IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

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Special Report: Comparative effectiveness research

[Editor's note: President Barack Obama and the U.S. Congress have agreed to spend more than $1 billion on comparative effectiveness research (CER), which some critics say will lead to an unethical strategy of the government justifying rationing health care. Others say it will provide needed information to clinicians about which medical treatment works best. But from an IRB perspective, will CER trials pose any new or more serious risks to human subjects? IRB Advisor *asks CER experts nationwide to help us answer this question and others about CER in two stories in this month's issue.]*

Is comparative effectiveness research the 'Big Bad Wolf' critics charge?

CER will improve health care, many say

Human subjects research is conducted chiefly for the ideal of improving medical practice, and comparative effectiveness research (CER) is a big step toward this goal, several CER experts say.

"The first important point about comparative effectiveness research and why many of us feel it is so crucial is there is so much information that is not in the right format for making medical decisions," says **Mark S. Roberts**, MD, MPP, president of the Society for Medical Decision-Making and a professor of medicine, health policy, and management and industrial engineering at the University of Pittsburgh School of Medicine. Roberts also is chief of the section of decision sciences and clinical systems modeling in the department of medicine at the University of Pittsburgh.

Roberts spoke about CER at a June 2009 listening session of the new Federal Coordinating Council for Comparative Effectiveness.

"Most of our medical information comes from randomized, controlled trials," Roberts explains. "The reason for that is they tend to have narrowly focused populations where the investigator is making

sure they can prove a particular medication or device being tested works."

In these trials, the comparison typically is between the device or drug and placebo.

"So, the clinical trial (CT) gives you different parts of answers to the problem, but it never gives you the specific information to answer a physician's question," Roberts adds.

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As CER increases, IRBs will become involved in the change.

"IRBs play a very important role in overseeing the conduct of clinical trials research and, increasingly, the establishment of comparative effectiveness will play a larger role in clinical trials, says **Caleb Alexander**, MD, assistant professor in the department of medicine at the MacLean Center for Clinical Medical Ethics of the University of Chicago Hospitals. Alexander recently published a paper on CER.[1]

With a $1.1 billion jolt of federal stimulus package funds entering the research funding pipeline for CER, IRBs soon will receive proposals involving CER. But they need not worry about this being an entirely new research concept for ethical review, one expert says.

"We've been doing comparative effectiveness research for 30 years," says **Joel Kupersmith**, MD, chief research and development officer for the Department of Veterans Affairs (VA) in Washington, DC. Kupersmith is a member of the Federal Coordinating Council for Comparative Effectiveness.

The VA has a cooperative studies program and a large health services research section that do comparative effectiveness research, he says.

"We also, as part of a health care system, have ways of translating research into practice through guidelines," Kupersmith says. "At times, these are the result of our comparative effectiveness research."

IRBs will need to review CER using the same ethical standards and considering all patient protection aspects, Kupersmith says.

"They also should make sure the research has scientific quality so we don't put patients through something that is not scientifically rigorous," he adds.

As part of CER, CT sites might use novel and different methodologies than are commonly used, Kupersmith says.

Some studies employing new methodologies might be exempted from IRB review; others might force the IRB to look at human subjects research in a slightly different light. Either way, IRBs will adapt to the change, Kupersmith says.

When these have been introduced in protocols at the VA, the VA IRBs have adjusted, he notes.

"We have the world's best trials methodologists, and they're highly respected," Kupersmith says. "Sure there are sometimes intense discussions within an IRB, but I don't think it's a problem at all."

CER critics say the federal stimulus bill that includes CER funding was passed too quickly and without public debate about its various components, including CER funding.

"It's not clear what comparative effectiveness research will affect and in what way," says **Grace-Marie Turner**, president and founder of Galen Institute in Alexandria, VA. Turner also spoke at the June listening session of the new Federal Coordinating Council for Comparative Effectiveness.

A worst-case scenario would be if CER were used to inform economic decisions about patients' treatment and if these decisions were made by the federal government, Turner says.

"It gets down to how it will affect any one patient," Turner says. "Even though the research is based on an average person, will it apply to every single patient?"

In the United Kingdom, patients' proposed treatments routinely are turned down because of health care economic policies affected by CER, she says.

