IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Recent lawsuit suggests IRBs need a formal appeals process

Researcher sues Brown University

A recent lawsuit against Brown University in Providence, RI, is an important sign that it's time for research institutions to create formal appeals processes in the event of contested IRB review decisions.

When a university professor's social-behavioral study was grounded by an IRB's decline of some requested revisions, the investigator filed a lawsuit with some broad allegations against the university. Experts say this episode highlights why research institutions need to have a formal appeals process for IRB decisions.

"The Brown case will have fairly large implications," says *Monika Markowitz*, PhD, MA, RN, MSN, director of the Office of Research Compliance and Education in the Vice President's Office for Research at Virginia Commonwealth University in Richmond, VA.

Virginia Commonwealth University recently developed a formal appeals process, which Markowitz and co-author *Elizabeth Ripley*, MD, MS, described in a poster presented at the 2010 Advancing Ethical Research Conference by the Public Responsibility in Medicine & Research (PRIM&R), held Dec. 6-8, in San Diego, CA.

When Ripley and Markowitz worked on creating an appeals process they discovered that this was not on most IRBs' radar screens.

"We have not been able to find another institution that has a formal appeals process," says Ripley, who is a professor of medicine, Division of Nephrology at Virginia Commonwealth University.

The Brown case is proof that times are changing, and investigators might not accept a "no" decision from

> ***The Brown case is proof that times are changing, and investigators might not accept a "no" decision from an IRB.***

an IRB.

Jin Li, a Brown University associate professor of education, filed a lawsuit in the U.S. District Court for the District of Rhode Island on Feb. 25, 2011, alleging that Brown University has deprived her of an opportunity for review of the actions of its IRB.

Li's study involved educational testing of Chinese American children and interviews with their parents. It was funded through private foundations, and Li's IRB application stated that each family would receive $600 for three years of participation in the study, according to court documents. The IRB approved the study.

As the investigation was underway, Li observed that the lower-income subjects were spending more time completing surveys and interviews than the middle and upper-middle income families, so she decided the lower-income families should receive $600 for three years, but the other families should receive a rate of $300. She included the different payment rates in informed consent documents signed by subjects. When she submitted a request for modification of the study to the IRB, the IRB denied the request and said she could not use any data collected from families that were paid $300 unless she made arrangements to make additional payments to those families. The lawsuit states that she did not have the funds available to make retroactive payments.

"Should the IRB ruling stand, Plaintiff would be deprived of the fruits of years of research, and the educational community would be deprived of the results of the same," the court document says.

The lawsuit also alleges:

- "The limitations imposed by Brown's IRB on the Plaintiff's investigation has impeded the progress of the investigation and has interfered with Plaintiff's ability to complete her investigation in a timely, efficient, and effective manner," the court document says.
- Brown's IRB has interfered with the relationship between the Plaintiff and the foundation that awarded her the grant to conduct the investigation.
- The research is exempt from IRB review because it does not involve federal employees, federal funds, or regulation by any federal agency and it poses no threat to any human subject.
- Brown's IRB contains no minority members and fails to comply with the requirements of 45 CFR 46.107.

"One of the pieces we thought was important in having an appeals process was the idea of due process," Markowitz says. "Investigators could have a way to legitimately and fairly have their case heard."

Virginia Commonwealth University had its own event that led Markowitz and Ripley to come up with the idea of developing a formal appeals process.

"Basically it involved a study that had been approved, and it included recruitment from a

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clinic that was not associated with VCU," Ripley explains. "The IRB panel did not approve direct contact of individuals who would not have any reason to think we'd be contacting them, and this became a heated exchange with both the investigator and IRB panel firmly believing their position was correct."

There were many discussions and attempts to resolve the conflict, but the IRB panel did not think they should change their decision, she notes.

"At that point the university opted to bring in consultants," Ripley says. "The consultants' decision matched what the IRB panel said."

Also, the institution changed one of its policies about contacting people from outside the institution, and the case eventually was resolved, she adds.

The institution formed its appeal process two years ago, and the hope is that investigators will have confidence that there is an alternative pathway they can follow when a dispute seems intractable, Markowitz says.

