IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

FEBRUARY 2017 Vol. 17, No. 2; p. 13-24

INSIDE

The 21st Century Cures Act Easily Passed, But is it Good for Research Protection?

IRBs will feel its effects

By Melinda Young, Contributing Editor

A multibillion-dollar research funding bill, like the 21st Century Cures Act, that receives bipartisan Congressional support has been a very rare occurrence these past eight years. Only a handful of U.S. senators voted against the Cures Act. Plus, it was signed on Dec. 13, 2016, by President Barack Obama, who had paid particular attention to promoting and funding research. Those facts might suggest that the 21st Century Cures Act is both popular and a good thing for patients and research participants.

But the bill's broad popularity and its $4.8 billion in spending for new research at the National Institutes of Health (NIH) might not offset some of the bill's problems tied to research protection, some critics say.

> THE BILL'S BROAD POPULARITY AND ITS $4.8 BILLION IN SPENDING FOR NEW RESEARCH AT THE NIH MIGHT NOT OFFSET SOME OF THE BILL'S PROBLEMS TIED TO RESEARCH PROTECTION, SOME CRITICS SAY.

"We thought this final bill provided an early Christmas present to the pharmaceutical and medical device industries because it contains a number of giveaways to those industries that further weaken the review and approval of drugs and medical devices," says **Michael A. Carome**, MD, director of the health research group of Public Citizen in Washington, DC.

"For that reason, we had urged it to be turned down," he adds. "I think many

Financial Disclosure: Contributing Editor **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Ebook Design Specialist **Dana Spector**, Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics, and Nurse Planner **Kay Ball**, RN, PhD, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

IRB ADVISOR

IRB Advisor,
ISSN 1535-2064, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.
GST Registration Number: R128870672.

POSTMASTER: Send address changes to:
IRB Advisor
P.O. Box 550669
Atlanta, GA 30355.

SUBSCRIBER INFORMATION:
Customer Service: (800) 688-2421.
Customer.Service@AHCMedia.com.
AHCMedia.com
Hours of operation: 8:30 a.m.- 6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday, EST.

SUBSCRIPTION PRICES:
Subscription rates: U.S.A., Print: 1 year (12 issues) with free AMA Category 1 CreditsTM or Nursing Contact Hours, $419. Add $19.99 for shipping & handling. Online only, single user: 1 year with free AMA Category 1 CreditsTM or Nursing Contact Hours, $369. Outside U.S., add $30 per year, total prepaid in U.S. funds.

MULTIPLE COPIES: Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

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

AHC Media, LLC designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias Learning, LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity has been approved for 1.5 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider #CEP13791, for 1.5 Contact Hours.

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

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

CONTRIBUTING EDITOR: Melinda Young
EDITOR: Jill Drachenberg, (404) 262-5508 (jdrachenberg@reliaslearning.com)
EBOOK DESIGN SPECIALIST: Dana Spector
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger

EDITORIAL QUESTIONS
Questions or comments?
Call **Jill Drachenberg**,
(404) 262-5508.

members of Congress were persuaded to ignore the harmful provisions in exchange for additional funding provided to NIH for research on cancer, brain disorders, precision medicine, and additional funding for the treatment of opioid addiction."

While funding for those purposes is a good thing, the trade-off was bad for patients, Carome says.

"The $4.8 billion in additional funding is not that huge of an amount because its funding is spread over 10 fiscal years," he explains. "And there's no guarantee that the money will be appropriated in future years because each year Congress has to vote to appropriate that money, and it's possible that Congress won't appropriate it in a year or two or four years."

"In general, the 21st Century Cures Act supports simplification of IRB and informed consent processes over protection of research subjects, which raises a number of concerns," says **Michael S. Sinha**, MD, JD, MPH, a postdoctoral fellow in the Program on Regulation, Therapeutics, and Law (PORTAL) at Brigham & Women's Hospital and Harvard Medical School in Boston. Sinha served four years on a rural academic medical center's IRB and writes about informed consent in clinical and research settings.