"That's what they do," Turner adds. "They ration and decide what they'll pay for and what they won't."

Others argue that CER poses no ethical threats in itself.

"I'm not aware of any serious new ethical challenges posed by CER," Alexander says.

"I think the most contentious area of these efforts is the question of assessing the costs of treatment and not just the clinical effectiveness," he says. "These are people who say once you start assessing costs you're on a slippery slope."

They raise concerns that with greater focus on costs, treatment will be denied and quality will suffer, Alexander says.

"And I think they're wrong," he says. "There is an Alan Garber quote that talks about how assessing value without costs is like trying to look at the restaurant menu without looking at prices."

Alan Garber, MD, PhD is a professor of medicine, biochemistry and molecular biology, and molecular and cellular biology in the division of diabetes, endocrinology and metabolism at Baylor College of Medicine in Houston.

"It's simply foolish to think we're not already rationing care," Alexander says. "We ration care through a number of means, so arguments that we should not look at costs because it will lead to denials of necessary care are misguided."

Skeptics of CER say it takes control of medical decisions out of the hands of physicians and patients and places them in the hands of a governmental bean counter.

"Absolutely, there will need to be decisions made about balancing resources," Turner says. "But do we want the government to make those decisions, or do we want doctors and patients making those decisions?"

It comes down to how comparative effectiveness research would be used, Turner says.

"I think it's a great idea to compare one treatment to another," she says. I just don't want the government to decide in an abstract way that this treatment is right and this treatment is wrong."

Since it's the Obama administration pushing for more comparative effectiveness research at the same time national health care reform is being debated and considered by Congress, the topic is bound to create controversy, some say.

"Since the push for this partly is from Washington, and since people differ in their ideas of the role cost should play in the research, naturally there is room for people to disagree and for debates to become contentious," Alexander says.

What is not being disputed is that the establishment of CER will play a larger role in clinical trials.

"I think that increasingly IRBs will review research that includes a goal of establishing comparative effectiveness," Alexander says. "But it will take place in the role of clinical trials."

Alexander recommends that IRBs begin discussing comparative effectiveness research now with the general idea that enthusiasm is building for this type of research and how it might improve clinical practice.

"I think it's important that IRB members are aware of the current directions of health policy at the local, as well as at the national level, and comparative effectiveness research is a part of the current picture," he says.

"IRBs already are reviewing and supervising very complex clinical trials, often of new and unproven therapies that have a variety of toxicities and risks," he adds. "So, I don't think comparative effectiveness research is likely to introduce any new and substantively different risks or administrative complexities."

Reference

1. Alexander GC, Stafford RS. Does comparative effectiveness have a comparative edge? *JAMA* 2009;301(23):2,488-2,490. ■

How will CER impact IRBs? Inquiring minds want to know

Experts offer clues

Whenever the research enterprise is pushed into a new direction, some different ethical issues and considerations arise. Experts say this likely will be the case as more research institutions engage in comparative effectiveness research (CER), as well.

But how might CER affect IRBs and change IRB deliberations?

Here are some issues that might arise and expert opinion on the impact:

• CER trials might enroll participants with comorbidities and who are frail and elderly. What are the ethical considerations of this change?

One issue that might arise with CER is that study populations sometimes will match the general patient population, including patients who are elderly, frail, and have comorbidities. These types of patients often do not meet the exclusion criteria in placebo-controlled, randomized CTs.

This might raise questions with IRBs, but they should look at the big picture when discussing risks for these types of study populations, says **Mark S. Roberts**, MD, MPP, president of the Society for Medical Decision-Making and a professor of medicine, health policy, and management and industrial engineering at the University of Pittsburgh School of Medicine. Roberts also is chief of the section of decision sciences and clinical systems modeling in the department of medicine at the University of Pittsburgh.

"I think IRBs need to become a little less worried about doing studies of research in frail populations because we need to know more about what happens with frail populations," Roberts says.

Clinical trials often eliminate participation by patients with cancer, renal failure, and heart disease, and yet those are the kinds of patients doctors see, he adds.

"You need some way to understand how a drug will react in those people," Roberts says. "Many of us think research trials need to be much more general in their populations."

