IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Fallout from controversial OHRP decision regarding IC may confuse PIs, IRBs

Media attention highlights unclear guidance

Whatever IRB members might think happened in the recent regulatory controversy over studying the use of infection control checklists in Michigan hospitals, the truth might be stranger.

It was at least a complicated situation when the Office of Human Research Protection (OHRP) of Rockville, MD, clashed with researchers at Johns Hopkins University (JHU) School of Medicine in Baltimore, MD.

What started as a straightforward research assessment of using proven infection control practices to reduce infections among patients on catheters in the intensive care unit of hospitals, turned into a national controversy that involved hospitals across the state of Michigan and a 45-mile radius in Maryland that includes Johns Hopkins researchers, IRBs, and OHRP regulatory officials. **(See how it unfolded, p. 40.)**

OHRP's investigation into the infection control research was prompted by a telephone caller who complained that investigators had not obtained IRB approval. Only, this complaint was inaccurate, a Johns Hopkins investigator says.

Before conducting the study, JHU investigators had contacted the IRB and were told the study was exempt from IRB review,[1] says **Peter J. Pronovost**, MD, PhD, professor of the departments of anesthesiology and critical care, surgery, and health policy and management at JHU School of Medicine. Pronovost also is the medical director of the Center for Innovations in Quality Patient Care and director of the Quality and Safety Research Group, also in Baltimore.

"The Hopkins IRB is quite sophisticated," Pronovost says. "We originally had intended to submit the study for expedited review, and they said that it was quality improvement and it was exempt, so we submitted it as exempt."

After some exchange back forth, OHRP Director **Kristina C. Borror**, PhD, sent JHU officials a letter on Feb. 14, 2008, stating that the research likely would have been eligible for review by the IRB in an expedited manner.

"This highlights how there is lack of clarity in the regulations if a

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sophisticated IRB could interpret it differently [than OHRP]," Pronovost says.

A bigger problem was OHRP's initial stand that JHU needed to obtain informed consent from all patients and IRB approval from each of the 67 hospital sites, he notes.

Since the infection control measures were used for all patients to compare outcomes to previous experience, obtaining informed consent would have been a major obstacle. Plus, it could be argued that the health care team, whose IC practices were being evaluated, could be the study's participants.

Even if the patients are seen as the likely subjects, their risk was greater if the infection control practices were not implemented, Pronovost says.

The infection control practices were based on previous research evidence that such practices as using full barrier precautions when inserting central venous catheters were optimal for preventing infections.[2,3]

Waiver of informed consent is allowed when the below four conditions are met, according to **Ivor Pritchard**, PhD, acting director of OHRP, who answered IRB's questions about the controversy in an e-mail:

- the risk to the subject is minimal;
- subjects' rights and welfare will not be adversely affected by the waiver;
- conducting the research without a waiver is not feasible or practical; and
- if appropriate, subjects are provided subsequently with additional pertinent information.

OHRP's original stance was that since the research had not sought IRB approval, the informed consent could not be waived. But in the Feb. 14, 2008, letter by Borror, OHRP noted that "the human subjects research activities described in the initial grant and IRB applications, as well as similar activities, would likely have been eligible for waiver of informed consent."

Unintended consequences

The IRB review requirement also could have unintended consequences.

If IRB review is required for all sites involved in research that reviews quality improvement data about the use of evidence-based best practices, then there also is a social justice issue.

"I think requiring IRB approval at each site creates some challenges with social justice," Pronovost says. "Forty percent of Michigan hospitals are rural, and this [requirement] can constrain hospitals that don't have an IRB."

What might happen is that smaller hospitals that don't have an IRB would choose not to participate in the project, and then their staff would not learn to follow infection control best practices, and their patients would suffer from greater infection rates, as a result, Pronovost explains.

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Editorial Questions

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Pronovost suggests the entire controversy might have been avoided if investigators had checked a different box on the IRB submission forms.

"Even if we had submitted it as expedited instead of exempt, it would have been a trivial difference in work," Pronovost says.

When researchers responded to OHRP's request and letters, they did resubmit the protocol to the IRB, asking for an expedited review, he notes.

"We checked a different box, and it was quickly approved," he says.