Chief among Sinha's concerns are provisions limiting the scope of local IRBs. The Cures Act encourages the shifting of research protection away from local IRB review toward national or central IRB review in Section 3023, titled "Avoiding Regulatory Duplication and Unnecessary Delays."

"By limiting the ability of local IRBs to participate, this could result in forum-shopping by clinical sponsors," Sinha explains.

"The 21st Century Cures Act's move toward lead institutional review boards limits the ability of local IRBs to have some authority and autonomy over trials within their jurisdiction," he adds.

Local IRB review, with members from varied backgrounds, can better identify challenges that make local participation less likely, Sinha says.

At his IRB, rural research participants often faced geographic challenges to participation, including commutes of an hour or more to a research site, making routine monitoring logistically challenging.

In recent years, the U.S. Department of Health and Human Services (HHS) proposed changes that also would shift human subject research review more toward central IRBs in its 2011 Advance Notice of Proposed Rulemaking (ANPRM), its 2015 Notice of Proposed Rulemaking (NPRM), and the 2016 Final NIH Policy on the Use of a Single Institutional Review Board for Multisite Research. The new NIH policy, which has a goal of enhancing and streamlining the IRB review process in the context of multisite research, will take effect on May 25, 2017.

Having a local IRB review with board members from varied backgrounds provides a more rounded view and is more likely to identify local concerns, Sinha says.

For example, an IRB connected to a rural community would be more likely to note that rural research subjects would have difficulty making it to twice-weekly monitoring at an urban research site, he explains.

The Cures Act directly encourages the use of a central IRB and is in line with the NIH policy and with NPRM, says **David Forster**, JD, MA, CIP, chief compliance officer with WIRB-Copernicus Group in Princeton, NJ.

"What's nice is they say to avoid duplication and unnecessary delays, there should be an emphasis on shared

review and similar arrangements," Forster says. "It's not a mandate to use a central IRB, but, rather, an encouragement."

Earlier versions of the Cures Act had language that would have had local IRBs provide information about local attitudes and subjects, but that part was removed in the final bill, Forster notes.

"I think if the congressional act had included language about continuing to use local IRBs for local purpose, it would have taken away from the purpose of NPRM and others," Forster says.

This omission is one of the parts of the act that troubles Sinha.

"The local IRB I served on had a very good sense of our own patient population and our own patient needs," Sinha says. "That knowledge of a unique population is lost if you have a centralized IRB making determinations on your behalf."

Also, the Cures Act eliminates reporting to local IRBs in some situations. "They may not hear about local adverse events and problems in a timely fashion, which would make it very difficult for local IRBs to serve the protective function they've been designed to serve," Sinha says.

Another area of concern involves the Cures Act's section 3024 on waiving informed consent, Carome and Sinha say.

"This is a situation that has no clear legal precedent or justification," Sinha says. "We've seen legal exemptions for life-threatening situations or when informed consent is not feasible, but now we're talking about informed consent in a setting where there is no more than minimal risk, yet patients are consentable."

One problem with this provision is that minimal risk is not well-defined, and it's not clear who gets to define it, Sinha adds.

"If the pharmaceutical or medical device company is defining risk, they may be more likely to underestimate risk to avoid going through the process of informed consent," Sinha says.

The Secretary's Advisory Committee on Human Research Protections (SACHRP) recommended this waiver of consent, Forster says.

"Its most common use will be for research records review," Forster explains. "The problem with the current FDA framework is that you can only waive consent in an emergency setting, but what is disallowed under the current FDA framework is the waiving of consent for records review."

THE CURES ACT, MIRRORING RECENT NIH POLICY, EMPHASIZES THE POINT THAT RESEARCH INSTITUTIONS SHOULD USE CENTRAL IRBS AS MUCH AS POSSIBLE.

While any system can be abused, Forster says he sees this waiver provision as a way to enhance public health by allowing the FDA to obtain more data from sponsors.

"Right now, if a sponsor, for instance, says, 'We have 20 years of experience in using this implanted hip device and we want to go back and look at all of the records and submit these to the FDA to change our labeling,' the current FDA rules say you have to get consent from every one of these people or we cannot allow the data," Forster explains.

