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INSIDE

21st Century Cures Act raises big concerns for subjects protection

Bill allows more informed consent waivers

One short clause in a proposed health bill might unravel decades of efforts toward improving human research protection and create confusion among IRBs about some types of new drug and device research, according to critics of the 21st Century Cures Act.

The proposed Cures Act is intended to expedite the process of bringing new medical discoveries and treatments to market so people with serious conditions, including cancer, traumatic brain injury, and antibiotic-resistant bacterial infections, will have a greater chance of accessing life-saving treatment. It also brings additional funding to the National Institutes of Health. This has made it a popular bill in Congress. However, some of the bill's provisions could affect human research protection, experts say.

"The bill is very large and it covers a wide range of topics, the vast majority of which have nothing to do with human subject protection," says **Michael A. Carome**, MD, director of the health research group at Public Citizen in Washington, DC.

> "THE BILL IS VERY LARGE AND IT COVERS A WIDE RANGE OF TOPICS, THE VAST MAJORITY OF WHICH HAVE NOTHING TO DO WITH HUMAN SUBJECT PROTECTION."

"Within the bill is a small section that has provisions that have an impact on human subject protection," Carome adds.

For example, the proposed bill's Section 2263 is titled, "Alteration or Waiver of Informed Consent for Clinical Investigations." It has subparts related to devices and drugs and Food and Drug Administration (FDA) regulations. That small section makes possible a broad expansion of informed consent waivers

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with wording that exempts device and drug studies that "pose no more than minimal risk" to research participants.

"When we're talking about trials that involve testing of drugs and medical devices, we think whenever this research is conducted on human subjects, regardless of the level of risk, informed consent should always be required — except in extraordinary circumstances," Carome says. "And existing law already allows an exception to informed consent when it's not feasible."

This waiver for emergency research has worked for decades, he adds.

"With the Cures Act, we think the waiver will expand beyond extraordinary circumstances and that's inappropriate," Carome says. "Expanding the waiver to research that involves no more than minimal risk violates the universal principle for respect of persons, and there's no reason to do this; we don't believe existing law has inhibited clinical trials that promote new drugs, so we see no reason to expand the waiver."

Under the Cures Act, as the House approved it, there's potential for new drugs and medical devices to be approved on the basis of limited data that are not robust, says **Aaron S. Kesselheim**, MD, JD, MPH, associate professor of medicine at Brigham and Women's Hospital in Boston. Kesselheim also is an associate professor of medicine at Harvard Medical School, director of the Program On Regulation, Therapeutics, and Law (PORTAL). Kesselheim and Jerry Avorn, MD, co-wrote a recent commentary about the bill, published in the *New England Journal of Medicine*.

Some drugs approved with this more limited human research protection might be used by many patients before it's discovered that they are unsafe and ineffective, Kesselheim says.

With rare bipartisan effort, the U.S. House of Representatives passed the 21st Century Cures Act, 344 to 77 on July 10, 2015. It's now in the hands of the U.S. Senate, which on July 13, 2015, referred it to the Committee on Health, Education, Labor, and Pensions.

Proponents of the Cures Act, including more than 250 nonprofit organizations representing patients, providers, and researchers, sent a letter to Congress on June 18, 2015, in favor of the bill.

"This is a patient-focused bill that will advance the discovery and development of treatments, strengthen the patient voice in the regulatory environment, increase funding for the National Institutes of Health and Food and Drug Administration, and greatly improve our innovation ecosystem," the letter says. It was signed by organizations ranging from A Kids' Brain Tumor Cure to Yerkes National Primate Research Center. The letter is available online at: http://bit.ly/1M3qusJ.

But critics say the bill is a cure for a problem that — aside from the need for more research funding — isn't really a problem.

"If there is a promising drug that shows great advance, the FDA already has a pathway for faster approval," Kesselheim says. "Approval of investigational drugs at an earlier stage of development raises the risk that many more patients will be exposed to unsafe and ineffective drugs."

Public Citizen's chief concerns are that the bill will lower the standards for ensuring drugs and devices are safe and effective and that the bill

would delay generic drugs from coming on the market, which, in turn, would increase healthcare costs, Carome says.

"Determining minimal risk is difficult and objective," he adds. "If you're testing experimental drugs on people — even if you could reasonably conclude it's no more than minimal risk — then you can't waive informed consent."

Another issue is post-approval monitoring.

A fast track for even new antibiotic drugs could lead to unintended consequences. For instance, there would be pressure to quickly approve antibiotics. If they are approved with less vigorous clinical trial data, then the new drugs could be ineffective and cause an increase in antibiotic resistance — the opposite of the intended effect, Kesselheim notes.

Also, the bill includes a provision that would allow drug companies to market their products for unapproved uses. "I don't see any public health justification for that," Kesselheim says. "The rules about off-label marketing are there to prevent the bad public health outcomes that have emerged from overused, unsafe drugs that were not approved for those uses."

The bill's language that would allow drug and device sponsors to use uncontrolled patient experience data is a dangerous precedent, he adds.

