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## IOM panel recommends changes to review of prisoner research

*Enhanced OHRP, new focus on risk vs. benefits, among recommendations*

The world of a prisoner in a correctional institution is all about control, or the lack of it. The time you wake up, when you eat, where you go, whom you speak to — all is controlled by officers.

Under those circumstances, is true voluntary participation in research even possible? It's a question that researchers and IRBs have struggled with for years, trying to find ways to protect prisoners in their unique environments without closing the door to research entirely.

Now a committee of the Institute of Medicine has weighed in on the issue, recommending systemic changes in the way that prisoner research in the United States is reviewed and monitored.

The committee makes the case that prisoner research is valuable to science, and can provide benefits to the participants as well. But members say the current regulations to protect prisoners are focusing on the wrong issues, and are not applied evenly.

The committee had been commissioned by the Office for Human Research Protections (OHRP) to review the current state of prisoner research and suggest improvements.

The panel, which included IRB professionals, ethicists, prisoner representatives and a former prisoner, concluded that much prisoner research now under way is eluding IRB review — in some cases because it's being conducted without funding of the Department of Health and Human Services, or by a prison system that has its own in-house review procedures.

In addition, IRBs that do review prisoner research may or may not be applying the requirements of 45 CFR 46, Subpart C — the section of the federal regulations that provide specific protections for prisoners — says **Wendy Visscher**, PhD, a committee member who is director of the Office of Research Protection and Ethics at Research Triangle Institute (RTI) International, Research Triangle Park, NC.

The result, she says, is a system in which prisoner research is reviewed differently depending upon the prison system, the institution conducting the research and the funding source.

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"All of this made us come to one of our recommendations: That we needed to have universal protection for prisoners," Visscher says. "All prison research really needs to fall under the same regulations, get the same level of review. That's just not happening right now."

The panel also recommended a change from the current Subpart C, which requires that all

prisoner research fall into certain categories, such as studies of the causes and effects of incarceration, or studies of conditions such as HIV that affect prisoners as a class.

Members say they found the categories to be overly rigid and unhelpful in determining whether a study poses an undue risk to prisoners, or provides them any benefits. Instead, the committee proposes a modification of the current Subpart D section, which applies to research involving children, and is based on risk and individual benefits.

"What we didn't like about Subpart C was that those categories are really artificial," Visscher says. "They were developed back in the 1970s when there was a lot of abusive (prisoner) research going on. It was meant to be very, very restrictive.

"But there are studies that can be done, very ethically and very appropriately, that can offer benefits to prisoners but that you cannot fit into those categories," she says. "We wanted to bring the IRBs back to their roots and have them thinking about risks and benefits, which is what they should be doing anyway."

Under this system, the inclusion of prisoners in Phase 1 and Phase 2 clinical trials still would be prohibited. IRBs could use risk vs. benefit analyses to determine whether to approve Phase 3 studies.

### **Resisting calls for a ban**

The IOM committee resisted calls to ban all medical research with prisoners on the grounds that the prison environment is so inherently coercive that a prisoner cannot give true informed consent.

One of those voices was from an IOM committee member, **G. David Curry**, PhD, a professor of criminology and criminal justice at the University of Missouri in St. Louis.

Curry, a former prisoner, says prisoners considering a research study face a number of pressures — from other inmates, from guards, from the medical staff and from the unrelenting boredom that might drive some to agree to a study just to spend time in a different building or in a different routine.

He noted that in many prisons, access to health care is problematic, and prisoners might be persuaded to sign up for a clinical study to get access to health care or the attention of the prison medical staff.

"I really didn't want to recommend any changes in the regulations, and I kept that posi-

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#### **Editorial Questions**

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**Leslie Hamlin** at (404) 262-5416.

tion on the committee for a long time," Curry says. "I finally realized there are 15 other people there, and I'd have to compromise."

Among the terms he insisted on: An absolute prohibition against cosmetic testing, which had been among the most notorious of the abusive studies of the past; and a rule that in any biomedical study, prisoners should make up no more than 50 percent of the subjects, in order to fairly distribute the research burden.

Among the other recommendations of the IOM committee:

- **Expanding the definition of prisoner** —

Visscher says that when the current regulations were written, nearly all those in the custody of the criminal justice system were men and women literally behind bars. Now, a much greater number are in less restrictive environments, including halfway houses, those on house arrest, or on probation or parole.