The Cures Act's waiver provision will allow sponsors to obtain the data without informed consent.

"I see that as a huge advantage, especially with the increasing availability of big data," Forster says.

Informed consent should remain a bulwark of human research protection, Carome says.

"We think most of FDA research involving drugs and medical devices should still be getting informed consent — even with minimal risk," Carome says. "I think IRBs, generally, wouldn't grant a waiver for a minimal risk clinical trial, and nor should they."

A privacy protections provision of the Cures Act also is new, Carome says.

"There's a provision regarding privacy protections for human research subjects, and this requests the secretary of HHS to issue a certificate of confidentiality," Carome explains. "The certificate of confidentiality has existed for years, and they were voluntary."

Researchers involved in studies with sensitive topics, such as drug abuse, where a breach of privacy could damage the research participant's reputation or lead to criminal prosecution, could request the certificate of confidentiality to protect data even in the event of a legal proceeding, Carome explains.

"Sometimes an IRB that is reviewing research would say to investigators, 'You need to get one,'" Carome adds. "But this provision, as I read it, would require for any federally funded research involving sensitive identifiable information that they must issue a certificate of confidentiality."

Non-federally funded research would leave the certificate optional.

Even with the Cures Act's passage, local IRBs should continue with business as usual, keeping in mind their

important role as gatekeepers in terms of clinical research approval and local participation, Sinha notes.

However, Sinha acknowledges that some small IRBs at rural hospitals and medical schools may face pressure to dissolve or to farm out protocol review and monitoring to an independent IRB.

The Cures Act, mirroring recent NIH policy, emphasizes the point that research institutions should use central IRBs as much as possible, Forster says.

"That is a trend that is occurring in the United States, and it has been — for 20 years — moving more toward the European model where central IRBs are the predominant method of IRB review," Forster says. "I think it will help to change the mindset about IRBs." ■

Vulnerable Populations are a Cornerstone of Human Research Protections

Refugees, immigrants also vulnerable

Historical accounts of the biggest human research scandals of the past two centuries primarily involved vulnerable populations.

The list is long and includes orphans, minorities, the disabled, prisoners, and others. *(For more information, see timeline of exploited vulnerable populations, page 17.)*

"We've always had research on vulnerable populations, and in many ways the rules and our policies for protecting human subjects were reactions to scandals," says **Jeremy Block**, PhD, MPP, managing partner of Venture Catalyst and adjunct professor at the Marxe School of Public and International Affairs at Baruch College in the City University of New York (CUNY) System in New York City. Block spoke about vulnerable populations and research ethics at the Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA.

"If you look back through history, all of the big scandals were on what we now call vulnerable populations," Block says. "These were situations of groups of people exploited, manipulated, physically controlled, influenced, or coerced."

The research and ethics community have been talking about developing research ethics around vulnerable populations and situations for a long time. IRBs and the regulations that have created the human research protection system of IRB reviews and informed consent now provide ample protection from any systematic attack on vulnerable populations, Block says.

However, there are ways IRBs can ensure that vulnerable populations continue to be protected from even a single research project.

For example, sometimes the vulnerable population being studied is engaged in behavior that could result in stigma or even legal repercussions if individuals' names are discovered. In this case, IRBs and researchers have an obligation to make certain the research subjects are protected from disclosure to governmental or other authorities, he says.

"You're allowed to do what you need to do to protect them," Block says.

For instance, marginalized groups based on their sexual orientation, the LGBTQ community, or people who are refugees or undocumented immigrants can be considered vulnerable.

"We're creating a climate where there's a chill among those people," Block says. "Do you think they'll want to sign up for a study where all of their information will be kept centrally in a database?"

If someone tries to collect information about a vulnerable population that has been studied for a non-research purpose, then IRBs and the research community should protect the study participants from disclosure and possible harm, he adds.

"There are a significant number of students in my courses who fall into this category of being individuals who are immigrants," Block says. "I can tell you anecdotally that I received a lot of messages from my students, some who are Muslims who fled violence to come to this country, that they're afraid of people coming after them."