The issue also highlights the problem of regulatory agencies overreacting to complaints, Pronovost says.

"I believe the complaint about our study was signed by a concerned citizen, and that same person has filed several other letters to OHRP," he says. "If you think about the enormous work and burden that one letter caused, then we may need a more judicious response to letters."

The Michigan hospitals can continue to use the checklist and collect data for their quality improvement programs without considering the U.S. Department of Health and Human Services regulations regarding the protection of human research subjects, Pritchard says.

"The regulations do not apply when institutions are only implementing practices to improve the quality of care," Pritchard says.

"At the same time, if institutions are planning research activities examining the effectiveness of interventions to improve the quality of care, then the regulatory protections are important to protect the rights and welfare of human research subjects," Pritchard adds.

OHRP sends the wrong message to health care organizations when the agency suggests that medical institutions should engage in quality improvement projects without analyzing their effectiveness, Pronovost says.

"If there are any quality inferences made about quality of care, then we need to make sure data are accurate," he says.

In the JHU case, the follow-up research that would show whether the infection control measures and checklist have resulted in long-term reductions in infections is on hold until the Michigan hospitals receive local IRB approval, Pronovost says.

Although OHRP's latest response to Michigan hospitals is that they do not need to obtain IRB review because they are not using federal funding for the QI efforts, there remains a chilling effect on the data collection out of fear of further OHRP scrutiny, he suggests.

And this chilling impact can be seen with other institutions and IRBs around the country.

"Colleagues around the country say IRBs are hardening up because they don't want to be at risk, and no institution or investigator will want to accept that risk," Pronovost says. "So if there's that fear then what we need is greater clarity in the regulations."

OHRP has indicated that the issue should be laid to rest at the Michigan hospitals because the data collecting doesn't involve human subjects research.

"At this point the interventions that were originally part of the research study are now being implemented by the Michigan hospitals solely for clinical care purposes, and the only data being released by hospitals in Michigan to JHU for research purposes are de-identified data that are collected for clinical purposes," Pritchard says. "We believe that the project has now evolved to a stage where JHU is no longer engaged in human subjects research as defined by the regulations related to this project."

IOM may provide clarity

Pritchard also notes that OHRP will continue to work to develop guidance to assist institutions in determining when the regulatory protections are required and appropriate and when they're not.

"This area has always been murky for IRBs, and it's been murky for OHRP," Pronovost says. "OHRP says 'We're interpreting the regulations quite narrowly,' and they're certainly much tighter than some IRBs."

There will soon be an opportunity for a discussion about achieving greater clarity when the Institute of Medicine (IOM) of Washington, DC, convenes an invitation-only session on this controversy on May 1, Pronovost says.

"I think the IOM dialogue is going to get us there," Pronovost says. ■

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Here's how the Johns Hopkins and OHRP controversy unfolded

One complaint set it in motion

It all began when investigators published a study that had good news for the infection control industry.

Investigators at Johns Hopkins University (JHU) of Baltimore, MD, studied a quality improvement project that used an infection control checklist at 67 Michigan hospitals. The study was funded by a grant from the Agency for Healthcare Research and Quality. The goal was to reduce catheter-related infections in intensive care units.[1,2]

JHU investigators wanted to build on past literature regarding the successful use of routine infection control practices to reduce infections among hospitalized patients.

For example, each of the items on the checklist was based on infection control literature, showing efficacy, and they included such simple procedures as having clinicians routinely wash their hands.[1,2]

The research ultimately showed that the checklist was a simple way to dramatically reduce catheter-related infections.[1,2]

Someone who had read about the study's results in a 2006 issue of *New England Journal of Medicine* complained to OHRP that investigators had not sought IRB review.

This set in motion the OHRP investigation, ultimately resulting in confusion among the hospitals where follow-up data still were being collected. JHU investigators found that their follow-up data collection was put on hold until OHRP was convinced that all necessary human subjects protection measures had been taken.

Then on Dec. 30, 2007, *The New York Times* published an op-ed story by Atul Gawande in which he chastised OHRP for its "bizarre and dangerous" decision to shut down the QI program at Michigan hospitals.

OHRP responded to *The New York Times* article on Jan. 15, 2008, with an e-mail statement, saying that the agency had not prohibited Michigan hospitals from implementing the infection control checklist for QI purposes.