The current regulations only address the protection of so-called brick and mortar prisoners, although those in less restrictive environments may still encounter some of the same pressures, including wanting to please a parole officer, or the risk of loss of privacy.

**Monika Markowitz**, PhD, director of the Office of Education and Compliance Oversight in the Vice President's Office for Research at Virginia Commonwealth University (VCU) in Richmond, VA, was one of the IRB representatives who addressed the committee as it worked on the report.

Markowitz says she agrees with the committee that IRBs need to be sensitive to the special risks involved in research with people in various stages of supervision, such as probationers.

She says VCU's IRBs do look at those subjects' particular situations to determine potential risks.

"We really have recognized that people under different levels of criminal justice supervision are as vulnerable, if perhaps not even more so (than those in brick-and-mortar prisons)," Markowitz says. "The IRB really has to look at the potential risks to their participation and their ability to give voluntary informed consent."

"But I wouldn't necessarily want all those people labeled as prisoners, because there are different levels of supervision," she says. "There ought to be different kinds of risk assessment for people in those different levels."

The expansion would not apply to studies in which someone outside a prison, such as a parolee, voluntarily enrolls in an outside study

which doesn't focus on or ask about his status as a prisoner.

- **Introducing on-site prisoner advocates** — These prison research subject advocates (PRSAs) would be based at the prison, but would be independent of the facility and accessible to prisoners. Their role would be to monitor the study to ensure the protection of the subjects — for example, overseeing informed consent or ensuring that privacy protections are adequate. They would be used in cases where the study was especially sensitive or complex and could they serve on more than one study at a time at an institution.

The investigator would have to identify and pay the PRSAs using his or her grant money, Visscher says.

"I think the IRB will like it, because this person would serve as the eyes and ears of the IRB," she says. "I think there would be some resistance from the investigators because they're going to have to pay for it."

But Markowitz worries that the requirement could be impractical on the ground.

"In our IRB's experience, and from what I've heard in the field, it's really difficult even to find prisoner representatives to serve on the IRB," Markowitz says. "I don't know how they hope to get those PRSAs in place in all the different locations that they would need to be."

- **Building a nationwide database of prisoner studies** — Many members say they were shocked by the lack of basic information about prisoner research.

"The only informational database that exists, to my knowledge, is the Office for Human Research Protections, and they don't even have a comprehensive list of prisoner research," says **Michael Hamden**, JD, executive director of North Carolina Prisoner Legal Services and prisoner representative for RTI International's IRB. Hamden served on the IOM committee. "They have a very limited staff for enforcement and it extends to all research, not just prisoner research."

- **Eliminating the current OHRP certification process, while expanding OHRP's authority** — Currently, an IRB reviewing a proposed study that involves prisoners must submit it to OHRP for certification.

Markowitz says the two IRB panels that review prisoner research at her institution have found the OHRP certification process can take a month or more, although the agency rarely disagrees with the IRB's findings.

“That particular component just seems to be something that creates a lot of effort without a lot of extra value or extra protection to the subjects, which is really what we’re about,” she says.

The IOM committee proposes doing away with the certification step, while expanding the authority of OHRP (or some other designated federal agency) to establish a uniform system of safeguards for all prisoner research, regardless of funding.

OHRP, or this other designated agency, also would have to maintain the national registry, enforce the new regulations and provide assistance to IRBs.

This would require many more resources than the current OHRP has, and likely would need congressional approval, says **Lawrence Gostin**, JD, chair of the IOM committee and a professor of public health at Johns Hopkins University, Baltimore, MD.

“We think our proposals will require either a new oversight body or an enhanced OHRP, and how the federal government chooses to work through this is a matter for them,” Gostin says. He says he’s had several meetings with government officials about the committee’s recommendations but declines to detail them.

**Bill Hall**, a spokesman for DHHS, says that at this point, his department is still looking at the report. The next step in the process would be to work with congressional staff to make any changes the department would implement from among the committee’s recommendations.

**Mary Faith Marshall**, PhD, a professor of bioethics at the University of Minnesota in Minneapolis, who had made a presentation to the committee, says she is “delighted” with its final report.

Marshall says she sees the issue of prisoner research as a pendulum, which swung far to the side of protection after the excesses of the 1970s, and now may be swinging back to a position of more inclusion of prisoners.

