IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

AHC Media LLC

IN THIS ISSUE

Statement of Financial Disclosure:
Editor Suzanne Koziatek, Editor Melinda Young, Associate Publisher Coles McKagen, Managing Editor Gary Evans, Nurse Planner Kay Ball, and Physician Reviewer Mark Schreiner, MD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies related to the content in this CNE/CME activity.

FEBRUARY 2009
VOL. 9, NO. 2 • (pages 13-24)

What impact will Obama administration have on human subjects research?

Experts cite several possibilities

President Barack Obama's long-stated goal for universal health insurance could have a ripple effect on the human subjects research field, possibly removing an incentive for people to enter clinical trails. That is one of several possible changes on the horizon as a new administration takes the helm, experts tell *IRB Advisor*.

"The major issue is affordable medical care insurance for all," says **Paul W. Goebel, Jr.**, CIP, president of Paul W. Goebel Consulting Inc. of Monrovia, MD. "If something passes there might be small changes to the regulations affecting research."

Moreover, if more Americans have access to affordable health care then there might be an indirect impact on human subjects research recruiting, Goebel suggests.

"There are people now taking part in studies because they can get access to health care during the study when they might not have access otherwise," Goebel says. "I don't know if this [incentive] will go away -- it all depends on the details of what they finally come up with."

From an IRB perspective, recruitment for the purpose of obtaining health care would not be a hidden motive to consider if potential subjects already have access to health care, Goebel adds.

Some other possible changes can be seen from bills that have repeatedly been introduced in Congress only to go nowhere in a Republican administration. These might gain support in the next year.

For example, U.S. Rep Diana DeGette (D-CO) introduced in September, 2008, an amendment to the Public Health Service Act. DeGette has introduced this amendment numerous times with the purpose of reforming the U.S. human protections system to plug-in some of its holes, says **Jerry A. Menikoff**, MD, JD, director of the Office for Human Subjects Protections (OHRP). **(See story on potential federal bills, p. 15.)**

Current human subjects protection regulations have jurisdictional triggers, Menikoff says.

"You have to be federally financed, or you have to be dealing with

an FDA-regulated product," Menikoff says. "So you could be doing substantial and risky research and not be federally financed and not be subject to any of these rules."

Many regulatory review bodies have voiced complaints over this gap.

"One of the goals of the DeGette bill is to plug in the holes in the system in terms of having the rules cover more research," Menikoff says.

"So basically, if you were doing human subjects research in this country you would be subject to federal regulations regardless of whether or not it was federally funded or dealing with an FDA-regulated product," Menikoff explains.

If the new Congress and president decide to support this bill, then it could possibly pass and eliminate human subjects research protection loopholes, he notes.

Such a change would not add a tremendous amount to OHRP's workload, but it finally supplies an answer to the ethical question of "Why shouldn't people who aren't being protected now be subjects with some protections?" Menikoff says.

"The issue is whether you should or should not be providing protections to people," he adds.

Stem cell research on way?

Another possible change would be the lifting of the ban on federal funding of stem cell research, says **J. Mark Waxman**, JD, a partner with Foley & Lardner in Boston, MA.

"This would lead to an increase in the number of stem cell trials," Waxman says.

DeGette in the fall of 2008 sponsored an amendment to the Public Health Service Act to provide for human embryonic stem cell research and to direct NIH to issue guidelines for stem cell research. Nothing has happened on the bill so far, but this could soon change since Presdent-elect. Obama has said that he supports lifting the ban on federal funding of stem cell research.

"If Obama lifts the federal ban on stem cell research funding, then that will open the door to more stem cell research," Goebel says. "I think as it becomes more common, there will be a lot of extra work [for IRBs] right at the start."

But as IRBs think through the ethical issues and the human subjects protection community reaches consensus on how to handle these studies, then there will be less uncertainty, he adds.

"Someone will come up with a flow chart of what to do when you're presented with these issues," Goebel says.

One change could be that research institutions are required to have a special oversight committee look at stem cell research proposals, which may or may not be sent to the IRB.

"A lot of this depends on how the studies are conducted," Menikoff says. "But it's certainly true now and it could be true in the future,

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

POSTMASTER: Send address changes to ***IRB Advisor***, P.O. Box 740059, Atlanta, GA 30374.

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 18 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 15 Contact Hours.