"At the same time, if institutions are planning research activities examining the effectiveness of interventions to improve the quality of care, then the regulatory protections are important to protect the rights and welfare of human research subjects," OHRP officials wrote in the e-mail statement.

OHRP sent separate letters to JHU and the Michigan Health & Hospital Association of Lansing, MI, on Feb. 14.

In the letter to MHHA executive director Brian Peters, OHRP Director **Kristina C. Borror**, PhD, writes that OHRP acknowledges that no federal funds support the continuation of the quality improvement research initiative at the Michigan hospitals.

Borror also says that the Michigan hospitals do not need to obtain IRB approval because the research activities no longer involve human subjects and because there is no federal funding involved.

"If you still wish that IRB review and approval be obtained before continuing these activities, we note your desire to go above and beyond the regulatory requirements in this case," Borror writes.

In the letter to Daniel E. Ford, MD, MPH, vice dean for clinical investigation at JHU, Borror notes that the principal investigator of the QI study was granted IRB approval on Jan. 4, 2008.

"However, as noted above, the activities no longer involve human subjects research," Borror writes. "Therefore, it is not a regulatory requirement for you to obtain IRB review and approval for these activities before continuing with data analysis."

On Feb. 21, 2008, the *New England Journal of Medicine* published two editorials about the controversy.[2,3]

The first opinion piece says that OHRP is wrong about needing informed consent for quality improvement research. The writers state that it is justifiable from both ethical and regulatory perspectives to waive informed consent for low-risk research when soliciting IC is not practical.[2]

The second editorial makes the case that by adding bureaucratic complexity to QI research, OHRP is exposing patients to more harm than benefit.[3] ■

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Survey helps evaluate IRB's efficiency, performance

Provides checks and balance

How well is your IRB doing? It depends on who you ask. The subjectivity of any answer makes it a difficult question to measure.

This is why an IRB chair at the Boston University School of Medicine in Boston, MA, decided to take the direct approach and survey IRB members anonymously about their own impressions of the IRB's successes and shortcomings.

"As a chair of the IRB, it made some sense to find out what committee members felt about the committee's performance," says **James A. Feldman**, MD, MPH, a research director for the department of emergency medicine and an associate professor of emergency medicine at BUSM.

Feldman reviewed available literature about IRB performance measures and found little out there. While some IRBs have used trained observers of IRB meetings to measure performance, Feldman decided to simply ask board members for their opinions, under the theory that an anonymous survey would elicit more candor.

So Feldman and a co-investigator developed an anonymous survey instrument to compare several different IRBs within one institution.[1]

The survey tool used a 6-point Likert scale to determine whether the IRB meetings were efficient, and it also had a section for comments.[1]

"We took the feedback seriously, and we went through all of the qualitative comments and discussed them," Feldman says.

Researchers presented the survey's results and comments to the IRBs and encouraged discussion about any suggestions or comments that might show a need for improvement.

For example, one comment was that reviewers would present their conclusion before all IRB members had a chance to speak. The comment said this was intimidating for anyone who might disagree with the reviewer's conclusion, Feldman recalls.

"When I told IRB members about this comment, they said they were surprised because they hadn't thought about it and had only presented conclusions first to help move the meeting along," Feldman says.

Although the survey results showed that overall IRB members agreed strongly that the chair allowed all sides to be heard on important issues, the qualitative comment provided an additional perspective that would be addressed.[1]

Feldman's IRB has four reviewers, and it is possible to see how they might bias the committee's opinion of whether a protocol is approved or rejected, he notes.

Efficiency and fairness

The three IRBs surveyed all showed that members felt their IRB meetings were efficient, Feldman says.

"It was reassuring that people had quite positive feelings," Feldman says. "People on the boards feel we do focus on major risks to human subjects, and when we don't approve a protocol, it's based on the regulations."

Feldman sees this as the kind of response research professionals might desire from the IRB.

"You want a sense that people on the board feel that they're coming to decisions that are founded and grounded in the regulations and that they don't reflect some other factor of why someone thinks a study should not be done," Feldman says.

For instance, investigators would be more comfortable with an IRB that concentrated on the risks to human subjects and did not spend a lot of time micromanaging the informed consent form, he says.