The Cures Act was passed quickly and probably has not been well vetted by individual members of Congress because some of its provisions are worrisome, notes **Diana Zuckerman**, PhD, president of the National Center for Health Research in Washington, DC.

"Our major concerns are that it drastically lowers approval standards for drugs and devices and it replaces scientific evidence from controlled clinical trials with, for example, case studies, clinical experience, and pre-clinical studies in Phase II trials, instead of using Phase III trials," Zuckerman explains.

"A member of Congress might not understand that when a bill says case studies can be used as evidence for FDA approval that this can mean one patient or two patients," she adds. "Someone put that language in the bill intentionally."

> "IF YOU'RE TESTING EXPERIMENTAL DRUGS ON PEOPLE — EVEN IF YOU COULD REASONABLY CONCLUDE IT'S NO MORE THAN MINIMAL RISK — THEN YOU CAN'T WAIVE INFORMED CONSENT."

Although the bill has the support of some patient advocacy groups and had wide bipartisan support in Congress, much of the support was related to the increased NIH funding, Carome says.

"We support the increased funding for research in NIH, but it creates a horse trade that comes at the price of bad provisions that weaken our standards for approving drugs and devices and undermines human subject protection," he adds.

Hopefully, the Senate will make some changes and perhaps correct some of the problems in the current bill proposal, Carome and Kesselheim say.

Zuckerman met a centenarian neighbor, Frances Kelsey, MD, whose experience at the FDA 55 years ago highlights the damage that can occur when drugs are approved too quickly and with limited human research data. *(Editor's note: Kelsey passed away just before press time on Aug. 8 at age 101.)*

As a new FDA drug reviewer in 1960, Kelsey was asked to review a drug sold under the name Kevadon, which had been used for years as a tranquilizer and painkiller and, more recently, was being used in Europe and Africa to help pregnant women with morning sickness.

"As the first woman scientific reviewer, they gave her this drug to approve as her first task because they thought it'd be easy to approve," Zuckerman says. "She saw the studies and thought they looked more like marketing research than scientific studies, so she began to look at the effects on offspring."

Kelsey insisted on more data and singlehandedly delayed approval of the drug for use in the United States. Soon, evidence mounted that the drug — generically known as thalidomide — crossed the placental barrier and caused birth defects. Babies, whose mothers took the drug, were born with undeveloped arms or legs, deformed hearts and eyes, and most died.

Thanks to Kelsey's thoroughness and ability to slow down the approval process, the drug never was used by pregnant women in the United States, Zuckerman adds.

"Everything we've learned over the decades and history of the FDA is of the country strengthening the law in response to medical disasters," Zuckerman says. "Now they are thinking of throwing all that out with this idea that clinical trials are so passé, we don't need to bother." ■

IRBs have improved polices regarding COIs, but some problems remain

New study highlights issue

Conflicts of interest (COI) issues in research institutions and IRBs have drawn more attention in recent years, resulting in better institutional policies and changes. A new study examined the nature and consequences of relationships between industry and IRB members in the years between 2005 and 2014, finding both good news and not-so-great news.

"Some things have improved, but there are a few things left to work on," says **Eric G. Campbell**, PhD, director of research at Mongan Institute for Health Policy, and professor of medicine at Harvard Medical School in Boston. Campbell was the lead author of the study about IRBs and COI.

On the positive side: "IRBs are doing a much better job of having their members disclose their relationships and making sure their members know they have to disclose those," Campbell says.

IRBs also are doing a better job of making sure members with COIs on specific protocols leave the room during discussions, and they've eliminated the problematic relationship of having members speak on the Speaker's Bureau, he adds.

One continuing problem discovered by the study was that there has been no significant improvement in members with COIs abstaining from voting at IRB meetings, Campbell says.

About one in four IRB members surveyed reported voting recently on a protocol in a way that violated federal guidelines, he adds.

The study advises that additional attention should be focused on deterring IRB members from inappropriately voting on or presenting protocols in a biased manner.[1]

When preparing to do the survey of IRB members, researchers made certain that the IRB that reviewed the COI study was not included in the study to avoid that conflict of interest, Campbell notes.

"We felt it would be unethical for them to oversee the study and also be subjects," he adds.

Another troubling finding from the research was that nearly one-third of IRB members surveyed said they didn't know if their IRB had a conflict of interest policy, Campbell says.

"All members should know if there is a policy, and all IRBs should have a policy," he says.

"The context of this is there is a debate in academia right now as to whether institutions have gone overboard in regulating conflicts of interest in a way that harms medical innovation and research," Campbell says. "This is being played out in the *New England Journal of Medicine* and *British Medical Journal*."

IRBs are a special case when it comes to COI because they're the primary and sole mechanism by which organizations and the government oversee the integrity of the research process, Campbell says.

"We have to make sure those industry relationships are disclosed to the IRB," he adds. "This appears to be happening more frequently, and it also appears that people with conflicts are taking appropriate actions."

Problems with voting when it's not appropriate need more attention, however, he says.