This activity is intended for clinical trial research physicians and nurses. It is in effect for 36 months from the date of publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcmedia.com). Hours of operation: 8:30 a.m. -6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.
Subscription rates: U.S.A., one year (12 issues), $389. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. **Back issues**, when available, are $65 each. (GST registration number R128870672.)

For recent permission, please contact: Stephen Vance, *Telephone:* (800) 688-2421, ext. 5511
• *Fax:* (800) 284-3291 • *E-mail:* stephen.vance@ahcmedia.com
• *Address:* 3525 Piedmont Road, Building 6, Suite 400, Atlanta, GA 30305

Editors: **Suzanne Koziatek** and **Melinda Young**.
Associate Publisher: **Coles McKagen**, (404) 262-5420 (coles.mckagen@ahcmedia.com).
Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Ami Sutaria.**

Editorial Questions

Questions or comments?
Call **Gary Evans** at (706) 310-1727.

depending on how it's done, that this type of research may not come under 45 CFR 46."

Some research on stem cell lines might involve a human subject, and others may not, Menikoff says.

"If you are asking somebody to donate some of their materials to create a new fertilized egg, for example, then that part would probably involve human subjects research," he explains.

In other cases, stem cell research might be handled in a similar way to how studies using tissue samples are handled, Menikoff adds.

"Therefore, you get into the same issues that you do with tissues right now, and that doesn't necessarily end up going under IRB review," Menikoff says.

Another bill to watch is the Fair Access to Clinical Trials Act, which would strengthen a national data base of clinical trials information, Waxman says.

But the bill that could have a significant impact on IRBs is the Physician Payments Sunshine Act of 2008, which calls for transparency in physician relationships with pharmaceutical and device companies, Waxman says.

"It's been pending in Congress for the last couple of years," Waxman says. "A number of states are looking at the relationship between physicians and drug/device companies, so IRBs may want to take another look at conflicts of interest policies."

This bill highlights the need for IRBs to focus on conflicts of interest again, Waxman adds. ■

New OHRP director on new priorities, changes

Q&A with Jerry Menikoff

The Office for Human Research Protections (OHRP) of Rockville, MD, announced in October, 2008, that **Jerry A. Menikoff**, MD, JD, is the new director. Menikoff also has served as the director of the Office of Human Subjects Research and has worked as a bioethicist at the National Institutes of Health (NIH). Prior to his NIH appointments, Menikoff was a chair of the human subjects committee and the hospital ethics committee at the University of Kansas Medical Center.

IRB Advisor asked Menikoff to discuss his vision and priorities for OHRP in the next few years, as well as how he thought the new Obama/Biden administration might impact human subjects research regulations **(See cover story, p. 13.)**. This question-and-answer story

Will proposed bills find new political life?

Several could impact human subjects research

There have been a handful of bills introduced in the past few years that could have an impact human subjects research.

Although these have not succeeded in past Congressional sessions, several research ethics experts say there is a possibility the same bills will find greater success in 2009 and beyond as a new Congress and President Barack Obama make some changes.

Here are the most likely bills to be given a second look:

• **S. 3807** — The Fair Access to Clinical Trials (FACT) Act: First introduced by Sen. Christopher Dodd (D-CT) in 2005 as S. 470, the FACT Act would require the Food and Drug Administration (FDA) to expand the clinicaltrials.gov database to create a national data base that could be viewed by the public. It would include details about ongoing clinical trials and their findings, whether or not these were published. Sen. Michael B. Enzi (R-WY) introduced S. 3807 in 2006, and it received a hearing, but no further action.

• **HR 5605** — Physician Payments Sunshine Act of 2008: This bill would amend title XI of the Social Security Act to provide for transparency in the relationship between physicians and manufacturers of drugs, devices, or medical supplies that receive reimbursement under Medicare, Medicaid, or SCHIP.

• **HR 7140** — Human subjects research protection: U.S. Rep Diana DeGette (D-CO) introduced in September, 2008, an amendment to the Public Health Service Act, for the protection of human subjects in research. The bill was referred to the subcommittee on health.

• **HR 7141** — Human embryonic stem cell research: DeGette sponsored an amendment to the Public Health Service Act to provide for human embryonic stem cell research and to direct NIH to issue guidelines for such stem cell research. The amendment was referred to the House subcommittee on health in September, 2008. ■

contains some of his answers to questions about OHRP's new directions and any anticipated changes.