As chair, Feldman feels responsible for keeping the IRB meetings no longer than necessary, while still covering everything that's needed.

The survey showed that IRB members were satisfied with the meetings' timeliness, and that was gratifying, he says.

"It's a tremendous, unpaid time commitment for people," Feldman notes. "To devote time to read detailed and accomplished protocols it takes a lot of time for me as the chair and for members of the committee."

Feldman created a PowerPoint presentation with the survey's results.

With this he showed how respondents strongly agreed that inviting principal investigators to meetings helped clarify some issues. Also, he showed that IRB members agreed that the educational sessions were useful, but their agreement was less enthusiastic than it was for other questions.

Here are some sample questions, answered with a 6-point range from strongly disagree to strongly agree, from the anonymous IRB survey:

• Board meetings make efficient use of my time;

• The chair allows all sides on important issues to be heard;

• The IRB is effective in its mission to protect human research subjects;

• I feel free to present my opinion to the board;

• Inviting principal investigators to board meetings has helped clarify important issues; and

• When protocols are not approved by the board, the reasons are based upon the 111 criteria.

In another section of the survey, participants are asked to describe some items according to whether they are too short, about right, or too long on a 5-point scale.

Here are some samples of those items:

• duration of meetings;

• time reviewers take to present protocols;

• amount of time spent discussing new protocols; and

• amount of time spent reviewing protocols to prepare for an IRB meeting.

Feldman presented the qualitative comments to the IRBs, as well. But he omitted some that were not relevant to a performance improvement discussion, such as a comment saying, "The chair is great," he says.

Here are some sample items from the qualitative comments:

• "Would like us to remind investigators to write study summary in terms that all can understand."

• "Reviewers should never read out loud a report that's already in system — just hit the high points. Most do this."

• "We don't necessarily need to review the entire protocol for a progress report — just discuss the big picture of how the study is doing."

• "Possibly an ombudsperson for PIs planning to submit new protocols."

• "I'd like us to think more about an approval that is a true final approval but excises minor changes by the investigators who subsequently report compliance."

• "More board education!"

• "Should have a standard of confirming comprehension for studies that deserve special scrutiny — a description to be made by the board."

In all, the anonymous survey proved to be a useful tool for finding areas that an IRB could improve and discuss, Feldman says.

"I've received a very positive response to it, so it's well worth doing," Feldman says. ■

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IOM committee finds Privacy Rule causing problems for research

Changes to regulations, HHS guidance urged

An Institute of Medicine (IOM) committee studying the effects of the HIPAA Privacy Rule has painstakingly documented the strain it is putting on research.

It commissioned surveys of investigators who complain that HIPAA regulations stymie important research and are interpreted inconsistently from one institution to the next.

A survey of IRBs showed concerns about the complexity of patient forms and the lack of guidance in interpreting the rule.

Even privacy advocates made their case to the committee that the Privacy Rule is not protective enough of patient privacy.

"It seems like nobody is very satisfied with what's going on," says **Sharyl Nass**, PhD, study director for the IOM HIPAA project. "It's a little disquieting, because it's a fairly substantial set of recommendations and it probably costs a fair bit of money to adhere to them, and if no one's happy with them, it's a problem."

Nass says the IOM launched the committee last spring, in response to a forum that aired anecdotal stories about HIPAA's stunting effect on research. The committee's goal is to craft a set of recommendations to address the problems posed by the Privacy Rule.

To do that, however, committee members realized they would need more than anecdotes describing individual problems with HIPAA, Nass says.

"We wanted to try and get a more national systematic examination of the issue and that's a difficult thing to do," she says. "It's not something that the IOM normally takes on. We usually look at the available evidence that's already out. But in this case, because we knew there was relatively little out there, we actually took the

unusual step of commissioning several surveys to try and provide some additional input to the committee."

The committee heard presentations on these surveys at meetings in October 2007 and February 2008, and has begun deliberations on a final report.

Nass says a draft report of the recommendations, which could include new guidance, proposed changes to the Privacy Rule, or both, likely will be completed later this year, with final publication sometime in early 2009.