Markowitz and Ripley wrote the appeal process written policy and procedure (WPP) and had it reviewed by IRB chairs, investigators, and other interested parties. The WPP was edited, and they included a flow chart, but a consensus on the wording quickly was met. *(See table of how appeals process works, p. 51.)*

The result is a two-page WPP document that is available as a resource for VCU staff and other IRBs or research institutions on the VCU website at www.research.vcu.edu/irb/wpp/flash/VII-9.htm.

"Since we've put this appeals process in place it has not been utilized," Ripley says. "It's the kind of thing that you hope will not need to be utilized and that you can collegially deal with issues in the usual pathways."

VCU's IRB Leadership and Enhancement Committee was involved in developing the appeals process. This committee has members representing each IRB panel, investigators, a non-affiliate IRB member, and leaders of the IRB administration and education. The appeals committee is derived from this group. The appeals committee is comprised of at least six individuals, including IRB chairs and vice chairs, a nonaffiliated IRB member, a patient advocate, the director of the Office of Research Subject Protection, one person selected by the investigator, and it's chaired by the director of the Office of Research Compliance and Education.

When an appeals committee is called, it does not consist of IRB members affiliated with the IRB decision that's in dispute.

Also, if the appeals committee disagrees with the IRB's decision, then it will send the study back to a different IRB for review and approval per the appeals decision.

"Out of fairness for everyone, we don't want to bring it back to the original panel," Markowitz says. ■

VCU office simplifies IRB appeal process

It's completed in five steps

The Vice President's Office for Research at Virginia Commonwealth University in Richmond, VA, has developed a formal process for investigators who wish to appeal an IRB determination.

The VCU's website includes the appeal process policies and procedures and describes the simple process in this way:

• **Exempt study**: Determined not to qualify for exemption by reviewer. First consider ways to modify if practicable. If no resolution, can be discussed with Panel Chair. Moved to Expedited Review.

• **Expedited**: If needed, initial discussions between reviewer and Chair can be informally referred to panel or IRB Leadership and Enhancement Committee for general discussion of issues. If no agreement, referred to Full Board.

• **Full Board:** Discussions by investigators, reviewers, panel members and informed discussions with Directors of ORSP or ORCE, the Senior Chair, consultants, and can be informally discussed with the IRB Leadership and Enhancement Committee. Full IRB Panel will make formal determination. The investigator may formally appeal to the IRB Leadership and Enhancement Committee.

• **IRB Leadership and Enhancement Committee**: The Senior Chair or Director of ORCE will receive the appeal and documents. The IRB Appeals Committee will be assembled and a meeting scheduled.

• **IRB Appeals Committee**: At the meeting the committee will focus on the unresolved issue but will review in the context of the entire project. The investigator may present the protocol and issue(s) at hand. Consultants (approved by the Chair of the Appeal Committee) may be invited to present relevant information, background, or precedent

in regard to the issue. The Chair/Vice Chair and reviewers will present relevant information from the panel's discussions and decisions. After hearing the information and reviewing the documents, the investigator(s), consultants and Panel members are excused for the discussion and voting of the Appeals Committee. Committee will reach a final decision by majority vote to either agree or disagree with the panel's decision regarding the procedure, wording, or plan as outlined by the investigator. The investigator, IO, investigator's Chairperson and IRB panel(s) are informed of the decision in writing. ■

R&D center adapts for multicenter studies

Here's how they handled the change

As a research institution's human subjects research increases, so must an IRB's work. In some cases this means expanding to handling multicenter protocols, which bring may result in new challenges.

IRB offices will need to develop new policies and procedures, as well as staff roles and tasks to handle the influx of new work that comes with multicenter protocol reviews, an expert says.

"At our site, these types of studies have been increasing for the past 10 years," says **Stephanie A. Skoler-Karpoff**, MPH, manager of the Research Support Office in the Office of Clinical Research at Memorial Sloan-Kettering (MSK) Cancer Center of New York, NY.

In 2000, Memorial Sloan-Kettering had two studies in which a Memorial Sloan-Kettering investigator wrote the protocol for a multicenter study. By 2010, there were 87 such studies, Skoler-Karpoff says.

"Every year these increase, and there are a couple of reasons," she adds. "We can accrue subjects faster and get results to transfer into practice faster."