IRB Advisor: Would you please explain your goals and vision for OHRP? What do you feel would be a good direction to go during your tenure?

Menikoff: I'd say my vision ties into why is OHRP here in the first place and that OHRP has this unique role. We're trying to make sure that people who are taking part in research are going to be adequately protected. That's the major goal OHRP has. But at the same time, we clearly have to make sure we're not applying the rules in an inappropriate manner. There has to be a balance in how OHRP applies its purposes. There has to be adequate protections in terms of the subjects, and at same time we're not over-regulating, not applying the rules in a manner that it inadvertently creates major burdens to research while not in any significant way adding protections to subjects.

IRB Advisor: That's been a complaint of a lot of research organizations that IRBs are so busy now because of the perceived increased regulations and media scrutiny. Is that the trend you're addressing?

Menikoff: Partly, yes. It certainly has gotten some attention, and it's appropriate that there be some response to the concerns. In a sense, what OHRP is dealing with is not that different from scenarios we see in applying other regulations in other areas. But any regulatory agency shouldn't be losing sight of why the regulations are there in the first place. And the regulations that OHRP administers are clearly there to protect research subjects. So OHRP should be making sure to the extent possible that happens and that it happens in an appropriate manner. Any administrative agency has limited resources in terms of fulfilling its goals and the constituency it deals with out there, in terms of making sure the regulations are adhered to, also have limited resources. We only have so much time in day; there's only so much effort we can expend; there's only so much money in terms of personnel, etc., etc.

Getting back to that, in terms of balancing, on one hand OHRP should be making sure that IRBs and others involved in protecting subjects know how to best apply their limited resources. So, for example, there are certainly studies out there that are very, very low risk. Generally, you can take any study out there and you could certainly expend more and more effort making sure that there are adequate protections in that study. But you don't necessarily get more benefits out of expending more and more effort — in terms of protecting research subjects. So everybody involved — OHRP, IRBs, the administrators, PIs, everybody—should be applying the rules in a reasonable manner. That includes not spending more time than is appropriate on a very, very low risk study where the regulations themselves suggest that not a lot has to be done to adequately protect the research subjects of that study.

That certainly is getting into the theme that investigators and others are complaining about.

Also, by recognizing the need to not spend too much time on very low-risk studies, there's a very beneficial effect of freeing up time and resources to spend on parts of the system that perhaps are not getting enough attention—studies that are much riskier and that may involve life or death issues.

IRB Advisor: OHRP has started to publish correspondence about IRB reviews and some findings on your web site. Could you please explain what this new transparency might mean for IRBs?

Menikoff: This started before I got here. Informally, everything I've heard has been very, very positive. This totally fits my goal. So it's great to come here and fit into a theme that OHRP is already doing with increased transparency.

There is some degree of concern on the part of some of OHRP's constituencies. These researchers, even research subjects have said that OHRP's positions on some issues are not clear. Some people are just nervous in general about dealing with a regulatory agency. So even though OHRP by and large has been quite open in responding to requests for information about its policies or about applying a policy to a particular study, some people just don't like to call or ask the question. They think you might show up on some regulator's radar screen and you might say the wrong thing during an email or phone call.

The result is that by not giving guidance in one area or another, you could have people inappropriately not doing the important research. They could do that research, and it might not be problematic at all. It could be totally consistent with regulations and subjects could be adequately protected, and OHRP might not have a problem with that. So this increased transparency could lead to what some people think is a paradoxical effect: by putting more guidance out there

you actually enable people to do things they previously didn't think they'd be able to do. ■

OHRP's new transparency includes correspondence

Here's a sample of a recent letter

The Office for Human Research Protections (OHRP) of Rockville, MD, recently added "OHRP Correspondence" to its Regulations and Policy Guidance portion of its Web site as part of an effort to improve transparency and provide some specific examples of how to interpret various guidelines.

OHRP will post correspondence with IRBs, investigators, research institutions, or federal agencies when the correspondent gives OHRP permission. The agency's goal is to provide information that might be useful to other institutions for understanding Department of Health and Human Services (HHS) regulations regarding the protection of human subjects under 45 CFR part 46.

One recent correspondence is a Sept. 29, 2008, Memorandum to the National Cancer Institute (NCI) regarding IRB review of protocol and informed consent changes. Here is an excerpt from that six-page memorandum:

"A. Temporary Suspension of New Subject Enrollment When CTEP [Cancer Therapy Evaluation Program] Identifies New or Modified Risk Information that Requires Changes to the Description of the Reasonably Foreseeable Risks or Discomforts in Informed Consent Documents.