“We want to be protective, but research does have benefits, and we don’t want to exclude a population from benefits,” she says. “I think the sense was we don’t want to commit the error of precluding research that would be important within that population.” ■

*To access the full report by the IOM’s Committee on Ethical Considerations for Revisions to DHHS Regulations for Protection of Prisoners Participating as Subjects in Research, visit [www.nap.edu/catalog/11692.html](http://www.nap.edu/catalog/11692.html). The publication also is available for sale at that site.*

## Improving prisoner research now: What can IRBs do?

*Recruit good prisoner reps, ensure adequate health care, and protect privacy*

While IRBs wait to learn the final outcome of the federal government’s review of regulations for research involving prisoners, there are steps they can take right now to improve the review of these types of studies, say experts in the field.

One of the most important is to include a true prisoner representative on the IRB, one who not only understands the complexities of prisoner research but who knows the workings of the correctional institution where a study is to be conducted, says **Michael Hamden**, JD, executive director of North Carolina Prisoner Legal Services and prisoner representative for Research Triangle Institute (RTI) International’s IRB in Research Triangle Park, NC.

“It needs to be someone who’s familiar with the particular institution, how that institution functions,” Hamden says. “That way, there will be somebody who will help the IRB appreciate the implications and overtones of a plan.”

### **Tapping former prisoners**

**G. David Curry**, PhD, a professor of criminology and criminal justice at the University of Missouri in St. Louis, served as a prisoner representative and later as IRB chair on his institution’s board. He was recruited for the IRB because his bosses knew he had been imprisoned during the 1980s on a drug charge. He received a full pardon in 2000 from President Clinton.

Curry says he was able to use his experience to help his IRB understand complex issues such as the potential benefit to prisoners of participating in social-behavioral research.

While Curry generally opposes biomedical research involving prisoners, he does believe that social-behavioral studies can be beneficial, to prisoners as a class and to individual prisoners who participate.

“It does relieve boredom, and it helps the prisoner be introspective,” Curry says.

He says he also pushed to include means by which prisoners could report adverse effects from studies, which can be difficult in a prison setting.

Curry says that if an IRB is searching for a good

prisoner representative, it may be able to find one among the ranks of its own faculty. He says there are many prisoners currently obtaining higher academic degrees, and some have gone into fields such as criminology. A group called Convict Criminologists gathers at the annual meeting of the American Society of Criminology.

"If anybody really wanted to find somebody who's a prisoner advocate, they could probably get the name from that group," Curry says. He also recommends people who have a background in fighting against the death penalty. "They are great prisoner advocates."

Among the IRB's responsibilities in reviewing medical research involving prisoners is to assure that all prisoners at that institution have access to adequate health care, Hamden says.

Without that assurance, the study environment could be inherently coercive, with prisoners opting to participate to get medical treatment they couldn't receive otherwise.

"If the care in an institution is substandard and the prisoner has but one choice to obtain adequate care, then that's not really informed consent," he says. "It is absolute coercion, it's just not ethically appropriate."

The IRB's role should be to require investigators to provide proof of adequate health care at the prison before approving a study, says **Wendy Visscher**, PhD, director of the Office of Research Protection and Ethics at RTI International.

### ***Privacy protections essential***

IRBs also need to pay special attention to the privacy issues raised by prison research, both biomedical and social-behavioral, Hamden says. Research involving prisoners can involve such sensitive subjects as HIV infection, alcohol abuse or incidence of prison rape.

"If a person wants to participate in a research study and the [prison] population knows about the study and the participant is removed from his cell, it can be obvious what's going on and almost impossible to protect privacy in that situation," he says.

However, he says, researchers can limit the amount of information about a study that's known in the general prison population.

"For example, if we're looking at the efficacy of a new HIV treatment, it's not necessary that the prison population know that that is the subject of the study," he says. "But it would be satisfactory and probably would suit everybody to know that there was a study going on of some kind."