While it's a positive trend to increasingly use multicenter studies, there are responsibilities that follow.

For instance, the IRB handling these multicenter studies will need to provide some guidance on regulatory and human subjects protection issues to the satellite sites. MSK opened its Office of Clinical Research's multicenter protocols group (MCPG) at the end of 2009 in order to provide this guidance and support.

Having a specific office handle the training and oversight of these studies can result in improved regulatory compliance and reduce duplication of effort.

"Our goal for starting this office was to provide institutional support and a repository for all of the common tools and best practices involving oversight, safety, and compliance," Skoler-Karpoff says.

Multicenter studies require more resources and staff time than single-site studies, she notes.

Having a specific office handle the training and oversight of these studies can result in improved regulatory compliance and reduce duplication of effort, Skoler-Karpoff says.

"In addition, people are just happier, having a central place to ask questions about multicenter studies," she adds.

She describes how oversight of multicenter protocol reviews works:

• **Develop new standard operating procedures (SOPs):** Research oversight and IRB offices will need new SOPs to describe regulatory requirements for multicenter study principal investigators (PIs) as well as for participating sites.

"We developed an institutional SOP that defines the responsibilities for the PI, describing what the PI's responsibilities are in a multicenter study," Skoler-Karpoff says. "It sets requirements for document language and submissions."

The SOP also sets regulatory and data submission timelines, such as describing when researchers have to submit data and amendments, she adds.

• **Create training module:** Skoler-Karpoff provides training and inservices based on the SOPs.

The training sessions last an hour and are held regularly because there are new multicenter studies beginning on a regular basis, she says.

Research staff also has access to tools and templates that help reinforce the training.

• **Use standard protocol language:** Research sites that are part of a multicenter study need to use some of the same language for both therapeutic and non-therapeutic studies, coordinated by Memorial Sloan-Kettering Cancer Center.

For instance, sites should include language pertaining to deadlines of when data and the case

report forms (CRFs) are submitted, Skoler-Karpoff says.

"We have something posted on our website that is our suggested language, and they can cut and paste these to the protocol," she says. "This way the site will know exactly what our expectations are."

• **Collect best practices**: "One thing we're doing is collecting all regulatory documents, IRB documents from outside institutions, including their informed consent form, continuing review approvals, and amendments," Skoler-Karpoff says.

Also, MSK has an intranet page that posts best practices, definitions, and templates that are useful in multicenter protocol management.

"We created processes and guidelines for sites," Skoler-Karpoff says. "We have guidelines for auditing participating sites and best practices for communication."

Also, there is a PowerPoint presentation available to use at start-up meetings, she says.

"It's a skeleton that they can fill in with details as needed," she adds. "So it's a lot easier for them, and there is no reason to reinvent the wheel."

• **Track each site's protocol life cycle:** "We have a sophisticated system that tracks all IRB documents, including serious adverse events (SAEs), and other data, and it's available for all research studies" Skoler-Karpoff says. "The system, which was not part of the multicenter initiative, allows us to see each site's information, including their accrual information."

The tracking system also allows the oversight office staff to look at the study's latest amendments and continuing review data. And it can send out automatic email reminders to the different sites about upcoming deadlines.

"We can see all the documents associated with that IRB approval, any correspondence and documents," she says.

The system will show the timeline for each site's local IRB approvals and it emails the MSK oversight staff information about continuing reviews. "It will send an email to me that says, 'In 30 days, this institution's site's IRB approval is expiring,'" Skoler-Karpoff says.

The tracking system also enables oversight staff to easily look up the names of consenting officials at each site, saving them the time and trouble of calling coordinators for this information, she adds.

Investigators benefit from this assistance.

"We remind them each week of documents that are pending and need to be submitted for approval," Skoler-Karpoff says. ■

Assuring IRB submissions are mistake-free

Address policies, encryption, etc.

IRB application submissions often lack consistency, have omissions and errors, and other problems that IRBs should teach investigators to anticipate and correct before filing their application. Among these mistakes are policy errors, data security concerns, and other procedural problems.