"It's not a 'one person, one time' kind of problem," Campbell says. "It also shows that it might be due to things as simple as people not knowing what the rules were or people with a conflict not voting even when the board needs a quorum."

Another educational issue relates to the definition of conflict of interest. Universities and research organizations generally believe that any financial relationship with a parent company constitutes a conflict of interest, he explains.

"Say, for example, somebody had a financial relationship with the cardiac division of Company X, and a protocol came from OB-GYN division of Company X, the question is whether that should be a conflict of interest they recuse themselves for," Campbell says. "Generally, when universities think about [the financial relationship being with the one company], they believe that regardless of whether it's with the cardiac division or the OB-GYN division, you still have to disclose this as a conflict of interest."

Going forward, the big question is whether IRBs are willing to further improve their handling of COIs, or whether it's time for the government or a third party to step in and assist them with overseeing studies and subjects, Campbell says.

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Building a QI/QA program from basement on up

Education, prevention are focus

Sometimes best practices emerge from an experienced and dedicated leader taking over a struggling program and turning it into an efficient, well-organized enterprise.

At least that's what happened when **Enid A. Virago**, PhD, CIP, CCRP, became the QI/QA program administrator in the office of research and innovation at Virginia Commonwealth University (VCU) in Richmond.

When Virago started the job, the quality improvement (QI) office was building so slowly that only three site visits had been conducted. QI was delegated to human protection professionals who could shuffle around some part-time hours.

By contrast, now the office has an experienced full time administrator/monitor, who aims to conduct 24 visits a year and has the goal of building more rapport and trust between principal investigators (PIs) and the office of research subject protections.

"When I started, there wasn't really much in the way of developed policy, and there was no standardized process," Virago says. "It probably took me two years to feel like I was educated enough to find good examples of programs I could modify and change in such a way that it would work in our system."

Virago started her self-learning process by asking other QI directors for advice and then shadowing a QI peer, Josy Lyons, DEd, MEd, assistant director of quality management at Penn State University in University Park.

What she learned was that a QI program run by one person would have some limitations, but could accomplish a great deal with the right processes and efficiency measures in place.

"You're only going to be able to do so many QI visits," Virago notes. "We have 700-800 PIs and multiple studies."

Once she made it her goal to have the office become a resource that would help PIs improve their human research protection and avoid problems, she found that she could make a huge difference: "I have people calling me and saying, 'I'm writing something and need to know more about the consent process,'" Virago says. "It's important to create that good will so PIs will come to you."

Virago builds rapport with investigators: "I try to explain by saying that when you send something in to the full IRB board, you have 15 great minds looking it over and trying to help you make it a little bit better," she explains.

Since revamping the QI program, which is called the Post Approval Monitoring and Quality Improvement Program (PAMQuIP), Virago has received feedback that principal investigators now are more confident with their IRB submissions and human subject protection.

"There is one investigator who has come back to me several times for advice about his studies," she notes. "He'll contact me and say, 'I'm about to put this in the informed consent, and I'm worried about this one thing, and I can't remember what you've said about it, so will you look this over?'" she says.

The program's goal of prevention and education works well enough that investigators and study coordinators increasingly are requesting the visits to help them with protocol issues of concern, Virago adds.

The following are best practices Virago employed to develop PAMQuIP:

• Research QI programs. For nearly a year, Virago spoke with QI experts and took a post-approval workshop from Public Responsibility in Medicine & Research (PRIM&R). The research program's executive director at VCU also attended the workshop.

Virago's research included looking at QI program and post-approval monitoring program tools. She gained permission to use various institutions' tools, and borrowed and adapted some items.

"The post-approval monitoring community is so fantastic about sharing ideas, templates, and things like that," Virago says. "There's a real camaraderie within this hidden group."

Another resource was VCU's data security chief, who met with Virago and assisted with issues related to keeping data HIPAA compliant and secure, she adds.

• Develop policies, letters and tools. PAMQuIP's policy describes the primary objectives as the following:

- conduct post approval monitoring and quality improvement study visits,
- perform quality assurance reviews of the IRB process and documentation,
- serve as liaison between investigators and IRB panels,
- provide educational resources for

the human research community, and

- research, develop, and evaluate quality improvement initiatives to foster efficiencies in human subject protections.

Virago developed a letter template for notifying investigators of a post-approval monitoring visit, and she pulled together resources for investigators on data destruction and data storage policies.

PAMQuIP has a four-page service request form that identifies the level of concern, the study's risk level, the nature of the risk, and whether the request is for a quality assurance or quality improvement, as well as other items, she says.

Virago also amended the institution's self-evaluation tool for principal investigators and made completing it a requirement, as it was rarely used previously.

The self-evaluation tool provides important QI data about PIs' educational deficits, she says.

• Provide PIs with a policy table. Searching through online tools created by other research institutions, Virago developed a tool kit that includes risk assessment and documentation information. She also pulled together many other research policies, including policies on data destruction and closing a study. Each policy incorporates all institutional rules, as well as federal and state regulations.