He says that in these situations, prisoners need

## Examples show how IOM recommendations would work

The Institute of Medicine's committee on prisoner research provided a number of examples of how its recommendations, if implemented, would affect individual studies involving prisoners. Here are some of the hypothetical studies it presented:

- A psychological study of personality traits among prisoners preparing for discharge to a community half-way house. A non-interventional study of this type, which doesn't elicit sensitive information, would generally be considered minimal risk. Under the committee's recommendations, the IRB probably would not opt to impose special safeguards, and wouldn't require a prison research subject advocate (PRSA) to monitor informed consent. At a minimum, the IRB might require that prisoners have some way of contacting the IRB to report problems or ask questions.
- A Phase 3 study that would enroll more prisoners than non-prisoners in an experimental treatment for hepatitis C. The study, which would compare an experimental treatment to the existing therapy, would be considered greater than minimal risk, but possessing potential benefits to the prisoners. However, it wouldn't be approvable under the committee's recommendations unless the percentage of prisoners in the study was reduced to 50 percent. Even if that were accomplished, the IRB would require a number of safeguards, including PRSA monitoring.
- A study that compares an experimental drug for impulse control disorders to a standard treatment currently not on the prison's formulary. In this hypothetical example, the standard drug is too expensive, so the prison uses a generic substitute, which is more likely to cause gastric side effects. Under the IOM committee's recommended rules, the IRB could not approve this study because prisoners might be willing to expose themselves to the risks of the study drug in hope of receiving the standard treatment. ■

to understand the possible risks of disclosure as part of the informed consent process.

Despite the difficulties involved in conducting prisoner research, Hamden says it's in the best interest of the prisoners and the public at large that studies be conducted, and conducted ethically.

"Although there's a shameful history of exploiting prisoners in medical research, that does not mean that research offers no benefit to prisoners," he says. "There are important potential benefits and they deserve consideration.

"These folks are going to be members of the community again. The correctional officers who supervise them are already members of the community, they return to their families at the end of each shift. To the extent that there's a risk of contagion in a correctional facility, it threatens all of us, whether we're incarcerated or not." ■

## New approach surveys subjects to measure informed consent

*Surveying subjects after they've participated can help determine effectiveness of training*

Every research institution wants to know that its participants have made a fully informed, unpressured decision to enroll in research. But, often, that basic question is hard to determine.

Researchers at The Rockefeller University in New York City are testing a novel approach to surveying research subjects after they've left the hospital, in order to provide a better measure of the effectiveness of informed consent and other aspects of human subject protections.

**Rhonda Kost**, MD, clinical research officer and research subject advocate at Rockefeller's General Clinical Research Center, says her institution originally wanted to test research staff to measure how a specific education program affected their administration of informed consent, but realized that testing subjects would provide a better picture of how well the process worked.

"Evaluating whether investigators say certain things in an interview after they have been 'educated' is really a surrogate," she says. "What you really want to know about your whole human subjects protection education program is, in the end, did the research subjects have the information that they needed and the supportive environment that they wanted in order to make the decisions they had to make?"

## Testing subjects instead of staff

Funded by a National Institutes of Health/National Center for Research Resources Human Subjects Research Enhancement Award, Kost says she began working on a plan to develop education modules for research staff at Rockefeller and other local hospitals. The plan originally was to test the effectiveness of the education by videotaping staff in standardized informed consent sessions with actors.

But in the meantime, she says, Rockefeller's physician-in-chief, **Barry Coller**, MD, learned about a joint project of the NIH Clinical Center and NRC+Picker, which produces a widely used survey of patient satisfaction for hospitals and other health care providers. Hospitals commonly use surveys such as Picker's to meet standards set by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

The NIH-Picker project would extend the standard hospital survey, which asks about such issues as meal quality, nurse attentiveness and physician wait times, to ask questions specifically geared toward clinical research participants. Did patients feel they had enough information about a study? Did they understand the conditions under which they could quit the study?

A team from Rockefeller worked with the NIH Clinical Center's **Laura Lee**, RN, and **David Henderson**, MD, to evaluate whether questions were specific enough to meet Rockefeller's needs, while still general enough to provide benchmarking with other institutions. Rockefeller's IRB reviewed the proposal, looking specifically at issues of privacy and confidentiality. The survey is mailed to subjects after they leave the hospital, Kost says, to allow them to reflect on their experience.

"Some people think, and I agree, that there's the risk of undue influence when you hand someone a survey and the research nurse is standing beside them waiting for discharge," she says.

Subjects must agree beforehand to allow the survey to be sent to their home.

"Some people might not want a research survey to come to their house, as it may reveal that they have participated in research the rest of their household does not know about," Kost says. "Particularly because our research includes HIV and drug addiction, we are especially sensitive to confidentiality issues."

## **Survey rolls out to more centers**

After two years of applying the survey at Rockefeller, it is being refined in collaboration with NIH, Picker and selected collaborating centers, and will be shared with a number of General Clinical Research Centers (GCRCs) across the country for use in their institutions. Kost, a past president of the Society of Research Subjects Advocates (SRSA), says she and the NIH collaborators presented the idea at an SRSA national meeting last year, and found enthusiasm for the survey approach to human subjects protection outcome measures.