An IRB expert offers this advice for how to correct and prevent the more common procedural and policy mistakes in IRB applications:

•Unable to verify if research procedure described in protocol is consistent with university policies: "Sometimes we don't have enough information about the recruitment procedures to see if it's consistent with our policies," says **Donna B. Konradi**, PhD, RN, CNE, chair of the IRB at the University of Indianapolis and an associate professor in the School of Nursing at the University of Indianapolis in Indianapolis, IN.

Institutional policies regarding involving students in research, using campus labs, and providing protection in the event of participant injuries are all items that need to be addressed in the submission application when they're relevant to the described research projects.

For example, if a study involves using a campus physical therapy lab and a participant is injured during a procedure, then the way this adverse event is handled needs to be fully addressed.

"We need to know those procedures are built into the research protocol," Konradi says.

REMEDY: "We refer investigators to the policies on our website," she says.

Institutions often have policies on medical emergencies and accidents, student research participation, access to the research pool, and other issues that investigators need to check for consistency with what is in the IRB application.

• **Data security concerns**: Investigators sometimes omit information or explanations about data security procedures they use, Konradi says.

"Sometimes their explanations are insufficient given the type of data they're collecting," she adds.

They need to describe their procedures for data storage and make certain their descriptions are consistent between documents.

For instance, the IRB submission should be clear on whether data are de-identified, coded, or

anonymous.

If investigators are storing coded data, then the data should not be stored in the same file as the code because that's insufficient protection, Konradi says.

"We need to know if they have coded data, where they're storing the code, and what their security procedures are for the code, such as data encryption and password access," she adds.

REMEDY: "Our information services department in the last year has done a good job of educating the research community about our new encryption software," Konradi says. "This conversation is very important; you need to give people the heads up that security is a problem and something they need to think about."

Institutions can prevent data security issues with technological changes, as well.

For instance, new campus computers at the University of Indianapolis now have encryption software embedded, which minimizes data security risks.

"Over time, some of these problems will be greatly minimized from the faculty perspective," Konradi says. "We'll still have some student work and a problem with transporting data."

• **Qualifications of research team members:** Researchers and staff need more than online CITI training, although that's a good starting place.

The IRB needs to know students involved in research projects have been appropriately trained to carry out their assigned activities.

"If they're administering a mini-mental status exam, we need to know they've been trained to do that," Konradi says. "There should be a brief paragraph describing the training."

Likewise, research staff members need to know how to operate all of the equipment that will be used in a research project, and the IRB should be told how they've been trained to handle cases of accidents and injuries, she adds.

REMEDY: IRBs should require investigators to post institutional procedures in labs and other locations where research procedures take place, Konradi suggests.

"They should train students and staff on the procedures and then post the procedure process in the lab so if there's a problem there is a ready reference available," she adds.

Investigators should provide staff qualifications on their IRB applications, showing that each person who will be performing a procedure has been trained or is otherwise qualified to do so.

• **Scientific design and design-related issues:** Investigators sometimes submit applications that fail to make it clear how the study they propose to do is related to the state of the science or previous research, Konradi says.

"They haven't shown us how this study is the logical next step in the research and how it builds on what is identified in the literature," she explains. "You can't just go out and do something because you want to do it – there has to be a logical progression."

Sometimes IRB members can find no link or relationship between the research question and the types of data they are collecting, she notes.

"Investigators need to make clear connections between all those elements," she adds.

Another design issue involves investigators not differentiating between inclusion criteria and research-related interventions, Konradi says.

"Maybe the inclusion criteria would say that participants have to receive health clearance from their physicians," she says. "But the investigator asks participants to provide study-related data before obtaining medical clearance for participation from the physician."

REMEDY: Educate research staff and investigators about this issue.

Also, it helps for investigators to have someone proof-read their protocol and make sure they've connected all dots and links to the research question and proposed data collection.

"Sometimes it helps having a researcher who is not in your area of expertise look at the protocol and see if these elements are lined up in a way that's appropriate," Konradi says.

• **Research-ready documents:** When an IRB submission involves an electronic survey, IRB members will want to see an active link to the survey. They'll want to be able to view the survey in the precise way that participants will view it, so just a print-out is not adequate for the review process.