While proposed legislation or changes to the federal regulations are under consideration, Nass says committee members are aware that would be a much more difficult route than suggesting new guidance from the U.S. Department of Health and Human Services (DHHS).

"Whenever they can, they'll probably try to make recommendations that don't require changing legislation or regulations, but would help people deal with what they have."

Researchers, IRBs surveyed

The surveys presented to the IOM HIPAA committee have confirmed what the research community has been saying for years: The Privacy Rule has made recruiting subjects more difficult and costly for investigators.

A web-based survey was distributed by 13 epidemiological societies, drawing responses from more than 1,500 investigators who have submitted IRB applications since the Privacy Rule was enacted. A majority reported that the degree to which the rule had made research harder was more than 60%. Both added costs and delays to research also were reported in the high range.

"Epidemiologists need to use very large data sets in order to examine the questions that they pose," Nass says. "So it had potentially big impact on the work they're doing."

A web-based survey of investigators within the National Cancer Institute's Cancer Research Network (CRN) found that more than 70% of the 89 respondents reported having at least one study directly affected by the Privacy Rule — changing the study's timeline, design, or both. At least half the affected studies were multi-site.

The CRN survey and an accompanying survey of IRB administrators in the NCI-funded HMO Research Network (HMORN), added data to a growing belief that a large part of the HIPAA problem is its inconsistent interpretation by different IRBs.

More than a third of the CRN investigators who have participated in multi-site studies since 2003 reported that different HIPAA concerns raised by different IRBs have led to protocol variability in their multi-site studies.

"This variability is, of course, a big concern," says **Sarah M. Greene**, MPH, a research associate with the Group Health Center for Health Studies in Seattle, WA, which conducted the CRN and HMORN surveys. "The validity of the study, the quality of the data, could all be potentially compromised depending on what degree of variability you see."

Greene says the survey of 10 IRB administrators in the HMORN also pointed to varying interpretations of HIPAA.

When presented with scenarios related to privacy breaches, and given choices about how their IRB would handle them, responses were "all over the place," she says.

"I don't think that there can be or should be a one-size-fits-all interpretation of HIPAA at all local levels, but I guess I was anticipating a little more consistency across these particular responses," Greene says.

While more than half the IRB respondents reported that they found it easy to work with the Privacy Rule, Greene says a majority did believe that study participants are unduly burdened by the complexity of HIPAA authorization forms.

When asked what improvements they'd like to see, many administrators asked for guidance in creating less complex authorization language, Greene says.

"I think that's something where we'd be able to make some inroads — it's a very concrete and attainable goal over the short run," she says, noting that the Group Health Center itself recently overhauled its HIPAA authorization form to a seventh-grade reading level.

"If we can do something somewhere in the process to develop easier-to-comprehend versions of the forms or strategies to explain HIPAA to people, I think promulgating resources like that will help."

Other items on the IRB administrators' "wish list" from DHHS included:

- a well-organized, comprehensive document for guidance on HIPAA;
- help in reconciling differences between the Privacy Rule and human subjects protection regulations; and

• further clarification on waivers and HIPAA agreements.

Balancing needs

Greene noted that a small but noteworthy percentage of CRN investigators (22%) did not believe that their local IRB was balancing the needs of all stakeholders — the patients, the investigators, and the institution.

"That's something that IRBs can be perpetually vigilant about," she says. "I think that's the toughest thing that IRBs deal with, maintaining that balance. To the extent that that can be attended to in this very HIPAA-complex world we live in, and help restore the investigators' confidence, I think that would help."

Greene says her participation in the work of the IOM HIPAA committee has left her much more optimistic that the problems associated with the Privacy Rule can be worked out.

"Before, everybody was throwing up their hands, basically," she says. "At the committee's very first meeting, the folks around the table were saying it would literally take an act of Congress to change this. But now I think there's a lot we can do without having to do that.

"The IOM has done a tremendous job amassing different points of view, and ensuring that every stakeholder is represented," Greene says. "It's so comprehensive, and I think the totality will result in a thoughtful look at not only the regulations and their impact, but where we can go from here." ■

Assent process should focus on children's understanding of research

Focus on capacity to understand, not competence

Giving children a chance to assent to their own participation in research is an important goal of the pediatric research community. Done properly, it can empower young patients, help them develop their decision-making skills, and prompt them to take their participation more seriously.