"We're redeveloping and validating these questions to now pilot the survey across a self-selected group of GCRCs, to learn whether it's more broadly applicable to those centers," Kost says.

"It worked well in our small center, it worked well at NIH, but in a larger academic medical center, we'd like to identify and address the obstacles to administration," Kost says. "We think it will be ultimately successful, because it's not that different from administering a non-clinical research hospital survey. We need to work out the kinds of issues that come up in the implementation before we offer this in a broader way."

Kost says Picker produces highly sophisticated survey tools, based on focus groups and thousands of patient interviews, and the research team is excited about the possibility of bringing the same degree of survey rigor to the clinical research questions.

"They use focus groups made up of patients, of caregivers, of ethicists, to go back and really scientifically validate these clinical research questions," she says. "So they're quite powerful at extracting the information we hope to have."

On the education side, Kost has developed 12 modules and made them available to Rockefeller staff through the University of Miami's Collaborative IRB Training Initiative (CITI) program.

Rockefeller's staff already used the CITI program for basic human subjects protection education, so Kost added advanced modules in areas such as informed consent. CITI adapted the Rockefeller modules so that they matched CITI's format.

Because the education project was funded in part with an NIH Human Subject Research Enhancement Award, whose conditions include sharing content outside the institution, Rockefeller has donated the modules to CITI, Kost says.

"If they find our modules valuable, they can offer them to other institutions, use them to enhance other modules or use them as ideas for developing new content," she says. "We've donated them to CITI as an educational resource."

Kost says the difficulty of education initiatives in the area of human subject protection education is that there's so little data about what works.

"There's adult learning theory, there's education in other fields, but there's very little information that I'm aware of about how to best educate researchers and participants in all these areas," she says. "We're driving on our best instincts."

That's why she's hopeful that the outcome measurement part of her project will provide more information to Rockefeller, and other centers that use it to make data-driven decisions in program development.

A key advantage to having this survey administered at centers around the country is the ability to benchmark, Kost says.

"What if you discover at your center that x percent of research volunteers still don't know, despite all of your best efforts, that they can quit participating in a research study at any time?" she says.

"And you know you've told them many times: You told them in the informed consent interview, in the informed consent form, in a post-consent interview and you sent them a letter reminding them they could quit and yet, they still answer that they don't know when they can quit. What do you do?"

"If you can look at aggregate data from other centers and you can see that pretty much across the country, everybody's got the same number, or you're doing better, or you're doing a little worse and you do need a different model," Kost says. "It's tremendously powerful."

She says the rollout to other centers will include confidentiality features that will protect an individual hospital's data. A hospital participating in the pilot will be the only one to see its individual scores — other institutions will only see aggregated data.

Kost says she believes this survey could become an important performance improvement tool for research institutions.

"Not only could it demonstrate in which ways their human subject education program best works, but it might provide data with which leadership could direct their performance improvement efforts based on where their problem scores are, just like they do for JCAHO for hospital performance," she says. "It could be very valuable." ■

# IRBs sometimes go overboard in requiring risk details in consent

## *Define reasonable protection*

When IRBs review protocols involving social-behavioral research, it's a good idea to define what IRB members believe are reasonable protections.

Once the definition is made, then the IRB may need to adjust policies accordingly. For instance, the IRB should examine whether it is necessary to require detailed explanations for standard informed consent items, according to an expert.

"IRBs need to be balanced between what is a reasonable protection versus an unreasonable protection," says **Elana Newman**, PhD, an associate professor in the department of psychology at the University of Tulsa in Tulsa, OK.

"Sometimes I think we're so concerned by presumed fragility or the resilience [of research participants], that we may shape the research enterprise in a way that's not a win-win situation for everyone," Newman says.

"For example, we may choose not to study something we need to understand to help survivors of trauma," Newman says. "Or we may say, 'You can't do this kind of thing because they're too weak.'"

It's important for IRB members to improve the process through respect and reasonable protections, based on facts, not fears, she adds.

Newman's work involves people who have been victims of trauma. Unless there was a head injury, these potential research participants are healthy and able to provide informed consent, Newman says.

However, during the aftermath of a traumatic event, people will need greater care during the informed consent process, she suggests.