CER will include more frail populations, and this might raise issues for IRBs, says **Joel Kupersmith**, MD, chief research and development officer for the Department of Veterans in Washington, DC. Kupersmith is a member of the Federal Coordinating Council for Comparative Effectiveness.

"We'll need a question that needs to be examined, applying the usual ethical principals to it," he says. "And if we decide the research can answer the question, the next issue is whether it is feasible to do this research when it's more complicated because of patients having a lot of comorbidities."

What Roberts would like is for IRBs to deliberate about how to best expand entry criteria in studies, to include broader groups of people.

"They need to understand the whole point of clinical trials is to improve decision making in treating that disease," he says. "If most people with that disease don't look like the clinical trial, but look like the people the clinical trial eliminated, then it doesn't really help much."

There are a number of trials conducted today that are not placebo-controlled, including trials for new asthma and hypertension treatments, because it would be unethical to have a placebo arm when there already is an accepted treatment, Roberts notes.

• Will informed consent and equipoise be different with CER?

New methodologies, more frail study populations, and other issues associated with comparative effectiveness research also could affect what future IRBs want in CER informed consent documents.

IRBs will play a role in adjusting informed consent for CER studies, as needed, says Caleb Alexander, MD, assistant professor in the department of medicine at the MacLean Center for Clinical Medical Ethics of the University of Chicago Hospitals.

"IRBs will need to consider the importance of equipoise in the context of having two treatments that are being compared," he says. "It would be important to be sure the equipoise exists between these treatments."

With comparative effectiveness research, there might be some fine-tuning of the concept of equipoise.

For example, if a majority of clinicians prescribe treatment A for a particular disease because they feel it is superior to treatments B and C, would a comparative effectiveness trial comparing the three treatments have true equipoise? Would there be genuine uncertainty regarding the comparative therapeutic merits of each arm of the study?[1]

The *New England Journal of Medicine* addressed

this very question 20 years ago in a paper that found that requiring investigators to have no treatment preference throughout the course of a trial presents nearly insurmountable obstacles to the ethical completion of a controlled trial.[1]

The paper further suggested that an alternative concept of equipoise could be based on the present controversy in the clinical community over the preferred treatment.

Therefore, this alternative view of equipoise might pose informed consent challenges for IRBs and would, at least, require boards to require investigators to conduct extensive analyses of various treatments' findings before proposing a clinical trial that compared several treatments head-to-head.

The research established clinical equipoise as an uncertainty in the community at large rather than for an individual, explained **Mark S. Schreiner**, MD, chairman of the Committee for the Protection of Human Subjects at the Children's Hospital of Philadelphia.

"[Freedman] posited that it was ethical for an investigator to proceed with a trial even if convinced that one treatment was better — provided that there was uncertainty in the community," he says. "The history of clinical trials has shown nothing if not that investigators' biases are frequently proved incorrect."

Reference

1. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317(3):141-145. ■

Using placebos in trials of new antidepressants

Researcher defends placebo controls

The U.S. Food and Drug Administration requires that new psychiatric drugs be tested against placebo to ensure that they are effective. Despite that fact, some ethicists criticize the use of placebo in these trials, saying all psychiatric patients who volunteer for studies deserve the best-proven existing treatment.

Researchers also can encounter that opinion in IRB reviews, says **Boadie Dunlop**, MD, director of the Mood and Anxieties Disorder Program at the Emory University School of Medicine in Atlanta.

Dunlop recently authored an article in the *Journal of Medical Ethics* defending the ethics of placebo use in clinical trials for major depression and anxiety disorders. He says his interest in the topic was based in part on his experience fielding questions in IRB reviews.

"I think a big motivation for writing this was to try to make more clear to members of IRB committees how as a researcher I see the ethics of placebo use," he says. "Rather than getting into a back-and-forth with the IRB asking for clarifications of why a placebo is justified, it would be nice to have a document to refer to, to say 'The arguments are enclosed in this paper.'"

Questioning safety, effectiveness

Dunlop notes that recent meta-analyses of research into psychiatric medications have raised questions about both the efficacy and safety of existing antidepressants:

-In a 2008 article in the *Public Library of Science Medicine,* a meta-analysis of data submitted to the FDA found that efficacy of newer antidepressants only was found to be clinically significant in the most severely depressed patients.