But too often, some ethicists say, the process of obtaining assent gets confused with the more familiar informed consent process, serving up more complicated forms and more stringent requirements than are helpful or understandable for the children involved.

"Assent is not consent — they're two entirely different things," says **Yoram Unguru**, MD, MS, MA, a pediatric hematology/oncology fellow at Children's National Medical Center in Washington, DC, and a Greenwall Fellow in Bioethics.

"If you view assent as consent, you're holding kids to an unfair standard," Unguru says. "You expect that they understand risks and benefits and by doing that, you're really limiting their ability to meaningfully participate in research."

Unguru, who recently wrote about the issue of pediatric assent for the journal *Pediatric Clinics of North America*, suggests that assent should be seen as an opportunity to give a child decision-making experience that is appropriate for his or her developmental stage and maturity.[1]

For one child, that might mean a simple explanation of the research and a verbal OK; for a more mature teen, it could mean an actual document to sign. In every case, Unguru says, the process should involve the child to the extent that it's possible, while still seeking true informed consent from parents.

"It's about being flexible, having a process that you can mold according to each child's individual abilities," he says.

IRBs judge capability

While parents or guardians provide the formal consent for children involved in research, federal regulations (45 CFR 46.408) state that IRBs also must determine that adequate provisions are made for soliciting the children's assent, if the IRB judges they are capable of giving it.

That judgment is to be based on a child's age, maturity, and psychological state, but no age requirement is given for seeking assent.

IRBs also are charged with determining how assent should be documented when it is sought.

Assent is not required if the study holds out the prospect of direct benefit to the child.

Unguru says he likes the fact that the federal regulations don't set an age limit for obtaining assent: "Your 7-year-old is different from my 7-year-old is different from the kid down the street. Every kid is different."

But he says the vagueness of the IRB's duty to decide based on age, maturity, and psychological state does not provide enough guidance.

As a result, he says, IRB assent requirements

can vary widely. IRBs in children's hospitals are more likely to be familiar with children's development and their capacity for decision making. On the other hand, he says, a hospital IRB reviewing protocols from the pediatric department may have less expertise, and be more likely to default to the more familiar consent process.

Unguru says that in contrast to the many elements that make up informed consent, he sees four main elements that should be part of a valid assent process:

- the voluntariness of the child's decision, particularly when the study does not offer the prospect of direct benefit;
- the ability of the child to make a reasonable and rational decision;
- the child's ability to understand what he or she is agreeing to do; and
- some way to gauge the child's preferences for his or her involvement in the research.

For Unguru, ensuring that the child understands the decision is key.

"This is probably the area that I find is one of the major problems with the federal regulations, that there's no requirement to ascertain that kids understand what it is that they're agreeing to," he says.

He notes that assent forms often exceed a 6th-grade reading level — far too complicated for a typical 7-year-old or 8-year-old to understand. Unguru says such documents need to be reviewed by someone who understands how to write language specifically for children.

And once the form has been read and explained, he says the investigator must use some method to gauge how well the child understands it. Unguru himself has created a questionnaire that can be administered in less than 15 minutes to test the child's comprehension of the information he or she has received.

"You run through this quick little survey with the child and you find out what it is they understand or don't understand," he says. "By doing that, you empower the child to tell you what they get and what they don't get. That makes the assent that you're getting more meaningful."

Once it's clear that the child understands, assent can be obtained, either verbally or for older children, by signing a form.

While some ethicists argue that children shouldn't be made to sign an assent, Unguru says he's found many children want to do so.

"Some kids really find it empowering, especially the older kids, the young teens," he says. "They take it much more seriously."

In cases where the child is hesitant to give assent and the study offers direct benefit, Unguru says gentle "arm-twisting" by parents is not inappropriate. But he says it still should be pursued with respect for the child's ability to understand the situation and give an opinion.

"Kids want to be making decisions with their parents and their doctors," he says. "A lot of the battle is they don't feel that parents and doctors are listening to them. In fact, when a parent and doctor listen to the kid, oftentimes they're happy, even if the ultimate decision doesn't go their way."

