "finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children."[1]

After the panel's review, the U.S. Department of Health and Human Services (HHS) canceled the trials, saying that bioterrorism preparedness plans had evolved to the point that the vaccine trials were unnecessary.[1]

• Transplants using animal organs: In 1984, an infant with a congenital heart defect called Baby Fae died from transplantation rejection complications 20 days after receiving the heart of a baboon. The infant was the first infant to receive an organ from an animal, and her surgery was considered an experiment.[3]

"An IRB had approved it," Prentice says.

In 1992, surgeons and researchers transplanted a baboon liver into an adult man, who also died soon after the procedure.[4]

Despite these early failures, researchers continued to move forward with transplants involving animals because of the potential benefit to society, Prentice says.

Medical researchers are interested in xenotransplants because of the very limited supply of human organs for transplant and the much greater demand, he notes.

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Spring clean IRB reviews by focusing on review criteria

IRB chair offers this advice

As IRB workloads shift to summer schedules, it's a good time to assess whether boards are staying on mission focus, an IRB chair suggests.

"IRBs are charged to evaluate studies under federal regulations; that's our obligation," says **Jonathan Green**, MD, professor of medicine, pathology and immunology, and associate dean for human studies at Washington University and Washington University School of Medicine in St. Louis. Green also is the executive chair of the Washington University IRB.

"It doesn't mean that IRBs can't do more, but they have to at least do that," he adds. "Sometimes through what some call 'mission creep,' they do not fully fulfill their obligations."

Green has one short answer for how IRBs can make sure they stay mission-focused: Review and emphasize the 45CFR 46.111 "Criteria for IRB approval of research."

"I believe the criteria for approval are necessary and efficient for a study to be reviewed ethically," Green says.

"IRBs in evaluating studies for approval are evaluating whether those principles are met," he says. "If a study meets all criteria for approval, then an IRB can be confident it's an ethical study."

The reverse also is true, he notes. "With all of the ethical disasters, you can look back and see which criteria they didn't meet."

IRB training and continuing education programs should begin with the criteria for review approval, Green suggests.

"This is not intrinsic knowledge that we're all born with," he adds.

A first step is to show IRB members how the criteria for approval relate back to core principles.

"We have people go through two-hour training sessions before they can join the committee, and before that they have an online training program," Green says.

After training, new IRB members observe a meeting and are paired with an experienced reviewer for their first IRB reviews, he adds. "We have an IRB buddy system."

For each review, IRB members are given a reviewer sheet that explicitly asks them to answer "yes" or "no" for each question in the criteria, Green says.

"Our process is electronic, but you can fit the sheet on one page," he notes.

The Washington University IRB relies on strong chairs who keep discussions from going off on tangents by asking each time a concern is stated how that concern specifically relates to the criteria for approval, Green explains.

"If it can't be related to the criteria for approval, then it's off the table," he says. "You have to be tactful, saying, 'That's a great point; which criteria for approval are you concerned about?'"

One of the causes for mission creep is that people have vague discomfort with certain aspects of a study. But those feelings are not necessarily based on the criteria.

Another step is to reinforce education at each meeting, such as having brief PowerPoint presentations, Green suggests.

The presentation will discuss what the criteria mean and how to review a study based on the criteria. Structuring an IRB meeting around the criteria for review can save time, Green adds. ■

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IRB ADVISOR

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CNE/CME QUESTIONS

1. According to NIH's National Center for Advancing Translational Sciences, Boston physicians in 2013 were able to do which research with rapid IRB approval because of the Harvard Catalyst Network?

A. They were able to study the emotional impact of a lone shooter killing a Boston doctor at a hospital
B. After the Boston marathon bombing, they were able to quickly study the outcome of blast-related ear injuries
C. After the hurricane hitting the Eastern seaboard, they were able to study the housing and migration patterns of displaced populations
D. All of the above

2. According to AAHRPP's 2014 accreditation survey findings, what percentage of research organizations seeking accreditation from AAHRPP have issues with the element pertaining to activities overseen by HRPP, including definitions of research and what goes to the IRB for review?

A. 52%
B. 66%
C. 75%
D. 81%

3. When an IRB reviews risks of a particular study, according to Ernest Prentice, PhD, they need to keep which two points about risks in mind?

A. Risks are situational and population-dependent
B. Risks must be balanced evenly with potential individual benefits
C. People in vulnerable populations might be at less risk because their health issues have already reduced their quality of life
D. None of the above

4. IRBs that want to fulfill their mission and make meetings more efficient could focus each meeting on what, according to Jonathan Green, MD?

A. Exclusion/inclusion criteria
B. Special populations rules
C. Criteria for IRB approval of research from 45CFR 46.111
D. None of the above