"It suggested that for mild to moderate depression, existing antidepressants were no better than placebos," Dunlop says. "There are concerns about the way that meta-analysis was conducted and people have critiqued it, but nevertheless, there have been other (studies) that have raised similar concerns."

-In 2004, the FDA issued a public health advisory for antidepressants, warning that they could increase the risk of suicidal thoughts or behavior. The warning was based on an analysis of placebo-controlled studies that showed that children taking the antidepressants had a small but statistically significant increased risk of these behaviors, compared to children taking placebos.

Dunlop points out that such an analysis would not even have been possible without the use of placebos. If experimental antidepressants had been compared to existing ones, and the risk increased for both drugs, it would not have been discerned in the study.

"You would think it's just part of the course of depression for people to develop suicidal ideation," he says. "It never would have been found that in a small number of young people there is an increase in suicidal or self-directed harm thoughts."

Even if future studies downgrade that risk, Dunlop says the placebo controls are necessary to

properly investigate it.

"Without placebo control, we'd never know whether we should be looking or not," he says. "It's easy to fall into the assumption these are antidepressants, how could people get worse? And that's the hubris about our knowledge. We just don't know — we're always in the state of accumulating more knowledge."

Placebo effect

It isn't just a "placebo effect" per se; it is the response rate in subjects assigned to a placebo, says **Mark S. Schreiner**, MD, chairman of the Committee for the Protection of Human Subjects at the Children's Hospital of Philadelphia. "Mild to moderate depression is a waxing and waning condition," he says. "Numerous studies have found the response rate in placebo-treated patients to be about 40%. This reflects the natural history of depression as much as it reflects the response to placebo."

Dunlop says one reason placebo controls are necessary in research involving treatment of mood and anxiety disorders is that those conditions have a high placebo response rate — a certain percentage of people who take a placebo for these disorders report improvement.

So, the only way to tell if a drug is truly effective is to see whether its effectiveness trumps the placebo's effectiveness. Otherwise, Dunlop says, you run risk of helping to approve a drug that isn't any better for patients than placebo.

"It is an ethical obligation of the researcher to make sure that the research they're conducting is valid, otherwise we're dishonoring the contribution of the volunteers for the study," he says. "Yes, they're in the study to feel better but they're also in the study to contribute to the advancement of knowledge.

"And if the data that emerges from the study is not something that can be interpreted with confidence, there's enormous ethical consequences to that."

Dunlop also notes that it's easier to achieve statistical significance in a placebo-controlled trial, meaning that fewer participants must be exposed to an experimental drug.

"If you eliminate placebo controls and go with equivalence designs, you need many more subjects," he says. "From the get-go, you're exposing many more people to the unknown and potentially harmful effects of an experimental medication."

Dunlop says he remains optimistic that researchers someday will discover biomarkers that show the biological changes proving that a drug has an antidepressant or anti-anxiety effect, eventually making placebo-controlled trials unnecessary.

"Right now, we haven't got that, so we have to maintain a humble approach to the brain," he says.

Reference

1. Dunlop BW, Banja J. A renewed, ethical defense of placebo-controlled trials of new treatments for major depression and anxiety disorders. *J Med Ethics* 2009;35(6):384-389. ■

When to give the green light to placebo controls

Severity of illness, length of trials among factors

Despite the value that placebo controls bring to psychiatric research, they are not appropriate for all clinical trials of antidepressants and anti-anxiety medications.

Boadie Dunlop, MD, director of the Mood and Anxieties Disorder Program at the Emory University School of Medicine in Atlanta, says an IRB confronted with a proposed study that includes placebos should keep the following points in mind:

Severity of illness — Participants should not be patients who are in need of urgent treatment, such as those with marked suicidal ideation or functional impairment.

"Those folks aren't going to be offered enrollment in the study because they need immediate care and it would not be appropriate to delay them care, either through the screening and evaluation process or potential placebo treatment." Dunlop notes that researchers already routinely exclude these patients from placebo studies.

He says it might be possible to conduct a placebo-controlled trial for severely affected patients, in order to see if a drug were particularly helpful for that population. Dunlop suggests that it could take the form of a discontinuation trial, in which all patients are given the study drug, and then some are later randomly assigned to either continue the drug or switch to placebo.