For NCI/CTEP-sponsored clinical trials, informed consent must be *documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative (45 CFR 46.117(a)). This written consent document must embody all elements of informed consent required by HHS regulations at 45 CFR 46.116(a) and (b), including a description of any reasonably foreseeable risks or discomforts to the subjects.

As we previously communicated to CTEP, when CTEP identifies or learns about new or modified risk information that necessitates changes to the description of the reasonably foreseeable risks or discomforts during the obtaining of informed consent in order to satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(2) (or any other element of informed consent required under 45 CFR 46.116(a) or (b)), such changes to the informed consent documents, as well as any accompanying changes to the protocol, must be reviewed and approved by the IRB before the changes are initiated, except when necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)(iii) and 46.117). In these circumstances, new subjects cannot be enrolled until revised informed consent documents, and any proposed changes to the protocol, have been reviewed and approved by the IRB….

[Editor's note: For more information on the OHRP correspondence program go to: http://www.hhs.gov/ohrp/policy/correspond/] ■

Listening to the community pays off for biobank project

Wisconsin effort a model for IRBs, investigators

When the Marshfield (WI) Clinic launched an ambitious biobanking project, organizers knew they'd need significant community buy-in.

The community consultation process they crafted, complete with multiple focus groups, an ongoing community advisory group and a regular newsletter to participants, stands as one of the few models available to investigators and IRBs who are looking to attempt this type of research project.[1]

Catherine McCarty, PhD, MPH, interim director of the Center for Human Genetics at the Marshfield Clinic Research Foundation in Marshfield, WI, is co-principal investigator for the Personalized Medicine Research Project (PMRP), which aims to use genetic information from volunteers in the Marshfield community to investigate the genetic basis of diseases.

She says her group knew they wanted to mount an in-depth education program prior to recruiting people for the biobank.

"We wanted to do right by the community," McCarty says. "We knew we wanted active consent, but more than that, we wanted to increase the general knowledge level in the community about genetics."

Jonathan Reeser, MD, PhD, chairman of the Marshfield IRB, says the community consultation process, particularly the creation of the commu-

nity advisory group, has been integral to the success of the biobank, which McCarty says now has nearly 20,000 participants.

"I think the IRB views the community advisory group as a really important component of the PMRP, gauging public perception and making sure that lay viewpoint is considered in the deliberations and planning of what PMRP hopes to do. Certainly from the IRB's perspective, it's a wonderful thing to have."

Both the IRB and a separate external ethics security and advisory board monitor the project and both boards send members to community advisory group meetings.

Confidentiality a concern

McCarty says participants in the biobank donate a blood sample, answer questionnaires about diet and physical activity, and allow broad-based access to their medical records through the Marshfield Clinic. They also can give permission to be re-approached to provide more information for future studies.

That proposal naturally raises issues of confidentiality and requires explanation of how the genetic research will be conducted and the data kept secure.

So for a year prior to the initial recruitment, the group carried out a series of focus group meetings, first with people from the community at large, then with a group of Marshfield Clinic employees (the clinic and hospital employ half of Marshfield's adult population, McCarty says). Later in the process a final focus group was held with people who had declined to participate in the project.

The focus groups uncovered issues that McCarty says drove the education efforts of the PMRP. Despite the trust community residents had in the clinic, they expressed concerns about the confidentiality of data and the potential for insurance discrimination. They also worried about the possibility of human cloning being conducted with their samples.

Answers to those concerns were incorporated into the communications plan for the project, which included a recruitment video and brochures.

The project also assembled a community advisory group to continue gathering community input as the project progressed. McCarty says she sought help from all areas of the clinic – research, government relations and corporate relations – to find potential members who would represent a cross section of the Marshfield community.

"We've got a couple of dairy farmers, a number of retired individuals, a baker," she says. "We wanted the media represented, so we have local radio and newspapers represented."

That group, which began with 15 members and was intended to run for 18 months, has been meeting twice yearly since 2001.

"We initially only had funding for the first couple of years," McCarty says. "I've found and continue to find this advisory group to be very useful for us, and so with some discretionary funds we continued to have this group meet until a grant came through a little over a year ago that now covers it." She says she's now considering bringing on new members and establishing term limits to carry the group forward.