Also, researchers might say their collection procedures are anonymous, but then they have the subject fill out forms in a way that is not anonymous, so the IRB needs to see the research-ready tools, Konradi explains.

"I want to see the survey as it fits into the electronic survey hosting system before doing the final IRB sign-off," she says. "And the informed consent documents need to be ready for an IRB stamp on the letterhead."

REMEDY: Again, educating researchers and staff is the main remedy.

Research institutions also might provide electronic letterheads so researchers could use these

instead of photocopied or printed letterhead paper when writing informed consent documents, she notes.

IRBs can delay looking at links to surveys and other tools until the final IRB review of the research protocol, Konradi says.

"The committee might be okay to look at the survey on paper or in an electronic document form, but before the final sign-off, I need to see it in the hosting system," she adds. ■

Protecting participants in first-in-human trials

Carefully review preclinical studies for clues to treatments' potential

First-in-human clinical trials raise difficult ethical issues for researchers and IRBs because of the uncertainty that accompanies them. Did the preclinical studies that preceded them provide enough information about effectiveness and risks and benefits to proceed with human volunteers?

Too often, positive expectations from those earlier tests do not end up translating well to results in human research, says **Jonathan Kimmelman**, PhD, an associate professor of biomedical ethics at McGill University in Montreal.

"I've studied areas like gene transfer, and there's an example of a field that's been characterized by this kind of boom-bust cycle where very promising preclinical trials come forward, they're rushed into human trials and the agent turns out not to have the activity that everyone was expecting and hoping for from the preclinical studies," he says.

Kimmelman says IRBs need to be able to look critically at proposed first-in-human trials, particularly in the area of balancing risks and benefits.

"The vast majority of drugs that enter into human trials never survive to licensure," he says. "So there's a lot at stake in making good decisions at the point of initiating human studies.

"If you make a bad decision at that point, you end up exposing many patients to a drug that has an unfavorable risk-benefit balance and you end up investing many resources into developing a drug that turns out not to be promising enough for licensure."

He says IRBs may mistakenly think that if the Food and Drug Administration has approved the drug for human trials, it has adequately vetted its potential for efficacy.

"If you make a bad decision at that point, you end up exposing many patients to a drug that has an unfavorable risk-benefit balance and you end up investing many resources into developing a drug that turns out not to be promising enough for licensure."

"The FDA is mainly concerned about making sure that the investigators have a pretty good handle on the toxicity of the drug," Kimmelman says. "It's really up to IRBs to be vetting first-in-human studies for clinical promise."

Preclinical studies key

The key to evaluating first-in-human trials is having reliable information about prior non-human studies, Kimmelman says.

In an article in the journal *PLoS Medicine*, Kimmelman and his colleague, Alex John London of Carnegie Mellon University, argue that predictions about the potential of an investigational drug are too often based on prior studies that may have problems themselves (such as lack of randomization in an animal study, for example) or that may not be comparable to the proposed human study under review.

Sorting this out can be difficult for IRBs, due to the complexity of early phase trials.

"These are not garden-variety clinical trials," Kimmelman says. "They involve a very high level of expertise, not just in the clinical realm, but also in understanding the preclinical realm. One of the challenges of reviewing early phase studies is that it can be very difficult for IRBs to have qualified personnel to review those studies."

He says IRBs should be ready to seek out the necessary expertise to deal with a particular study. And they should look, wherever possible, to outside resources such as the NIH's Recombinant DNA Advisory Committee, which reviews human gene transfer research.

"In certain areas, such as areas of gene transfer, centralized oversight really provides an opportunity for experts to weigh in on the quality of preclinical studies," Kimmelman says.

IRBs also should hold investigators and sponsors accountable for ensuring that all relevant

studies have been included.

"There is some pretty solid evidence that not all preclinical data get published," Kimmelman says. "And it's not entirely clear what proportion of preclinical data actually end up getting shared with IRBs. If you're an IRB member, you want to be sure that you're not just looking at the most positive outcomes from the preclinical studies, you want to make sure that you're looking at all the preclinical studies."

Informed consent issues

When there's a lack of strong data on a new experimental agent, researchers should cast the net wider, Kimmelman says, providing information to IRBs about other drugs that work in the same way or that have other important similarities to the study drug.