Dunlop notes in his article that such a trial would require an extremely well-designed informed consent process to ensure that

participants understood the risks involved.

Freedom to withdraw — It should be clear in the informed consent that participants are free to withdraw from the study if they feel they are not improving or their symptoms are getting worse.

Limited duration — Patients should only be exposed to placebo for a limited amount of time – Dunlop says Phase II and III clinical trials of new treatments for depressive and anxiety disorders typically last six to eight weeks.

"For most people with depression, it's been going on for many months, often more than a year or two," Dunlop says. "So, to receive a placebo for another six to eight weeks, even assuming the placebo is absolutely ineffective, doesn't generally put a person at increased risk."

Close contact with study team — Participants should be monitored very closely throughout the trial. Dunlop recommends that they are seen at least every one to two weeks, to be sure their condition is not worsening and to intervene quickly if necessary.

Dunlop says that it's very rare for suicidal ideation to emerge out of nowhere — it builds over time, making close monitoring the most effective means of protecting the patient. He notes that participants engaged in a placebo-controlled trial are actually monitored much more closely than they would be if treated in clinical practice.

"In clinical practice, we know these medications are ineffective in about a third of people with depression, and so they're essentially like an ineffective placebo in a third of people with depression," Dunlop says. "And they might not be seen for four weeks or more. There's greater protection to the patients participating in a clinical trial than there is in routine clinical care where they might be seen less frequently."

Informed consent — Dunlop says many patients fail to understand exactly what a randomized placebo-controlled trial involves. IRBs should be aware of this in reviewing the informed consent process. Participants need to understand that treatment will be assigned to them randomly, without considering their individual cases. They need to know exactly what a placebo is. They need to know that they can withdraw at any time.

"The main thing is there are procedures in place to take care of patients who fail to get better or who worsen during the trial," he says. ■

Infectious disease group calls for lessening of regulatory burden

Society recommends removing research from HIPAA

Another voice has been added t o the chorus of those blaming excessive regulatory oversight for a slowdown in vital research.

The Infectious Diseases Society of America (IDSA) recently published a paper listing several recommendations aimed at lessening the burden on researchers, from removing research from activities covered by the HIPAA Privacy Rule to encouraging the use of central IRBs and funding OHRP to provide more guidance to local boards.

William Burman, MD, an associate professor in the Division of Infectious Diseases at the University of Colorado at Denver and Health Sciences Center, was the IDSA's lead author of the article, which ran in a recent issue of the journal *Clinical Infectious Diseases.*

Burman, who serves on the IDSA's research committee, says the issue has been percolating within the society for several years, as infectious disease investigators have reported difficulty getting research approved.

"It became clear to us that this was one of the major factors affecting research that we think needs to be addressed to save lives of people with serious infections," he says. "It wasn't a single event (that prompted the paper); it was the cumulative effect of increasing burden as we perceive it."

Burman says the paper is a call for restoring balance between the need for research and the need for research oversight. He says that balance has been tilted in favor of oversight in the last decade.

"Both parts are absolutely necessary, there's no question, but we need to restore balance between them," he says.

HIPAA's burden

Burman says it was important to the group not to enter into the discussion blaming IRBs, who he says have been put into an increasingly impossible situation, particularly since the advent of the Health Insurance Portability and Accountability Act (HIPAA).

"HIPAA was a tremendous increase in the

workload of local IRBs, not just to review authorization forms themselves," Burman says. "HIPAA in essence defined a whole lot of data gathering and review activities as something that should be reviewed by an IRB that hadn't been before.

"It markedly increased the types of activities that IRBs review and I think to no benefit – to no benefit to IRBs, to no benefit to researchers, to no benefit to participants and patients."

Burman praises a recent Institute of Medicine report, which also recommends removing research from HIPAA oversight. The IOM report recommends that interventional research would be handled under the Common Rule. Informational research, which uses medical records or stored biological samples, would have a separate oversight system, with federal certification of organizations collecting and analyzing personally identifiable health information for clearly defined purposes, without individual consent.

"I think the IOM report is a wonderful document that fleshed out the negative effects of HIPAA," Burman says. "I think they very convincingly document the negative effects of the application of HIPAA to research. And then I think they have an interesting proposal for a resolution to this problem."