Virago created a policy table to make it easier for PIs to find a particular data security, maintenance and destruction policy — especially those that they didn't know existed.

In general, policies are available on the department's website.

• Categorize QI site visits. "One of the first things that happens is when I say, 'I'd like to schedule a visit with you,' is that people get panicky and say, 'Why are you picking me for a visit?'" Virago says. "I go ahead and respond to them that this is an educational visit or this is a focused visit, etc."

Categorizing site visits also makes it simpler for Virago to collect metrics with visit information. She easily can see which visits had educational issues, which had general problems, and other themes might emerge.

In all, there are six categories of visits. They are as follows:

- For cause: These are visits requested by the IRB, office of research subject protection staff, institutional officials, and department chairs. They generally are in response to a concern about study conduct, compliance, or the research participant's rights and welfare. IRB administrators sometimes will contact Virago to say, "The IRB had a really long discussion about this particular study, so you may want to put this one on your list," she says.

THE PROGRAM'S GOAL OF PREVENTION AND EDUCATION WORKS WELL ENOUGH THAT INVESTIGATORS AND STUDY COORDINATORS INCREASINGLY ARE REQUESTING THE VISITS TO HELP THEM WITH PROTOCOL ISSUES OF CONCERN.

- Routine: Routine visits are not initiated by any cause or concern. Studies are selected based on criteria, which include risk level, enrollment of vulnerable populations, use of investigational new drugs or devices, and involvement of complex procedures. They also include random selection from active studies.

- Focused: These are narrow reviews of research activities and concentrate on a particular aspect of study conduct, such as informed consent, recruitment, or treatment outcomes. This type of review, which is rarely done, may not be prompted by a specific issue or concern, and it's similar to the routine review.

- Preventive/educational or consult reports: PIs, study staff, IRBs, and others can request visits to address an educational need related to study conduct. These reports often are requested when there are new study staff and PIs.

- Targeted: Such reviews take a look at a particular category of research, including studies reviewed by an external IRB, expedited research, or IRB review of studies involving a vulnerable population.

- Preparatory review: PIs or research staff request this visit when they need assistance with preparation for an audit or before the start of recruitment for a new study.

• Educate and analyze. Virago meets with the executive director of the research subject protections office in biweekly meetings.

"The information shared there is helpful because I can tell people when policies are changing," Virago says. "And our department has just hired an education person, so I hope deficits found through visits will be incorporated into educational sessions."

Virago reviews PAMQuIP data each year to identify possible trends, educational needs, and problem areas. She also writes a year-end report that is reviewed by the department and available to the IRB. ■

Can IC be improved in Phase I cancer trials?

Pediatric oncology research issues reviewed

An interesting thing happened when researchers asked parents of children involved in Phase I oncology studies about their experiences with informed consent: Parents had a lot to say.

"Parents wanted to talk about communication with professionals about research," says **Liza-Marie Johnson**, MD, MPH, MSB, chair and bioethics consultant of the hospital ethics committee, clinical researcher, and a lead hospitalist at St. Jude Children's Research Hospital in Memphis, TN. Johnson was the lead author of a study about informed consent, communication, and parents of children enrolled in Phase I oncology trials.

Their suggestions and comments resulted in researchers designing a Phase I communication model, focusing on educating families about Phase I trials at specific time points during a child's illness. They also worked on a Phase I fact sheet to distribute to families.[1]

The one-page fact sheet, titled, "Phase I Clinical Oncology Trial: A Brief Overview," uses color borders to separate its various sections, which include the following:

• Purpose of Phase I Trials

• Some definitions, including:

- Maximum tolerated dose (MTD): "The highest dose of a drug that can be given safely without severe side effects."

- Dose limiting toxicity (DLT): "Serious side effects caused by a dose of the Phase I drug."

- Cohort

- Dose escalation

- Dose finding

- Palliative care

• Available Support Services and Contact

• Additional Contact Information.[1]

The fact sheet quickly became popular, and researchers received emails from doctors requesting it, Johnson notes. "One doctor wrote, 'When can I start using this sheet? I have these families crying in my clinic because they didn't realize the trial they're trying is not expected to cure their child.'"

The problem was that informed consent forms were 30-plus pages long and had too much required language, some physicians told researchers. Others suggested that because each family is so different there should be different levels of information, including downloadable information that people could use on their iPads. Still others asked for visual as well as written materials and better verbal communication with families.[1]

Parents talked about how much information they had read, what they were learning to deal with their children's illness, and about their experience with being involved in a Phase I trial: "We know darn well the trial is to figure out the doses and what the best way to… we all know that, but that's not in our heart what we're on it for," one parent said.[1]

"I think that hope is very powerful," Johnson says. "We want to accurately portray the risks and benefits, but we don't want to crush everyone's hope."

In an earlier study, researchers asked parents to identify the likelihood that their child would benefit from a Phase I study, and a lot of parents refused to answer the question, Johnson recalls. "We think they understood the likelihood of benefit was low, and they didn't want to put a number on it."