Members are paid $100 per meeting, with meetings often running for several hours. McCarty says they typically hear reports on recruitment efforts, on the various research projects being conducted with the biobank data and any results that are available. Community advisory group members also give suggestions on stories for the project newsletter, which goes out every six months to participants who have elected to receive it.

Group advises on database

Some of the issues tackled by the community advisory group have included:

Involvement in a larger database – McCarty recently received a grant through the National Institutes of Health for genome-wide association studies. The grant requires that Marshfield share data with the database of Genotype and Phenotype (dbGaP), which would make it available to outside investigators. Because that was not a part of the initial informed consent that participants signed, McCarty wanted to get the community advisory group's input.

"Although the consent form is pretty broad and allows for data and sample sharing, something to the level of dbGaP we didn't envision, because it didn't exist when we wrote our consent form six years ago," she says. "So our community advisory group suggested that we have a piece in our newsletter, and see what we got back in response. If we got a big negative response we could go back and think about re-consenting."

In the end, McCarty says, only one participant

contacted them with concerns.

Unanticipated findings – Over the past few years, Reeser says the Marshfield IRB has been working on a new policy addressing unanticipated findings. While it was not directly related to the PMRP, Reeser says he knew the community advisory group would be interested in hearing about it.

Currently, the PMRP's consent forms state that individual results are not returned to participants.

McCarty says the group opinion mirrored those of other lay groups that have discussed this issue. "They say they don't necessarily want the information, but they want the choice to decide."

Reeser says he expects a final policy in the next several months that will encompass return of research results in general as well as unanticipated findings. McCarty says the issue of whether and how to return individual findings from the PMRP likely will be the next big issue the community advisory group will tackle over the next 12 to 18 months.

While the IRB has monitored the community consultation and education process, it doesn't do so as closely as it once did, McCarty says. The IRB approved a recruitment video and initially wanted to see newsletters before they were distributed, but no longer requires that. Reeser and the external ethics board chairman, Norm Fost of the University of Wisconsin, attend community advisory group meetings when they can.

Reeser says he's been impressed with the depth of the discussions he's seen on the community group. "They're a well-reasoned and well-read group," he says. "I think Cathy's got a really nice collection of individuals that bring a lot to the table, and that's a good thing."

He notes that while the IRB has nonscientific members, this larger group provides an even greater opportunity for public input to the research process.

"If you go down the list of occupations and life experiences from those members, I think you'll find a fairly substantial diversity exists," Reeser says. "It gives everybody the reassurance that all angles have been considered and all opinions have been given an opportunity to be heard and voiced."

Reference

1. McCarty CA, Chapman-Stone D, Derfus T, et al. Community consultation and communication for a population-based community DNA biobank: The Marshfield Clinic personalized medicine research project. *Am J Med Genet A* 2008 Dec 1;146A(23):3026-33. ■

Protecting suicidal teens in research requires care

Participants bring special risks, but research is vital

Research with adolescents who are at risk for suicide can create daunting ethical and practical challenges for investigators and IRBs.

But a researcher who has been working with suicidal teenagers for 20 years says it's possible to craft protocols that protect them as much as possible while still providing valuable data. And she notes that the need for such research is vital: Suicide is the third most prevalent cause of death among youths ages 13-19.[1]

Cheryl King, PhD, ABPP, chief psychologist in the Department of Psychiatry at the University of Michigan in Ann Arbor, says dealings with her IRB over the years have been relatively untroubled.

The key, she says, is communication between the IRB and investigator, especially when a protocol involves unusual issues or particularly vulnerable subjects. In fact, she recommends that the investigator be present at the IRB meeting to answer questions and explain details in those instances.

"I recommend a chance for that back-and-forth discussion," King says, noting it saves a lot of time that otherwise would be spent sending written notes back and forth.

One important point for IRBs, King says, is that they understand the teens being sought for these studies, and the inherent risks they bring with them. She says an IRB may look at a suicide intervention protocol as too risky when it's not the intervention that carries risks, but the subjects themselves.

"They're at risk because of their condition," she says. "We know that multiple suicide attempters are at higher risk than others for suicide and if someone has made a suicide attempt, they're at higher risk than someone who has only thought about it."

In reviewing her first intervention study with suicidal youth, King's IRB initially asked her for very frequent adverse event reporting.