Unguru notes that there are cases in which a child's refusal to participate in research should be respected. He gives the example of a patient with relapsed cancer, who has had all of the standard treatments and whose parents are pressing for inclusion in a Phase 1 trial.

"If you've got a kid, say an adolescent, who says, 'I really don't want to,' then I think you have to weigh the child's input much more and give them much more say," he says. "In that scenario, where you're talking about a highly experimental intervention that may have limited efficacy at all, then you go with what the kid has to say."

Unguru says that IRBs looking at assent issues should focus on ensuring the forms are understandable for children and that there's some way to measure the subjects' comprehension.

He says IRBs should focus less on whether a child has the competence to make the decision, which is a legal determination, and instead consider whether the child has the capacity to understand, which is a more developmental approach.

"Assent shouldn't be viewed so much on an autonomy level but based on the best interest level for the kid," he says. "You've got to take into consideration the kid's preferences, emotions, what are the advantages and disadvantages of research participation. And doing that you need to focus on capacity, not competence." ■

Reference

1. Unguru Y, Coppes MJ, Kamani N. Rethinking pediatric assent: From requirement to ideal. *Pediatr Clin North Am* 2008;55:211-222.

Suicide rating scale can be valuable assessment tool in drug studies

FDA requests use of Columbia scale in some trials

The controversy of the past few years over possible suicidality associated with various drugs pointed out the importance of tracking suicidal thoughts or behavior in subjects involved in clinical trials.

But until recently, it was hard to find resources that could be used to accomplish that objective. Thanks to a project at Columbia University in New York City that was prompted by a request from the FDA, it's now possible not only to look back at suicidality in adverse events from previous clinical trials, but also to move forward with suicide assessments in current and future drug trials.

Kelly Posner, PhD, who is on faculty at Columbia and is principal investigator for the FDA/Columbia Suicide Classification Study, says that in the past, it has been difficult to gauge the suicidality associated with drugs because there was a lack of clarity in defining suicidal behavior and no common terminology to describe it.

"This cuts across all clinical and research settings," she says. "The same events get called 12 different things and it results in not being able to make sense of what you need to, either for the clinician, a study, or epidemiological data.

"If you can't properly identify suicidal ideation or behavior, you can't understand, manage, or treat it."

When the FDA first was faced with the challenge of looking at potential suicidality associated with antidepressants, the agency went to Posner's team, which had been running a treatment trial for adolescent suicide attempters for the National Institute of Mental Health.

The FDA asked Posner's group to develop a system of analyzing the adverse events from previous antidepressant clinical trials to try to make sense of them.

Posner says the adverse event reports from the trials were all they had to go on, as patients weren't questioned routinely about suicidal thoughts or behavior.

Even when an event occurred, "They weren't trained to ask the right questions to figure out if something is suicidal or not."

The result could be a true suicide attempt that wasn't identified as such or the opposite — an event that was inappropriately classified as a suicide attempt.

For example, one patient's overdose of the study medication, originally described as accidental, was later reclassified as intentional. On the other hand, a patient who slapped herself in the face was initially labeled a suicide attempt, and later reclassified.

Because of this inconsistency and inaccuracy in identifying suicidal behavior, Posner says it's difficult to know the true risk of the drugs being studied.

"For example, we assume there is a risk with antidepressants, but in fact, because the safety data relied on these adverse events, we actually don't know that, because association doesn't mean causality," she says.

It could be possible that patients on the active medication suffered side effects that caused them to spend more time with researchers, and reveal suicidal thoughts or actions, as opposed to the control group, which may have had similar thoughts or actions but not the same opportunities to discuss them.

Posner's team created the Columbia Classification Algorithm for Suicide Assessment (C-CASA), which helped categorize the adverse events as suicidal, indeterminate, or non-suicidal. Under this system, they found more total suicidal events than previously had been classified, but fewer actual suicide attempts.

Since the development of C-CASA in 2001, the FDA has asked pharmaceutical companies in "a handful of cases" to analyze their data using the tool, says **Crystal Rice**, spokeswoman for the agency.

"We've been asking for this information on a case-by-case basis, when other drugs in the same class have been linked to suicidality or when signals in clinical trial data suggest this might be a risk," Rice says. "We are not requiring this information broadly as a part of drug applications."