The study includes a chart of the trajectory for children with cancer. It begins with diagnosis. The next step is standard treatment or a diagnosis of incurable disease or poor prognosis. If standard treatment results in a relapsed or refractory disease and with the diagnosis of incurable disease, the next steps are one of these three: salvage chemotherapy, no cancer therapy, or Phase I trial.[1]

"Families have to choose between a Phase I trial where the purpose is not cure, although, certainly, some drugs go from Phase I to Phase III, so there can be drugs that have a really profound benefit," Johnson explains. "But for the most part the purpose is safety and efficacy: They may have reduced disease burden, a reduction in symptoms, and it may extend the length of their lives."

Parents choose to have their child participate in a Phase I trial to show they're not giving up on their child and out of a desire to help other families, Johnson says.

The option of no more cancer-directed therapy means the family likely will go home or the child will receive some oral chemotherapies with few side effects that can slow down the disease progression, but there will be no cure of the disease, she adds.

"Salvage chemotherapy, which is the second-line agents, might have some effect, but based on previous studies, it's unlikely to work," Johnson says.

Informed consent in a Phase I trial needs to begin with basic scientific concepts and the purpose of a Phase I trial, Johnson suggests.

"The definition the parents came up with was that Phase I trials were to identify and develop new drugs to treat childhood cancer," she says.

The definition also notes, "In a Phase I trial, researchers are trying to evaluate safety. This includes determining a safe dose range (MTD) and identifying side effects. It is unlikely that the treatment in a Phase I study will cure your child. Possible benefits could include symptom reduction and the opportunity to help others in the future. The Phase I trial is voluntary and you can decide not to participate. You can talk to your doctors to stop being in the study at any time."[1]

After starting to work on the basic definitions that would be used for the fact sheet, the research team discussed it and wrote a rough draft with some input from the organization's art department, Johnson says.

The fact sheet was pilot tested, presented to the IRB, and the feedback has been universally positive, she adds.

Since it was published in the journal *Cancer*, it is available for other institutions to use, as well, she says.

"This is something an oncologist can use when talking with a family about a Phase I study: 'We have this study your child may be eligible for. I'm going to give you this sheet that tells you what a Phase I study is. Read it over, and when you come to clinic, we can talk about whether or not you want her to be in a Phase 1 study,'" Johnson says.

"About 65% of children diagnosed with cancer in the U.S. will enroll in a clinical trial," she adds. "Not all families will need a Phase I study, but if there's a family whose child is eligible for Phase I, then the oncologist can give the fact sheet to them before talking about the specifics of the trial."

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Training research participants to become research assistants

CBPR improves access to vulnerable population

One emerging trend in social-behavioral research studies involves the use of peer researchers to better engage a particular community or vulnerable population.

A chief concern of IRBs reviewing such community-based participatory research (CBPR) proposals involves the training of peer researchers and ensuring they fully understand the rights of participants, notes **Douglas Bruce**, PhD, MSW, assistant professor in the department of health sciences at DePaul University in Chicago.

Bruce has been involved in a study that looks at sexual minority male youth experiencing homelessness and their resilience despite multiple lifetime traumas.

Some of the youth involved in research studies spoke eloquently about being tired of being asked about their risk behaviors, Bruce notes.

"There always was an emphasis on risk and the 'bad' things they do and not having people ask them about how they keep themselves safe or strong," he adds. "We were very interested in learning how they stayed safe under difficult circumstances, so in keeping with CBPR principles, I thought it was very important for youth themselves to be part of the research team."

When youths are trained to be part of the research team for studies involving youth, there's a potential advantage in having insiders discussing issues to which members of the outside world, such as academic researchers, may not have immediate access, Bruce explains.

Alternatively, it also happens that people will be less open with their peers than outsiders out of concerns around confidentiality, so research training is needed to ensure the best possible experience for research participants, as well as for the community or peer researchers, he adds.

Peer researchers need human research protection training that includes specific examples and instructions for handling issues like confidentiality because they often are part of a small population in which stories can be told, Bruce notes.

"I have trained undergraduate and graduate research assistants in these kinds of issues, but now there are community members who are included in the research design and

implementation," Bruce says.

The youth community members often had limited education and had previously been research participants, he adds.

Bruce established human research protection program educational sessions that would work for these community members of the research team. The chief aim was to train inexperienced community research assistants in research ethics and to assess whether they were ready to be in the field, he says.

"Secondly, I'd introduce them to qualitative methods, and I'd assess them later," Bruce says. "That was day one and day two."

Here's how it worked:

• **Engage community members, relying on their research experience.** "We started the education with a discussion of their previous experience with research," Bruce says.

The education session included explanations for why the particular research was being conducted and how it was taking into account the resilience young people have demonstrated, he says.

"They are marginalized youth who have been studied quite a bit," Bruce explains.

"There were many HIV risk studies they were part of, and needs assessment studies," he adds. "They were reasonably savvy in terms of how research happens, but didn't know how it was used or how we try to protect the rights of subjects, although they had all been through the informed consent process."