He says the report came out just as his group was finishing the IDSA statement.

"In fact, we were on one of the final drafts and somebody sent me the link and so I read it really quickly and thought, 'Great — it's always wonderful to have a body with the prestige and respect that is given to the Institute of Medicine agree with you.'"

In addition to the HIPAA recommendation, the IDSA also took on other issues that members felt were stymieing research:

Duplicative review of multicenter studies. Having local IRB review at every site in a multicenter study unnecessarily delays and complicates such studies, the IDSA report asserts. In particular, it often introduces language to consent forms that makes them longer and less readable.

"It's very clear that duplicative local review delays the initiation and completion of federally sponsored research," Burman says. "In some cases it can be severe, with months and even more than a year's delay in starting studies at some local sites."

To alleviate the problem, the IDSA report makes two suggestions: Expand the availability of central review panels for federally sponsored research and have NIH and other federal agencies create an incentive for the use of those panels by giving institutions that agree to use a central IRB points toward the peer-reviewed score of a grant application.

"My sense is that the level of concern (about using central IRBs) is not necessarily at the IRB level but that it may be at other levels of the administration of academic health centers in particular," Burman says. "It may revolve around concerns about legal liability, for example. I think the incentive isn't designed so much for the chair or director of the local IRB itself but rather for the larger institution."

Burman says the IDSA already has made some progress in this area, having corresponded with the National Institute of Allergy and Infectious Diseases to request creation of central IRBs for adult and pediatric studies. He says his group will work with other professional societies to urge similar conversations with their corresponding sections at NIH.

"I think there's a good chance that we'll get creation of additional central review panels."

Centralize AERs

Redundant review of adverse event reports. The IDSA report states that sending reports of serious adverse events to IRBs at all local sites of a multicenter study drains IRB resources, while often not providing enough information to the IRBs to be useful.

"You jam up the works with a bunch of reports which the local IRB cannot interpret because they're not provided with the key parameters that would allow them to do anything with them," Burman says. "How many received the drug for what period of time, what happened in the control group? IRBs have no knowledge of any of that."

He says data centers for multicenter trials have the means to conduct sophisticated analysis of adverse events, making local reviews unnecessary.

Burman says OHRP has published guidance stating that local IRBs shouldn't be involved in the review of off-site adverse event reports.

"I think it's an excellent document — anyone who says that the federal government can't produce clear guidance should read it," he says.

But he says a Food and Drug Administration (FDA) guidance on the subject is much less clear, which can be confusing to IRBs. IDSA recom-

mends harmonization between the two guidelines, and a refocusing of local IRB efforts on adverse event reports from single-site studies.

Clearer OHRP guidance — in such areas as risk assessment in pediatric research and criteria for IRB review of quality improvement activities.

Increased funding for OHRP — Burman says it's disingenuous to ask more of OHRP when it's already underfunded.

"What we proposed is an increase in funding and coupled with a clear mandate to produce results," he says.

Asked which of these issues he considers most pressing, Burman barely hesitates: "HIPAA. I think HIPAA has been destructive."

But he says he's optimistic that the time may be right for progress on that front. He says if a change is going to occur, the research community needs the support of patient and disease advocacy groups, who have so much at stake in getting research moving faster.

"I think we need to work with disease advocacy groups to make clear to them that HIPAA is delaying valuable research, that it's stopping valuable research, that it's increasing the costs of research, all of which has now been very clearly documented.

"We'll get action when it isn't me testifying to a committee of Congress, it's patient and disease advocacy groups saying, 'Why is the government requiring this when it demonstrably slows down, prevents and delays research which is needed to help my condition?'

"That's when we'll get action and that's why we're working a lot with disease advocacy groups at the start of this effort."

Reference

1. Infectious Diseases Society of America. "Grinding to a halt: The effects of the increasing regulatory burden on research and quality improvement efforts." *Clin Infect Dis* 2009;49(3):328-335. ■

Study results to help IRBs see what slows studies

Reports of how IRB stacks up against others

More than three dozen institutions who participated in a study of IRB response times will be receiving individualized reports that show how their institution stacks up against the rest of the group.