Although the C-CASA retrospective analysis of past drug trials can provide useful information, Posner says a prospective system — one that systematically asks patients about suicidal ideation or actions during a drug trial — is the ideal.

To address that, the Columbia group developed the Columbia Suicide Severity Rating Scale (C-SSRS), a brief questionnaire that researchers can administer to all the patients in a drug trial

at every visit.

"We're doing it consistently across the drug and placebo [arms]," she says. "And it also fixes all the other problems — it gives definitions, it gives the questions to ask to figure out what to call something, it deals with all the problems we've seen in the retrospective trials and data."

The C-SSRS asks about suicidal ideation, and creates a range from a passive wish to die through creating a plan and having intent. It asks about indicators that are highly predictive of a completed suicide — duration of suicidal thoughts, their frequency, and controllability.

There are questions about specific behaviors, and in the case of actual suicide attempts, about the lethality of the method used.

"It gives you everything that you'd want to track in any setting," Posner says. "It was developed to track adverse events and suicidality throughout any treatment trial or in any setting."

The scale originally was developed for use with adolescents and has been used across the age span. It has been translated into 80 languages and is being used around the world, Posner says.

Posner says the questionnaire itself can be administered in as little as five minutes, which makes it usable even in a busy treatment setting.

"It is increasingly used in primary care, non-psychiatry populations, and the feasibility is excellent," she says. "Obviously, people think of burden when you're doing it so often, especially in non-psychiatrist offices. But it just hasn't been the experience."

Rice says that similar to the C-CASA requests it has made of drug makers, the FDA now may ask sponsors of certain drugs to use the C-SSRS to collect suicidality data during current trials.

"These determinations are based on factors such as the class of the drug, what may be known from other members of the class, findings from animal studies, or signals of imbalances in psychiatric adverse events reported in controlled clinical trials," she says.

She says the FDA requests are made on a case-by-case basis, calling the amount of requests a "small subset of applications" the agency has reviewed. Rice disputes some recent media reports that suggested there were new FDA policies requiring the use of the C-SSRS in drug trials.

Even absent a request from the FDA, Posner says researchers are increasingly using the scale when conducting trials of new drugs, even non-psychotropic drugs, recognizing the importance of tracking this problem using a common language and methodology.

She says a study authored by **Madelyn Gould**, PhD, MPH, who helped develop the C-SSRS, has shown that the introduction of questions about suicidality does not increase risk to subjects.

"Asking these questions does not cause patients to be suicidal or cause them to be distressed," Posner says. "That's clinical lore and the data tell us something else. What we do know is it's critically important to ask about it, for the patient's safety and our understanding of data."

Posner says wider use of the Columbia Suicide

CE/CME Objectives

The CE/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

- IRB has complaint-proof method to releasing new forms
- Research raises questions about investigators attendance at IRB meetings
- Best Practices: Post-IRB approval monitoring program is featured
- Advance research directives can give dementia patients a voice in decisions

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CE/CME *questions*

13. Which of the following is *not* a condition that needs to be met before a waiver of informed consent is allowed?
    A. The risk to the subject is minimal.
    B. The waiver is reviewed by OHRP.
    C. Conducting the research without a waiver is not feasible or practical.
    D. Subjects' rights and welfare will not be adversely affected by the waiver.

14. When surveying IRB members about their views of the board's efficiency, which of the following would be a good question to include in the survey?
    A. Do board meetings make efficient use of my time?
    B. Does the chair allow all sides on important issues to be heard?
    C. Is the IRB effective in its mission to protect human research subjects?
    D. All of the above

15. When reviewing protocols that solicit assent from pediatric research subjects, an IRB should focus on:
    A. The child's capacity to understand information about the study
    B. The child's competence to make decisions about involvement
    C. Both A and B
    D. Neither A nor B

16. Asking subjects about suicidal thoughts or behavior does *not* increase risk of suicidality.
    A. True
    B. False

Answers: 13. (b), 14. (d), 15. (a), 16. (a).

Severity Rating Scale actually could debunk false ideas about risk, because it would eliminate the ascertainment bias that comes with only speaking to certain subjects about suicide.

In addition, it creates data that can be compared from study to study.

"I think what's exciting about this is that we're all going to be speaking the same language," she says. ■