Those other relevant studies shouldn't just influence IRB review, they should be included in the informed consent in a trial going forward, he says. Because first-in-human studies deal with such unknown quantities, informed consent must give participants any information possible that can aid in a decision.

"To simply say, 'We don't know how well this drug is going to perform,' you're telling a patient that there's somewhere between a 0 and 100 percent chance that the drug is going to have the clinical activity that's predicted in preclinical studies," Kimmelman says. "That basically has no informational content at all. What we're saying is if there is a record of similar interventions going forward, and not succeeding in clinical trials, patients should be told that."

And he says IRBs should consider carefully the type of subject who is to be enrolled in a first-in-human trial.

One approach taken in many studies is to limit enrollment to patients for whom there has been no effective treatment to that point.

"If you enroll patients who have advanced disease, they have less to lose if there is no clinical activity or if there turn out to be risks that were unanticipated," Kimmelman says.

On the other hand, a person whose illness is well managed by existing treatments has greater potential for his or her quality of life to be harmed by participating in a first-in-human trial.

"You want to have a good justification for enrolling patients who have other treatment options," he says. "You want to be able to say that your new agent is competitive with those other treatment options. And in order to do that, you need to be able to make reliable predictions about the clinical activity of your drug.

"If you apply the procedures that we recommend and you conclude that effects that you saw in animals are unlikely to generalize to human beings, then I think you should be very cautious about enrolling patients who have other treatment options."

REFERENCE

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Survey shows DSMBs' structure, operations

IRB members among those who say there should be tougher requirements

A data and safety monitoring board (DSMB) can be crucial to protecting participants in higher-risk studies, by reviewing the accumulating study data for potential emerging risks and if necessary, by recommending that a study be changed or even halted as a result.

While the FDA and NIH have created guidelines for setting up and operating DSMBs, they do not address all of the varied ethical issues that arise in trials that involve substantial risks, says **Patti Tereskerz,** JD, PhD, an associate professor of medical education and director of the Program in Ethics and Policy in Healthcare at the University of Virginia in Charlottesville.

Tereskerz says there's also a lack of information about how DSMBs are structured and how they operate. She and her colleagues set out to fill that void by surveying past and current members of DSMBs, as well as investigators and IRB community members, to see not only how DSMBs operate, but how participants thought they should be operating.

What they found were some significant differences between what participants thought should be occurring and how DSMBs actually worked – in training, in membership, in conflict of interest rules and other areas.

She says IRBs should take note of these discrepancies when they're reviewing data and safety monitoring plans for clinical trials.

"They should look carefully where there is a difference between what investigators and statisti-

cians thought should be happening and what is happening," Tereskerz says. "And maybe they should push for some more of the requirements that these folks think should be in place."

She notes that the IRB community members surveyed also differed from investigators and statisticians in how they thought DSMBs should be run, nearly always recommending tougher requirements than the other groups.

"I think that's an important take-home message – that IRB members wanted more stringent requirements."

Results from the survey were published in a recent issue of the journal *Accountability in Research*.

IRBs as public proxy

Tereskerz says that the community IRB members included in the study actually were intended to serve as a proxy for public opinion, rather than for any technical expertise. In fact, nearly 30 percent of the 95 community IRB members surveyed had never heard of a DSMB prior to this study.

But because of their service on IRBs, they were likely to be much more conversant with research ethics issues than the average person and so could credibly represent the public's opinion, Tereskerz says.

"We realized if you just did a survey of the general public, they probably wouldn't have any idea of what you're talking about," she says. "We wanted someone who would be representative of the community, but at the same time had sufficient knowledge of what data and safety monitoring involved and that's how we came up with IRBs."

Those who actually served on DSMBs and the investigators who worked with them were asked about the structure of those boards DSMBs:

—Were members trained, and were they paid? Did membership include a community representative, an attorney or a bioethicist?

—Were minutes kept of meetings?

—Were there conflict of interest rules? Were sponsors and statisticians blinded? Was an independent biostatistics center used?

—Were stopping rules established? Were there rules in case members or the sponsors disagreed?

Tereskerz's team also asked all of the participants, including the community IRB members about their opinions regarding all those issues.