The goal now was to break down the process for them and help them understand it in terms of the types of questions they would be asking peers and how this process related back to the ethical principles, Bruce says.

"Then, I presented a more didactic discussion of research ethics in general and opportunities to apply it to previous participation, as well as thinking about being potential interviewers," he adds. "That discussion formed the basis of what they would be tested on as an indication of their ability to conduct research in a safe and appropriate way with their peers."

The educational session also focuses on the meaning of vulnerability in research and the Belmont principles.

"Then we talked about qualitative methods and qualitative interviewing techniques," Bruce says.

• **Address literacy and contextual issues.** Literacy is a big issue with some vulnerable populations, including the group of homeless youths, he notes.

For instance, the research term "beneficence" is an abstract word that the youths didn't use or understand. But they did understand the word "benefit," Bruce says.

So the training sessions have to include explanations and definitions that lead into life experiences that could serve as a frame of reference for the community members of a research team. "We talked about their own experience as research participants, being interviewed by researchers, and giving data but not being sure how it was going to be used or how it was relevant to their situation," Bruce says.

"If we're doing this type of research, it needs to be aimed at improving the lives of the youth we're studying," he adds.

• **Explain what "vulnerable population" means.** Training needs to address why the research community considers certain populations to be vulnerable, listing the groups of pregnant women, prisoners, children, sex workers, people with limited education, the poor, people with difficult access to health services, and those with mental illness.

"Those characteristics stretch across the youth population: They're children; many have been in the criminal justice system; all are poor; many are sex workers, and some are pregnant," Bruce says. "So I said, 'You and your peers are by definition vulnerable participants, right?'"

Some of the youth being trained discussed, among their peers, use of illegal substances, sex work, and involvement in the criminal justice system, and how those behaviors place people at risk, he recalls.

"One youth talked about his hesitancy to talk about those kinds of issues in a research project that he previously participated in, and we talked about how we need to assure confidentiality and de-identify data," Bruce adds. "We talked about how the interviews are recorded, transcribed, who validates transcriptions, and how we keep participants safely de-identified."

• **Cover three main principles.** The first day of training covers the three basic principles from the Belmont Report:

- Respect for persons: The educational session went over why it is so important to have respect for research participants and to treat them with dignity. It also showed how people involved in human subjects research can assess autonomy and discussed how people have the ability to make their own decisions and choices.

- Beneficence: This philosophy of "Do no harm" applies to research in the risks and benefits area. Community researches are taught that a study should provide a maximum amount of benefit to society and sometimes to individual participants while it also reduces risks to research subjects. The educational session discussed potential risks of asking

people something of a personal nature about their lives, recording interviews, and the potential for violations of confidentiality.

- Justice: This principle refers to ensuring reasonable and non-exploitive procedures that are administered fairly.

"I went through the three principles, followed by risks and benefits, and then I introduced them to methods of interviews and what content the interview would be like," Bruce says. "They had input in that."

• Provide examples of confidentiality issues. To explain what confidentiality means and how it might be different from privacy, Bruce used examples that would resonate with their own experiences.

Here's one example: "Michael and Jason have a relationship, and both are participants. Michael asks you what the other one talks about in an interview. What do you do?" Bruce says.

The peer researchers discussed how the youths' participation wasn't anonymous because they knew about each other's involvement in the study. So they discussed how the peer researcher could maintain each participant's confidentiality, which means the researcher does not disclose any parts of the interview, and how the study's reports would not include participants' personal information.

If their participation was anonymous and one participant asked if the other had completed an interview, the peer researcher should not disclose information about who participated and who didn't.

• Go over informed consent. "We spent 20 minutes on informed consent as a process and really emphasized it as a communication process between a researcher and participant, and it starts before research begins," Bruce says.

"A lot of the youth felt informed consent was perfunctory, a form you filled out in order to get something," he adds. "Others had questions about its purpose and were questioning some of the language and what certain parts of informed consent meant."

They were told that the process of informed consent continues through the duration of the study.

Bruce encouraged the questions and pointed out that it was very important that the language be communicated in a way that the participant understands and that the peer researchers understand the information enough to paraphrase. He also taught them the teach-back method and emphasized that signed informed consent was waived for this population to maintain their privacy.

• Assessing competence. The last part of the two-day educational session included review of research ethics content and a 20-item quiz.

"After they completed and passed the quiz, we brought the draft interview instrument, and they took time to review it," Bruce says. "We looked at whether this approach would get at the areas of interest the study was trying to investigate, the wording of questions, reading level, and relevance to their lives."

This was a way to have the peer researchers apply some of what they learned and to encourage their excitement about being a part of the investigative team.

"I then did mock interviews the following week, where I was the person being interviewed," Bruce says. "I was assessing their ability to stick to the semi-structured interview script and to deal with surprising situations by throwing curve balls at them during the mock interview."