"There was a small study done that asked women 72 hours after a sexual assault if they could be contacted later for research," Newman says. "Ten to 29 months later they were located, and very few of the 15 women remembered signing an informed consent form."

Only one of the women objected to the research, but the study suggests that the informed consent process could be refined for this population, Newman says.

Newman's research has found that a majority of subjects in trauma research do not regret their research participation, even when they experience strong emotional reactions.<sup>1</sup>

It's possible then that when these subjects experience emotional distress it could be an indicator of emotional engagement with the research project rather than an indicator of harm.<sup>1</sup>

Another item for debate in research involving trauma victims has to do with recruitment.

"Say you've decided that for whatever study you're doing, it's important to find people who are trauma-exposed, such as hurricane survivors or rape survivors or whatever," Newman says. "There's some debate about whether you should tell potential participants that a portion of the sample has been selected based on rape or the trauma."

This disclosure could run counter to participants' interest when it's weighed against confidentiality or suspicion of harm, Newman says.

"We don't know the answer," she says.

Early in Newman's career she wanted to locate adults who as children were sexually abused, she recalls.

"I wanted to send them notes saying, 'You were once seen as a patient in this hospital. Could we contact you?'" Newman says. "The IRB asked me to write a note, saying, 'You were sexually abused. May we see you?'"

Newman disagreed with the IRB, arguing that their version of the note was not ethical because there was the potential that someone besides the survivor would open the mail and see the letter.

So what is the most ethical way of recruiting survivors of trauma without being deceptive?

The answer will vary with the situation, Newman says.

"If you're recruiting people from a domestic violence shelter or a Red Cross shelter, then there's no harm in saying, 'Well, you're here, but if you contact them in other ways you have to think about that,'" Newman says.

Another ethical dilemma arises in relation to mandatory reporting laws and whether to disclose these in the informed consent.

"When someone discloses abusive parenting, there are a lot of different principles that clash," Newman explains. "There's the ethical responsibility to protect children or confidentiality or subject autonomy — all of these can conflict."

Investigators handle this issue in a variety of ways.

For example, one research team evaluated 12 year olds, using a computer, Newman says.

"It prevented interviewers from directly hearing information that would fall under mandatory reporting," Newman says. "Although this strategy was legally defensible, was it ethically defensible?"

Also, IRBs would need to ask themselves whether this strategy would reduce the risk to families.

"We need to understand the costs and benefits of using these methodologies and how they should go about complying with the law that requires them to protect children," Newman says.

IRBs should also think about how much detail they wish to require in studies involving trauma victims.

For example, a review of survey methods to study child abuse showed that there were lower prevalent rates of physical abuse, but not sexual abuse, when the parents got information about the potential for mandated reporting, Newman says.

"We noticed that parents were less apt to report physical abuse when they were told about mandatory reporting," she adds.

IRBs need scientific evidence regarding the different reporting methods, Newman says.

"The same investigator could have two consent forms," Newman explains. "In one they really explain in detail what mandated reporting is and, in the other, they could do it in a more cursory fashion."

She suggests the two versions could read like this:

- In the event that you disclose that you're harming yourself or someone else, we may need to break confidentiality and report this as required by state law.

- This study is private and confidential, and all information will be kept private except that which is required by law. That is, if any respondent reports child maltreatment that was not previously disclosed to the authorities, the interviewers are required by law to report this information to the proper authorities. The team will only report the minimal information necessary. Similarly, if the child or guardian says they are in immediate danger of hurting themselves or others, confidentiality will be broken to establish a plan to keep the person safe, and the child will know this ahead of time, as well.

Newman finds that speaking frankly with potential research participants helps.

For instance, she might tell them that some questions will make them feel nervous, upset, or bored, and that they can skip these questions at any point they desire, Newman says.

"A small group of people find the surveys, the research experience, more upsetting than they anticipated," Newman says. "They aren't dysfunctionally distressed, but more distressed than they anticipated, and that seems like something that would be important to tell someone in advance."

While researchers and IRBs sometimes have a 'don't ask, don't tell' policy, Newman says her experience with trauma survivors has led her to a different strategy.

"My argument is that in the trauma field, we've been very careful about this, and I think these kinds of questions need to be asked in certain protocols without making it too impossible for the researcher to do his or her work."

Also, it's important to put this type of research into context: Even researchers who work with college student populations will unintentionally include in their studies young people who are dealing with severe psychological problems, Newman notes.

"There are silent trauma exposures in every sample," Newman adds.