In every case, actual DSMB practices failed to live up to the ideals set by the participants.

For example, while all the participants believed that people should be trained or required to serve an apprenticeship before serving as a DSMB member, only 15 percent of those who served actually were trained or apprenticed prior to their most recent DSMB service.

All but one of the 267 participants thought a DSMB should have conflict of interest rules, but only 55 percent of members reported that their most recent DSMB had such rules.

Two-thirds of those surveyed thought there should be a bioethicist on a DSMB, but only 16 percent reported that a bioethicist had served on their own DSMB.

Compared to the other survey participants, community IRB members were more likely to want members to be trained, an independent biostatistics center to be used and for there to be a community member on the DSMB.

They were less likely to ask for sponsor and statistician blindedness. Tereskerz says she's unsure why the issue of blindedness was not as important to IRB members as it was to statisticians and investigators. She does note that investigators are acutely aware of conflicts of interest that can arise in an industry-sponsored study.

"I'm not sure that IRB members are as aware of those issues in terms of conflict of interest," she says.

Conflict over IRB participation

Tereskerz notes that others involved in the study were somewhat critical of her plan to interview IRB members for this survey.

"I actually got pushback about including IRB members – I had to fight for that," she says. "The argument was that they don't have the technical knowledge, investigators should decide.

"And I said, wait a minute, this is research, this is about trust. You're talking about clinical trials, adverse events, stopping or not stopping a study," Tereskerz says. "If you want people to enroll in research, you have to have trust."

Tereskerz would like to see IRBs use this information to ask more pointed questions about data and safety monitoring plans during review. But ultimately, she says, the best way to address this issue would be to strengthen guidance about the structure and operation of DSMBs.

"You can use this data to say look, there's a discrepancy between what experts think should happen and what is happening," she says. "Don't we need to modify or begin to produce guidance that addresses some of these issues?"

REFERENCE
Tereskerz PM, Guterbock TM, Kermer DA, et al. An Opinion and Practice Survey on the Structure and Management of Data and Safety Monitoring Boards. *Account Res* 2011 Jan;18(1):1-30. ■

TMI in informed consent?

Contraceptive knowledge study raises issues about how much to tell participants

Can the informed consent process actually provide too much information? That's the contention of HIV researcher **Susan Allen**, who points to a recent study she tried to conduct in Zambia of participants' knowledge about contraceptive options.

She says that IRB-mandated additions to the informed consent gave away too much of the educational content of her study, making it impossible to discern how much participants learned about contraceptive methods from the program she was testing.

Allen says that when reviewing studies such as this one, which test participants' knowledge, attitudes and behaviors, IRBs need to be alert to the possibility of contaminating the group being studied.

"I have always been above and beyond the call of duty when it comes to what education you provide (in informed consent)," she says. "But when you're actually trying to test an intervention and then you muddy the waters by having to give information like that in the consent, it's really a problem."

Allen, MD, MPH, DTM&H, is currently director of the Rwanda Zambia HIV Research Group, based at Emory University in Atlanta, GA. However, her experience with the study in question occurred with an IRB at another institution.

She was studying knowledge about contraceptive options among two types of couples in Zambia – those where both partners were infected with the HIV virus and those couples where one partner was infected and the other wasn't (called sero-discordant couples).

The plan was to test couples' baseline knowledge of different contraceptive methods, including pills, injectables, implants, IUDs, tubal ligation and vasectomy.

The couples were randomized to interventions that included a video showing family planning information and a control group video that provided other health information. Participants then were retested to see how well the family planning education worked.

Adding to the consent

Allen says the Zambian IRB approved the study without reservations. But the American IRB raised concerns that some participants would not receive family planning information during the course of the study. As a result, the IRB required that contraceptive information be disclosed to all participants in the informed consent video they viewed beforehand.

"We said, 'Wait a minute, that's part of the intervention,'" Allen says. "If educating people about the different family planning options is included in the informed consent, then we're really not going to have a control group."

And she noted that even if participants didn't view the family planning video, they were being provided with an alternate video that talked about important health issues such as nutrition and malaria prevention.