Because of the nature of her work, "we have a lot of adverse events. By definition, if they end

up in the emergency department, it's an adverse event. If they're re-hospitalized – and a certain percentage of these are going to be re-hospitalized—it's an adverse event."

Within a year of her launching the study, the IRB told King she could start reporting every six months instead.

King says researchers in her field now routinely list suicidality and potential suicide attempts as an anticipated outcome in informed consent documents, based on long-term outcome studies of teens at high risk.

"An outcome study on what happens to those youth over the next five to 10 years is very relevant to understanding the cohort," she says. "IRB members should understand what we expect as outcomes and try to differentiate between what is anticipated or expected and what is unanticipated or unexpected."

King routinely uses a data safety monitoring board, even though her minimal risk studies generally don't require them. "I think between the IRB and the data safety monitoring board, we have a collaborative effort going to be sure that we're balancing scientific rigor with protections for the subjects."

Consent and assent

Another common issue in research with suicidal teenagers is the relationship between those teens and their parents or guardians, who must give consent. Everyone must understand and approve the youth's participation. Usually, King says, she approaches the parents first, and then meets with the teen either with his parents or separately, depending upon the circumstances.

Disagreements over whether the teen should participate aren't common, but make up "a significant minority," she says.

"Emotionality is often high if a youth has just been psychiatrically hospitalized and they really don't want to be," she says. She says that while the parent has initial veto power, it should be clear to everyone involved that the youth has the final say.

King says there may be unusual situations where it may be necessary to bypass parental consent – when the parents are suspected of abuse or when the child is homeless, for example. Those are the cases where she suggests an investigator should meet with an IRB in person.

"There are a lot of nuances to this, and as long as you understand what your question is, and how you can answer it while protecting the subjects, IRBs can understand and approve special circumstances," she says.

"I think sometimes, IRBs may be working from a template, almost as if they're going through a checklist. But I do think it's possible for the investigator to give a clear rationale for the problem, how they're going to address it, the protections for the subject and a cost/benefit determination. And the IRB will look at it as something that falls outside the usual template but that is justifiable and meets all the federal regulations of adequate protections."

In one case, King consulted with a subcommittee of the IRB before submitting a protocol in order to iron out thorny details.

Confidentiality limited

Other points for IRBs to keep in mind, King says:

-**Limits to confidentiality** – Often, King says, her investigators must end up revealing something a teen has said, usually having to do with harm to the youth or someone else. She says it's essential that the limits of confidentiality be spelled out clearly in the informed consent.

"You don't want a big breach of trust," she says. "They need to know up front when they sign that if we have serious concerns about any safety issue, including self-harm, that we will let someone know who can take care of it."

-**Clarity of informed consent** – Long, complex documents are often too much for parents to understand, let alone teens. King says she had a study where the reading level on the informed consent was judged to be too high "and it was all the IRB required language. This is a problem because I was working in a disadvantaged urban area with this study and the reading levels aren't that high."

King says she's been working with her IRB to simplify consent documents so they still cover the required elements but are understandable to families who are going through a crisis and already feel overwhelmed.

She says informed consent documents that describe an intervention should make clear the difference between research and treatment, and should describe any alternative treatments that are available.

-**A risk management plan**—King says every investigator who works in this area should include in IRB submissions a risk management

protocol detailing how problems will be handled. Team members should be trained in how to carry out the protocol.

"Who's going to be paged, for instance, if a follow-up assessment is done with a youth off-site and it looks like that youth is at high risk? I can't have the assessor, who may or may not be a mental health professional, leave the home when they've just found out a youth is acutely suicidal until I'm paged and we intervene."

She says such plans are not always required by IRBs. "But I can't imagine working in this area without one."

Reference

1. King, CA, Kramer AC. Intervention research with youths at elevated risk for suicide: meeting the ethical and regulatory challenges of informed consent and assent. *Suicide Life Threat Behav*. 2008 Oct;38(5):486-97. ■

Research with pregnant women still lags due to fears for fetuses

Reluctance can impede vital research to help women

Despite general agreement that medicine and medical research need to do more to meet the needs of pregnant women, there still are serious roadblocks that prevent wider enrollment of women during pregnancy.

The overriding concern about protecting a developing fetus can keep important studies – studies that could benefit both women and their children – from ever going forward, says **Ruth Faden**, PhD, MPH, director of the Johns Hopkins Berman Institute of Bioethics in Baltimore, MD.