"We simply have to be aware of these issues, gather data on them, and then make rational choices," she says. "But to me the biggest issue is that we don't stifle research." ■

#### Reference:

1. Newman E, Kaloupek DG. The Risks and Benefits of Participating in Trauma-Focused Research Studies. *J Trauma Stress.* 2004;17:383-394.

## Why isn't there more research into improving pregnancy conditions?

*Sponsors shy away from this population*

Experts say there may be some opportunities missed in research with pregnant women. Despite some concerted government efforts that have succeeded in increasing research in this area, major industry sponsors shy away from this population.

“Clearly, this is a critical area where you want to have the best studies you can to advise pregnant women and their families as to what their options are,” says **Catherine Spong**, MD, branch chief of pregnancy and perinatology branch of the National Institute of Child Health and Human Development (NICHD) in Rockville, MD.

“Unfortunately, because of the special circumstances, it’s more difficult to get these studies done and to get people interested in doing a study,” Spong says. “You have two patients to look at, and you have to take the interest of both the mother and developing child into consideration.”

This is why there are many drugs that are not labeled for use in pregnant women, and why obstetricians must make decisions based on limited research and their own common sense, Spong adds.

Pregnant women and even women who could become pregnant have been excluded from research for a long time, says **Karen J. Schwenger**, MD, FCCM, an associate professor of anesthesiology and critical care medicine at the University of Virginia (UVA) School of Medicine in Charlottesville, VA.

“Go back two decades and women of child-bearing potential were excluded completely from research until the late stages of drug development,” Schwenger says.

While the industry’s attitude toward women of childbearing age has changed in the past 10 years, there hasn’t been a lot of change among research involving pregnant women, Schwenger says.

“I think there’s still a fear among the industry and investigators about doing studies involving pregnant women,” Schwenger says. “We do have some studies at UVA, but these primarily are studies that have a direct benefit to the mother with minimal risk to the fetus.”

For example, one study looks at the management of labor pain using different types of labor epidurals. Another addresses bladder disease in pregnancy and the development of gallstones, she says.

“So I am seeing studies like that coming through from our investigators,” Schwenger says. “But these are investigator-initiated studies; I have not seen a study sponsored by the industry that targets pregnant women.”

Also, many of the studies are retrospective analyses and are not as specific as a randomized trial, she notes.

Even commonplace pregnancy health issues are little studied, Schwenger says.

For instance, high blood pressure is common among pregnant women, but most drugs used to treat the condition have not been studied in pregnant women, she says.

“That leads doctors and obstetricians to choose a drug that may not have enough research evidence that it’s safe,” Schwenger explains. “Clinicians have to use their best estimates, and it’s a judgment call on what the best treatment would be, based on evidence in non-pregnant individuals.”

Most of the studies involving pregnant women that Schwenger has seen are those that provide a direct benefit to the woman and pose minimal harm to the fetus, she says.

“We see retrospective studies that have no risk, obviously,” Schwenger adds.

NICHD has a 20-year-old program called the Maternal Fetal Medicine Unit Network, that has sought to increase research knowledge about pregnant women, Spong says.

Fourteen network sites across the United States tackle important problems and critical issues in pregnancy with the goal of developing evidence-based practice, Spong says.

“What we’ve done is identify practices in place that were not really beneficial to pregnant women and their children,” Spong says.

“One example is previously there were studies that had shown a condition called bacterial vaginosis (BV) or *Trichomonas vaginalis* that is associated with pre-term birth,” Spong explains.

Two studies had shown that women at high risk for pre-term delivery could have this risk reduced through treatment for BV, she adds.

This led to obstetricians treating every woman who had this condition.

The network chose to study the treatment and recruited asymptomatic pregnant women who were screened for BV. They were randomized to antibiotic treatment or placebo, but the trial was stopped early, Spong says.

“The women with *Trichomonas* who were treated had a higher rate of pre-term delivery,” she says.

As a result of the clinical research, obstetricians were advised to stop screening every pregnant woman for the infection.

“If they’re symptomatic, then treat it, but if they’re not complaining, then there’s no reason to treat,” Spong says. “Whatever the flora is for that person may be more beneficial than what takes over when you eradicate the flora.”

This example demonstrates why clinical research in pregnant women can lead to better and safer practices.

In another example, the network demonstrated through research a treatment for preventing pre-term delivery, Spong says.