Bruce also observed their first interviews with peers, as well as debriefings with the interviewees post-interview to check in and see whether they felt their confidentiality was assured through the informed consent process and interview, he adds. ■

Coping with unexpected risks in SBER studies

How to handle issues that arise

Social, behavioral, and educational research (SBER) studies can sometimes reveal risks that are unanticipated and unimagined.

Handling informed consent for these studies requires an IRB and research team to be flexible and able to adjust quickly as issues arise.

"Ninety percent of our research is behavioral," says **Cynthia Monahan**, MBA, CIP, director of Charles River Campus IRB at Boston University in Boston.

"With biomedical research, you identify the risk and make sure it's appropriately told to subjects," she says. "With behavioral research it's not that easy. Sometimes there's a behavioral intervention or some other type of interview where someone could become upset, so how do you quantify that?"

When reviewing SBER studies, IRBs need to know appropriate ways to handle these reviews and how to look for issues related to particular populations being studied, she notes.

For instance, if researchers are going to conduct a study involving a questionnaire that asks participants about past traumas, alcohol use, illicit drug use, or similar past behaviors and experiences, they should state up front about these questions in the consent, Monahan says.

"We require it to be right up front in the second section of what will happen in the study," Monahan says. "We let people know up front that we'll ask these types of questions so the subject can say, 'It will be too upsetting, so I won't be in your study.'"

When researchers are interviewing a vulnerable population — which often happens with SBER studies — they should inventory the resources they have in place to help participants when they're upset, she suggests.

"We want to see that a licensed clinician is available to help them," Monahan says. "This is easier if the survey is taking place face-to-face."

For behavioral surveys and questionnaires online, there can be two impediments to handling problems as they arise:

• First, there could be a lengthy time frame between when the survey is accessed and when the study team is made aware of a problem. The solution to this issue is to make certain survey answers are reviewed fairly promptly so if a participant gave an answer about being upset over a question, the researcher will be able to follow up on that quickly, Monahan says.

• Secondly, surveys conducted online as not greater than minimal risk studies might be entirely anonymous, so investigators are unable to follow up on a participant's written comments or responses about trauma unless the participant also took the step to call the IRB or research team.

Monahan knows of an example of that scenario playing out with a SBER study. "We had one study we reviewed that we thought was not greater than minimal risk, and we thought there was appropriate information about the study in the consent form," she says.

Participants could answer the survey in a lab or online.

"One subject who did it online became so upset that the person contacted the investigator and contacted me," Monahan says. "The person explained how the questions and photos were extremely upsetting."

Immediately, the investigator put the study on hold, and the IRB took a second look at the study. The IRB also asked university faculty with experience in psychology to look at it, and they had the IRB re-review the consent form, she adds.

"We determined that the necessary information was in the consent form," Monahan says. "One thing we always question is whether people read the informed consent."

It appeared possible that the distraught participant had skipped over the informed consent language about the nature of the photographs that would be viewed. So the IRB and researcher decided that it would be wise to add a separate page to the survey that would remind people that some questions in it might be upsetting to them, she explains.

"After signing the informed consent, another page comes up," Monahan says. "We had information in the risk section, so we put that same information back up."

In this example, the IRB had waived documentation of consent because the study wasn't greater than minimal risk, although there still was a consent document for people to read. The study involved asking people about how advertisements have changed over the decades, and so it involved viewing some ad photos and copy.

"The consent form had all of the required elements, and then people would click on a button that says, 'I agree to participate,'" she adds. ■

COMING IN FUTURE MONTHS

- Dealing with common noncompliance issues
- Building an IRB library
- How best to train new IRB administrators
- Ethics of using EHRs for study recruitment

IRB ADVISOR

CNE/CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to AHCMedia.com, then select "MyAHC" to take a post-test.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CNE/CME QUESTIONS

1. The 21st Century Cures Act would make what type of change to current regulations about informed consent in studies involving human subjects?

A. It would require fully signed and documented informed consent for every tissue sample that is donated to science
B. It would require two parents to sign an informed consent document whenever a child is enrolled
C. It would expand informed consent waivers for device and drug studies that pose no more than minimal risk to research subjects
D. All of the above

2. A study that compared IRBs' handling of conflicts of interest over a 10-year period found which of the following?

A. IRBs have improved in the area of having their members disclose their COI relationships
B. IRBs also have improved in making members with COIs leave the room during discussions
C. IRB members with COIs continue to vote at IRB meetings when they should instead recuse themselves
D. All of the above

3. Which of the following would not be a good primary objective for a new quality improvement program, according to Enid Virago?

A. Have IRB members serve one week a year in the QI office as reviewers
B. Conduct post-approval monitoring and quality improvement study visits
C. Provide educational resources for the human research community
D. Research, develop, and evaluate quality improvement initiatives to foster efficiencies in human subject protection

4. According to Cynthia Monahan, which of the following is a potential solution for handling a situation in SBER research of a lengthy time frame between when a survey is accessed and when the study team is made aware of a problem?