But she says the IRB argued that in a low-resource country such as Zambia, this might be participants' only chance to receive family planning information

"Their position was that since they could not get those methods elsewhere, it would be unethical to withhold that information."

So Allen's team went forward with the study as approved by the IRB, but also found a way to create a control group to look at the effects of the changed informed consent, by looking at results from a separate observational study of sero-discordant couples in Zambia. That group had not been given family planning information in their informed consent.

The results were as Allen had predicted – despite any significant differences between the two groups of couples, those who had viewed the family planning study's informed consent video had much higher levels of knowledge about some of the contraceptive methods.

Allen says that by creating that higher baseline knowledge in those who watched the family planning informed consent video, it became impossible to accurately measure the effects of the later family planning video education.

How can you enroll women into your study when you know that 75 percent of them are married and that their greatest risk of getting HIV is from their husbands?

"The informed consent changed things before the intervention even began," she says.

In discussing the aftermath of the study, Allen says that it might have been possible to craft a debriefing after the family planning study that could have brought control group participants up to speed on contraceptive methods without contaminating the sample.

But she says this study is an example of a more widespread tendency among American IRBs to want to give research participants in poor countries such as Zambia greater access to health care resources found in countries such as the United States, even to the detriment of research that might improve public health in those poorer nations.

"IRBs need to get comfortable with the idea that in low-resource settings, people are not getting a lot of things," Allen says. "The standard of care in these settings is often pretty poor.

"Your research study is going to change that for a couple thousand people, but it's not going to change it for the other 2 million people. Asking researchers to make a little cocoon for the 2,000 people while doing a disservice to the 2 million is not a good thing."

Couples testing option

Ironically, Allen herself lobbies vigorously for enhancing informed consent in HIV studies in Africa, saying that it should include information about voluntary couples HIV testing, which she calls a low-cost, high-impact intervention.

Compared to interventions such as male circumcision and vaginal microbicides, couples testing works just as well, she says. But Allen says informed consents for trials of these other interventions usually fail to discuss couples testing as an option.

"How can you enroll women into your study when you know that 75 percent of them are married and that their greatest risk of getting HIV is from their husbands?" she asks.

"I've really been trying to advocate that you must include two or three sentences in your informed consent that say: 'If you are married, your greatest risk of HIV comes from your spouse. We strongly encourage you to be tested with your spouse and we will either provide that service for you or we will refer you to a place that provides it.'"

REFERENCE

Stephenson R, Grabbe K, Allen S. The influence of informed consent content on study participants' contraceptive knowledge and concerns. *Stud Fam Plann* 2010 Sep 1;41(3):217-224. ■

CNE/CME OBJECTIVES

The CNE/CME objectives for IRB Advisor are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

- ■ Bridging cultural gaps by using translators
- ■ How is the battle against "mission creep" going?
- ■ Improve your IRB's response time for expedited reviews
- ■ Assess member education effectiveness
- ■ Research ethics becomes focal point of new presidential panel

CNE/CME QUESTIONS

17. A recent lawsuit (Li v. Brown) contains allegations by a professor and investigator that Brown University and its IRB did which of the following to an investigator seeking approval for changes made to a study's subject incentives?
A. Impeded the progress of the investigation
B. Interfered with the relationship between the plaintiff and the foundation making the grant award
C. Deprived the Plaintiff of an opportunity for review of the actions of its IRB
D. All of the above

18. Which of the following is not a good strategy to employ when a research institution expands to multicenter studies requiring institutional oversight?
A. Create a training module based on standard operating procedures
B. Use standard protocol language for both therapeutic and non-therapeutic studies
C. Have one investigator become the point person for all questions posed by research coordinators from the other sites involved in the study
D. Collect regulatory documents, IRB documents, and other best practices from outside institutions

19.True or False: Informed consent for first-in-human trials should include information about the performance of drugs that work in similar ways as the study drug.

20.Among investigators, biostatisticians and IRB community members surveyed about data and safety monitoring boards (DSMBs), IRB members:
A.Wanted more stringent operating requirements for DSMBs in most areas;
B.Wanted less stringent requirements than others surveyed;
C.Were less concerned about sponsor blindedness than other groups;
D.Both A and C.

Answers: 17. D; 18. C; 19. True; 20. D