Faden, who helped author a recent paper in *The International Journal of Feminist Approaches to Bioethics*, compares the dilemma to that of trying to bring about pediatric research.

"There is a significant chunk of people who have health needs in pregnancy and we don't know nearly as much about how to take care of them effectively as we do for other groups of people," Faden says. "In that sense, it is directly analogous to the claims that were made with regards to pediatrics.

"The notion of protecting children ended up being inimical to their interests," she says. "And we argue that protecting pregnant women (from participating in research) is inimical to their interests and also to the interests of their babies. Nobody wins."

She and her co-authors recommend a number of steps – including improved guidance for IRBs – to help incorporate pregnant women more fully into clinical research.

Little progress

The Institute of Medicine's 1994 report on the inclusion of women in research recommended that pregnant and lactating women be considered eligible for research, effectively reversing the existing presumption that they should be excluded.

Current federal regulations (45 CFR 46 Subpart B) allow pregnant women to participate in research if it holds out some prospect of direct benefit to the woman, the fetus or both, or barring that, does not subject the fetus to greater than minimal risk.

However, there's been little progress since the IOM report in actually increasing the number of studies conducted with pregnant women, write Faden and her coauthors: "…many researchers and institutional review boards (IRBs) continue to regard pregnancy as a near-automatic cause for exclusion, regardless of the costs of exclusion or the magnitude or likelihood of the risks of participation."

And those costs are real ones, Faden says. Because of reluctance to do research with pregnant women, little is known about how best to treat them when they have existing conditions such as hypertension, diabetes, cancer and psychiatric illness. In addition, conditions of pregnancy such as extreme nausea, and preeclampsia are understudied.

Just as women are not like men in their responses to medicine and children are not simply "little adults," pregnant women are unlike even other women in how they are affected by drugs. Pregnancy can affect the absorption and excretion of drugs in ways that can be hard to predict. It's also unknown exactly how most drugs affect a developing fetus.

Despite those uncertainties, pregnant women do take drugs – one study showed that two-thirds of pregnant women took four to five medications during pregnancy and labor.

Faden notes that those women represent an opportunity to researchers; because they already have shown themselves willing to take medica-

Pregnant pause: Is research being subtly discouraged?

IRBs should look to their policies to see

There's little data about exactly what is impeding research with pregnant women, says **Ruth Faden**, PhD, MPH, director of the Johns Hopkins Berman Institute of Bioethics in Baltimore, MD.

Is it funders who don't provide the money, IRBs who won't approve the studies or investigators who assume they can't get approval and don't even attempt it?

Faden says she doesn't believe that IRBs by themselves constitute a major obstacle to research with pregnant women. But she does think they lack good guidance on how to review such studies.

"You can't ask IRBs to solve this on their own," Faden says. "If you look at the situation with respect to pregnant women, the guidance is inadequate, I believe. And so when we start to look for creative solutions, starting with the IRB doesn't make the most sense."

But she says there are steps that IRBs can take to ensure they're not subtly discouraging research with pregnant women. She suggests that IRBs look at their own policy documents with an eye toward language that may be "off-putting" to investigators.

Obviously, IRB policies must conform to federal regulations. But if they go beyond the regulations with commentary, Faden says it matters how it's presented.

"If you've got a section with the heading, 'Pregnant women,' how you set that section up can affect how people think about it," Faden says.

For example, she says such a section could start by saying, "Pregnant women are a vulnerable class because we worry about, etc…." indicating to investigators that they're going to have a hard time getting a study with pregnant women approved.

On the other hand, the section could start by saying, "The IRB recognizes the importance of medical research to advance the health of pregnant women, and is happy to review proposals…" and then go on to say what the current regulations require, Faden says.

Will semantic changes such as these help encourage more research with pregnant women? On their own, probably not, Faden concedes.

"It may be a minor point, we don't really have a reason to think that fear of IRB rejection is why this work isn't getting done," she says. "But if we're talking about the little pieces that make up a cultural frame, and we want to shift that frame, then all these little steps help." ■

tion during pregnancy, they could participate in a study of the medicine with no more additional risk than a simple blood draw.

Encouraging such opportunistic studies – what Faden and her colleagues call "low-hanging fruit" – is one of the steps that they recommend in their paper.

"If various funding agencies announce this is an initiative where they'd like to see work, and they release RFPs, work will be done," she says.