A. Make the survey sufficiently benign to prevent all potential problems
B. Have the IRB staff review all survey answers within a week of completion
C. Make sure survey questions are reviewed promptly so if a participant is upset over a question, the researcher will be able to follow up on it quickly
D. None of the above

IRB Advisor

Confidential Salary Survey

This confidential salary survey is being conducted to gather information for a special report. Watch in coming months for your issue detailing the results of this survey and the overall state of employment in your field.

Instructions: Select your answers by filling in the appropriate bubbles **completely.** Please answer each question as accurately as possible. If you are unsure of how to answer any question, use your best judgment. Your responses will be strictly confidential. Do not put your name or any other identifying information on this survey form.

1. What is your current title?

_____

_____

_____

2. What certifications do you hold?

_____

_____

_____

3. What is your highest degree?

- O A. associate or 2-year
- O B. diploma (3-year)
- O C. bachelor's degree
- O D. some graduate work
- O E. graduate degree
- O F. other _____

4. How many people work in your department (IRB administrative side)?

- O A. 1
- O B. 2
- O C. 3
- O D. 4
- O E. 5
- O F. 6 or more

5. What is your sex?

- O A. male
- O B. female

6. What is your age?

- O A. 20-25
- O B. 26-30
- O C. 31-35
- O D. 36-40
- O E. 41-45
- O F. 46-50
- O G. 51-55
- O H. 56-60
- O I. 61-65
- O J. 66+

7.'What is your annual gross income from your" primary healthcare position?

- O A. Less than $30,000
- O B. $30,000 to $39,999
- O C. $40,000 to $49,999
- O D. $50,000 to $59,999
- O E. $60,000 to $69,999
- O F. $70,000 to $79,999
- O G. $80,000 to $89,999
- O H. $90,000 to $99,999
- O I. $100,000 to $129,999
- O J. $130,000 or more

8. Where is your facility located?

- O A. urban area
- O B. suburban area
- O C. medium-sized city
- O D. rural area

9. In the last year, how has your salary changed?

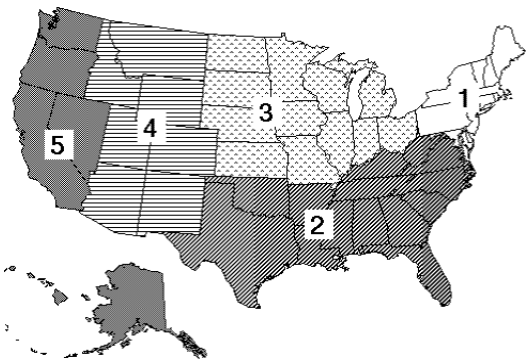
- O A. salary decreased
- O B. no change
- O C. 1% to 3% increase
- O D. 4% to 6% increase
- O E. 7% to 10% increase
- O F. 11% to 15% increase
- O G. 16% to 20% increase
- O H. 21% increase or more

10. What is the work environment of your employer?

- O A. academic
- O B. agency
- O C. health department
- O D. clinic
- O E. college health service
- O F. consulting
- O G. hospital
- O H. private practice

11. Please indicate where your employer is

- O A. region 1
- O B. region 2
- O C. region 3
- O D. region 4
- O E. region 5
- O F. Canada
- O G. other



12. Please indicate how many of each type of protocol you have reviewed in the last year.

A. Full review _____

B. Expedited _____

C. Continuing review _____

13. How long have you worked in your present field?

- O A. less than 1 year
- O B. 1-3 years
- O C. 4-6 years
- O D. 7-9 years
- O E. 10-12 years
- O F. 13-15 years
- O G. 16-18 years
- O H. 19-21 years
- O I. 22-24 years
- O J. 25+ years

14. How has your workload changed in the last year?

- O A. increased
- O B. decreased
- O C. remained the same

15. How many people do you supervise?

- O A. 0-3
- O B. 4-6
- O C. 7-10
- O D. 11-15
- O E. 16-20
- O F. 21-40
- O G. 41-60
- O H. 61-80
- O I. 81-100

16. How many hours a week do you work?

- O A. less than 20
- O B. 20-30
- O C. 31-40
- O D. 41-45
- O E. 46-50
- O F. 51-55
- O G. 56-60
- O H. 61-65
- O I. 65+

17. If you work in a hospital, what is its size?

- O A. <100 beds
- O B. 100 to 200 beds
- O C. 201 to 300 beds
- O D. 301 to 400 beds
- O E. 401 to 500 beds
- O F. 501 to 600 beds
- O G. 601 to 800 beds
- O H. 801 to 1,000 beds
- O I. >1,000 beds
- O J. I don't work in a hospital

18. In the last year, has your department lost or gained staff?

O A. lost O B. gained O C. no change

19. What is your biggest personnel issue?

_____

_____

Deadline for Responses: Nov. 2, 2015

Thank you very much for your time. The results of the survey will be reported in an upcoming issue of the newsletter, along with an analysis of the economic state of your field. Please return this form in the enclosed, postage-paid envelope as soon as possible. If the envelope is not available, mail the form to: Salary Survey, AHC Media LLC, P.O. Box 550669, Atlanta, GA 30355.