It's the first step of what organizers hope is an ongoing effort to help determine what slows studies down in IRB review and how to achieve improvements.

The study was conducted by a committee of the Clinical and Translational Science Awards (CTSA) consortium, as a part of the consortium's goal of progressing more efficiently from scientific breakthrough to patient treatment.

IRB review had been identified as an area of concern, with several committees looking into how to better facilitate reviews of multicenter studies. In order to do that, the institutions first had to figure out just how long reviews were taking at various institutions.

"The IRB task force was focused on trying to figure out what the baseline metrics are for the 38 CTSA institutions," says **Ray Hutchinson**, MD, associate dean for regulatory affairs at the University of Michigan Medical School in Ann Arbor. Hutchinson is one of the co-chairs of the CTSA's Clinical Research Management IRB committee.

"The way we have defined the purpose of this is to establish a set of data points that exist at all IRBs, regardless of the processes they use, to be used in future research to identify, implement, monitor and standardize improvements to the protocol approval process."

Collecting dates

In order to do this, organizers set out to gather very specific information about 25 consecutive clinical trial protocols reviewed by CTSA institutions' IRBs during the month of February 2009.

Most of it consisted of dates:

- when the application first was received by the IRB review office;
- dates of any pre-review and changes sent to the principal investigator, along with the dates that any changes sent back by the PI were received;
- when the application first was reviewed by a fully convened IRB;
- date of any request by the IRB to the PI for changes to the protocol, as well as the date those changes were returned to the IRB;
- the number of times the study was reviewed by a fully convened IRB, including the date of the meeting at which it received final approval;
- and lastly, the date that the IRB sent

notification of final approval to the PI.

In addition, the researchers gathered basic information about the protocols themselves – whether they're initiated by investigators or by sponsors, and whether they were single- or multisite studies.

Institutions sent their data this summer to data managers at Vanderbilt University, where it is being analyzed, Hutchinson says. He says the first step is for institutions to see how they compare to the group as a whole.

"Individual institutions would not be seeing identified data from other institutions," Hutchinson says. "But you can look at the other 37 and say, 'Well, we're roughly in the middle, at the top or at the bottom.'"

Kathleen Uscinski, MBA, CIP, deputy director of Yale University's Human Investigation Committee in New Haven, CT, and co-chair of the CTSA IRB committee, says that information alone will be of value to the participating institutions.

"The goal is for them to look at their own measurements and see where they might want to improve," she says. "You can start looking at your data in relation to others and start thinking about best practices you could implement."

Measures and metrics

Uscinski and Hutchinson says the eventual goal is bigger — to use the data to improve practices across the entire CTSA consortium, providing guidance about where slowdowns typically occur in the IRB process and how to eliminate them.

Uscinski says a new measures and metrics committee has been created to begin that process. Hutchinson says the analysis would attempt to target institutions that are particularly adept at various parts of the process and gain their permission to share their practices with others.

"Maybe one institution is really good in the pre-review, or another is really good at getting a rapid response from PIs," Hutchinson says. "We'll be able to target small areas of the process that are particularly good and maybe reach out to that institution and find out what has eventuated in their doing so well."

He says the initial data collection also could lead to future surveys to hone in on specific areas needing improvement.

"Maybe we notice that 15 of the institutions have a particular problem in one phase of the review process and we could structure a subsequent survey or subsequent intervention to try to enhance that and recollect and analyze data," he says.

Uscinski says the group of 38 institutions has proven to be relatively open and committed to the effort.

"The important thing is that all of these institutions were able to work together, and it was done pretty much on time," she says. "The fact that we were able to get an 80% response was pretty impressive, I think.

"It will be interesting as we move down this path to see some best practices evolve," Uscinski adds. ■

Expert outlines main struggles, solutions to better informed consent

Get rid of one-size-fits-all notion

Most principal investigators (PIs) are not very good at conveying complex ideas in simple terms, an IRB and research expert says.

"My experience is that investigators tend to begin with a scientific protocol and then try to dumb it down in order to craft the consent form," says **David H. Strauss**, MD, chairman of the institutional review board at the New York State Psychiatric Institute and director of the office of human subjects research, department of psychiatry, College of Physicians and Surgeons at Columbia University in New York City.