She and her co-authors also want to see more research into the public health impact of the lack of knowledge about the effects of medication on pregnant women and their babies. Those studies could help answer questions about what priorities should be set in pregnancy research. For example, is there a health cost to requiring that pregnant women continue to use older drugs for conditions such as hypertension rather than studying the effects of newer drugs?

Faden's colleagues recommend better guidance for IRBs to help them recognize the possible harms of excluding pregnant women from studies, and determine what are and are not reasonable justifications for excluding them.

While it's taken a long time to get to this point, Faden thinks the timing is right for there to be a concerted effort on this issue, because even those who disagree on other issues such as abortion can agree on this.

"No doubt this issue has been tied up with our deep moral disagreement about how to think of early human life – to think otherwise is just silly," she says. "But there's nobody who doesn't think it's a good thing if we know better about how to improve the health of pregnant women and how to protect the health interests of babies. Nobody is going to argue against that." ■

Ask2-4U:

Vulnerability issues not clearly outlined in regs

PRIM&R faculty member offers advice

Helen McGough, MA, CIP, is retired from the office of research at the University of

Washington in Seattle, WA, and has worked as a faculty member of PRIM&R. McGough also has worked with the Collaborative IRB Training Initiative (CITI), and she served on an IRB for many years. McGough discussed with *IRB Advisor* how vulnerability in research is determined and what IRBs might do to expand their understanding of the topic.

***IRB Advisor*:** When do IRBs make assumptions about research participants' vulnerabilities when they shouldn't?

McGough: Every IRB administrator or chair has his own list of anecdotes about when assumptions are made. But they are implicit assumptions, and we often make them without recognizing that that's what they are.

For example, are pregnant women really vulnerable? And how do we deal with adolescents who are regulated by a subpart [of human subjects regulations] that deals with children? A lot of adolescents are straddling the competence and borderline [of adulthood] and may be less vulnerable than we think.

The paradox

It's hard to know what we don't know. Other subjects with vulnerability are parents of kids who have recently died. Also, trauma victims are a common vulnerable group. We assume trauma victims are in a fragile condition and that asking them to take part in research would perhaps add to their fragility. But I'm not sure that's the case. We don't have a lot of data yet to answer that question.

People who have been through a difficult situation, especially nurse researchers and public health researchers, want information from these people to help them minimize their problems or help them recover better. But the dilemma is the question of whether they are so vulnerable that they cannot participate in that research.

***IRB Advisor*:** So how do you decide what a vulnerability is and how do you handle it?

McGough: We need more research. We certainly have identified some populations that we assume are vulnerable. A first step is actually doing empirical research to find out if something is correct or not.

In terms of an IRB, I think one of the best things an IRB can do is invite a consultant or contemporary of the IRB who deals with a population over and over again to inform the IRB about what steps to take. So if you're dealing with parents of children who've died, then have a consultant speak about which issues those parents deal with.

The only danger is that you're [receiving the information] from just one person. So it would be better to have research on the subject. ■

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

- ■ Find the right members for your IRB
- ■ Follow best practices in training PIs, IRB members, staff
- ■ Get ready for the eIRB conversion
- ■ Comparing U.S. IRBs to those in the developing world
- ■ Do IRBs play a role in clinical trial failures?

CNE/CME *Questions*

5. What would the Physician Payments Sunshine Act of 2008 mean for IRBs?
   A. physician investigators would have to send a separate disclosure letter to IRBs regarding their conflicts of interest
   B. IRBs would need to take closer looks at physician conflicts of interest and institutional COI policies
   C. extend IRB membership to those previously ruled out due to relationships with manufacturers of drugs and devices
   D. All of the above

6. In an effort to increase transparency among OHRP and research institutions, the federal agency has begun to do what?
   A. Publish correspondence between OHRP and research institutions on its Web site
   B. Provide links to OHRP on 100 different federal Web pages
   C. Hold e-open houses on a monthly basis
   D. All of the above

7. Research involving youth at high risk for suicide might involve
   A. interventions that are minimal risk;
   B. might not need more frequent adverse event reporting since the risks are related to the subject's condition and not the research;
   C. informed consent documents that clearly delineate between the study intervention and routine treatment outside of the research;
   D. All of the above.

8. What amount of all pregnant women take four to five medications during pregnancy and labor?
   A. One quarter
   B. One half
   C. Two-thirds
   D. Nearly all

Answers: 5. B; 6. A; 7. D; 8. C.