"It's the number one cause of neonatal death and long-term morbidity for children," Spong says.

One of the network sites screened high-risk pregnant women who had already delivered a pre-term baby and evaluated them to see if they were interested in a trial using progesterone to prevent pre-term delivery, Spong explains.

The women received weekly progesterone, and the trial produced such positive results that the data safety monitoring board (DSMB) decided it would be unethical to continue to randomize patients. The study found that weekly progesterone, started in the 16th to 20th weeks, prevented pre-term deliveries of less than 32 weeks, 35 weeks, and 37 weeks, Spong says.

"We were questioned quite harshly after the progesterone trial about whether it was safe," Spong recalls. "But no one questions giving progesterone to women [treated for infertility], and they're given it at a more vulnerable time during the first trimester."

The problem is that clinical trials involving pregnant women are needed to guide future studies with pregnant women, Spong says.

"The opportunities for pregnant women to participate in clinical trials are limited, despite a push from the Food and Drug Administration and others," Schwenzer notes.

Also, IRBs and investigators should consider the ethics of removing women from typical adult clinical trials when the women become pregnant, Schwenzer says.

"Is that ethical to deny treatment to a woman that she couldn't get otherwise?" she says.

On the other hand, there are clinical trials involving drugs that are known to be harmful to a fetus, such as the thalidomide trials for

cancer, and so the ethical concerns are not just theoretical.

"Suppose there's a trial where the potential for therapeutic benefits for a woman is there, and so you enroll women knowing there is the potential of their getting pregnant," she says. "You give separate consent forms, detailing the type of risk that's involved and the type of birth control that needs to be used to avoid pregnancy."

These types of trials often require women to use two types of birth control, and they're given a pregnancy test, Schwenzer says.

"Sponsors won't use pregnant women in trials involving some potentially helpful drugs because of the risk," Schwenzer adds.

However, the NICHD network has made some important contributions to the scientific world's collective knowledge about pregnancy.

The Maternal Fetal Medicine Unit Network currently is enrolling 10,000 pregnant women in a preeclampsia prevention trial that involves the use of vitamin C and vitamin E, Spong says.

"Clearly, preeclampsia is a condition we need better understanding of, and we need to develop therapies," Spong says. "This is the largest trial we've ever done."

Ideally, pharmaceutical sponsors and more investigators would do research with pregnant women because the potential benefit to society could extend far, Spong says.

Pre-term delivery and low birth weights are associated with health problems that may occur even decades after the baby is born, she adds.

"I would love to have more people do research in pregnant women," Spong says. "If you could improve the uterine environment and improve outcomes, then we'd have less disease, strokes, heart attacks, and other health problems." ■

[Editor's note: For more information about the Maternal Fetal Medicine Unit Network, see the Web site: [www.bsc.gwu.edu/mfmu](http://www.bsc.gwu.edu/mfmu).]

## COMING IN FUTURE MONTHS

■ Quality assurance within IRBs

■ Congressional update: What's new in human subjects protection?

■ Track data, use checklists to improve IRB office best practices

■ Evaluate risk in biomedical research following these guidelines

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## CE/CME Objectives

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

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

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

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

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

## CE/CME questions

14. The IOM committee on prisoner research recommended that regulation of prisoner research be based on what kind of approach?
  - A. A category-based approach
  - B. A risk vs. benefit approach
  - C. None of the above
15. The committee recommended that prisoners make up no more than what percentage of total research subjects in a biomedical study?
  - A. 25 percent
  - B. 50 percent
  - C. 75 percent
  - D. no limit on percentage of prisoners.
16. The Maternal Fetal Medicine Unit Network has helped increase knowledge about pregnant women through clinical trials involving this population. Which of the following was one of the network's studies?
  - A. A study about preventing pre-term delivery through weekly progesterone
  - B. A preeclampsia prevention trial that involves the use of vitamin C and vitamin E
  - C. A study into screening and treating women for bacterial vaginosis (BV) or *Trichomonas vaginalis* to prevent pre-term birth
  - D. Two studies had shown that women at high risk for pre-term delivery could have this risk reduced through treatment for BV
  - E. All of the above
17. Research involving trauma victims has found that most do not regret their research participation, but they do have which of the following reactions?
  - A. Positive views on the possibility of future research participation
  - B. Strong emotional reaction
  - C. Dislike for investigator/interviewers
  - D. None of the above

Answers: 14. (b); 15. (b); 16. (d) 17. (b)