"What I encourage investigators to do instead is to write a consent form using language, phrasing, and emphasis the way they might if they were giving a presentation to an advocacy or consumer organization or to a group of medical students," Strauss says. "In other words, they should use a conversational tone and nontechnical phrasing."

IRBs sometimes make a mistake of thinking that certain models or standardized informed consent forms are the solution to creating comprehensive and simple informed consent (IC) forms.

"The term that gets used is one-size-fits-all model — a size that fits none," Strauss says. "We haven't developed methods for providing information during consent that are based on what people want or what people need."

When institutions create an IC template, it's rarely based on empirical evidence of what potential participants need to know and how they need to learn it.

"Instead, what we see is a regulatory-driven list of criteria and a format," Strauss says. "Then added to that are a whole series of institutional risk management considerations."

The problem with this approach is that it doesn't do a good job of emphasizing what's important to a person who is trying to decide whether or not to take part in a study, he adds.

"We tend to not match the informational needs of prospective subjects to the information we provide," Strauss explains.

"The other thing we find is that we assume that every subject wants and needs the same amount of information," Strauss says. "It's not at all clear what we actually expect subjects to retain or use of the information we give them."

For example, Strauss recently reviewed a 13-page IC form.

"It's common to see a lengthy consent form," he says. "But the idea that someone will actually read this and draw from it what they need to make a decision is farfetched."

Strauss offers these additional suggestions for improving IC forms:

• **Provide an outline:** One useful approach to improving the clarity of an informed consent form is to provide an outline or overview in a simple and brief format, Strauss suggests.

This could be a single page with bullet points emphasizing the key study points, he says.

"Essentially, it serves as a guide to what the rest of the consent form includes and is a preview to coming attractions," Strauss says.

For instance, the bullet points could emphasize that a study is placebo-controlled or that it requires an inpatient hospitalization, he says.

"It includes some of the things that are likely to be important to someone who is thinking about taking part in the study," Strauss says.

• **Discuss alternatives to research:** Research participants need to know what the alternative treatments are to what is provided in the research study. This section might be titled, "What are my options?"

And it needs to be placed more prominently in the IC document, not buried in a small paragraph on page 11, Strauss says.

"Move it up so it occurs right after the purpose," Strauss says. "Put the key procedures in the paragraph, and then say that the person doesn't have to take part in research in order to receive treatment for his or her condition."

Also, if a study is a nontreatment study, the study should make this clear to participants, and the alternatives section is a good place to emphasize this point, he adds.

• **Clarify personal benefits:** Therapeutic misconception is very common among research participants, and this partly might be due to the IC document overestimating a study's benefits to individual participants, Strauss notes. ■

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

■ New, streamlined on-line UP/SAE submission process reduces workload

■ IRB sometimes clears up misunderstandings by speaking directly to sponsor

■ Improving adverse event reporting

■ Issues in IRB review of geriatric psychiatry research

CNE/CME *questions*

9. What is comparative effectiveness research?
   A. It's a way to compare costs of various popular treatments to help a governmental panel or insurer to decide which one would be the most cost-effective to use in a large population
   B. It's a new type of research that is used extensively in Europe and Asia and is beginning to make inroads in the United States
   C. It's research that compares one treatment directly with another treatment to see which works better
   D. None of the above

10. Which of the following would be a good strategy for improving an informed consent document?
   A. Provide an outline that is one-page and has bullet points emphasizing key study points
   B. Include alternatives to research so participants know what treatment they could receive if they choose not to participate in a study
   C. Clarify any personal benefits the participant might receive from participation and clearly state there are none when that's true so that the IC document will reduce the potential for therapeutic misconception
   D. All of the above

11. True or False: Placebo-controlled studies are ethically problematic because they expose more subjects to an experimental medication than would a comparative study of two active drugs.

12. Which of the following is not a baseline metric of clinical trial review gathered from IRBs in the Clinical and Translational Science Awards consortium as part of a study of IRB review times?
   A. Dates when clinical trial protocols first were received by the IRBs.
   B. Dates when the IRBs sent final notice of approval to principal investigators.
   C. Whether the trials were single-site or multicenter studies.
   D. None of the above; all were gathered as part of the study.

Answers: 9. C; 10. D; 11. False; 12. D.