Another aspect involving vulnerable populations is its very definition. "It's not just groups of people like pregnant women, prisoners, or children who are vulnerable," Block says. "We need a broader understanding of situations that can leave people vulnerable."

He offers this example. "If you take a middle-aged white man who has a good job, we wouldn't think of him as automatically vulnerable," Block says. "But if he has chest pain and is put in the emergency room,

then I would argue that he's vulnerable."

For people who are acutely ill or at the end of their lives, they could be considered vulnerable based on their situation, he adds. ■

Here's a List of Vulnerable Populations Historically Exploited in U.S. Research Studies

People who are part of vulnerable populations were exploited in the name of research over the years leading up to our current institutional review board and human research protections. The following is a brief list of some of the vulnerable people abused in research studies.

1908: Philadelphia researchers infected children at St. Vincent's Home for Orphans with a virus that left some children blind. They planned to study the disease.

1911: Rockefeller Institute for Medical Research physician Hideyo Noguchi injected 146 children with syphilis to study the disease.

1939: Speech Pathologist Wendell Johnson — who was a stutterer — and research assistant Mary Tudor, used psychological abuse with the goal of inducing stuttering in normal-speaking children. His subjects were 22 children at the Iowa Soldiers' Orphans' Home in Davenport.

1932-1972: The Tuskegee syphilis experiment studied the progression of syphilis in hundreds of poor black men. They were denied penicillin after it was available for treatment of the disease in 1947.

1940s: The Stateville Penitentiary Malaria Study, conducted by the United States Army, State Department, and the University of Chicago, looked at the effects of malaria on prisoners of Stateville Penitentiary. Psychiatric patients at Illinois State Hospital also were infected with malaria for the testing of experimental treatments.

1940-1953: Pediatric neuropsychiatrist Lauretta Bender performed electroshock experiments on more than 100 children diagnosed with "autistic schizophrenia" at Bellevue Hospital. A later study of the children found that nearly all were worse off, with violence and suicidal tendencies.

1946-1948: A Guatemala study involved U.S. researchers using prostitutes to infect prison inmates with syphilis and other sexually transmitted diseases in order to test the effectiveness of penicillin as treatment.

1946: Vanderbilt University researchers gave more than 800 pregnant women in Tennessee "vitamin drinks" that contained radioactive iron. Researchers studied how fast the radioisotope crossed into the placenta. Some of the babies died from the experiments, and some of the effected children later died of cancer.

1946-1953: The U.S. Atomic Energy Commission, the Walter E. Fernald State School, and the Quaker Oats Corporation fed oatmeal spiked with radioisotopes to 73 mentally disabled children to track how nutrients were digested.

1950s: Dr. Robert Heath of Tulane University, also known for inventing dubious gay conversion therapy techniques, gave 42 schizophrenia patients and prisoners at the Louisiana State Penitentiary LSD and Bulbocapnine to take their EEG readings. Heath also implanted electrodes in black prisoners in New Orleans.

1950: Dr. Joseph Stokes of the University of Pennsylvania infected 200 female prisoners with viral hepatitis.

1953: The U.S. Atomic Energy Commission at the University of Iowa studied the health effects of radioactive iodine in newborns and pregnant women.

1955-1960: Mentally handicapped children with cerebral palsy and other disorders were given painful spinal taps and had air injected into their brains as part of research at Sonoma State Hospital in California. Some died from the experiments.

1950s-1972: Researchers infected mentally disabled children at Willowbrook State School in Staten Island, NY, with viral hepatitis for vaccine research. The children were fed the virus through an extract made of feces from infected patients.

1960-1971: University of Cincinnati researcher Eugene Saenger irradiated 88 poor black men, women and children. Some died within hours.

1964-1968: The U.S. Army funded experiments with mind-altering drugs on 320 inmates of Holmesburg Prison to determine the minimum effective dose needed to disable 50% of a population. Also, Albert M. Kligman conducted skin experiments on prisoners, injecting 70 prisoners with dioxin. ■

IRB's New Member Handbook Improves IRB Training

Like many IRBs, the Virginia Commonwealth University IRB has been on a mission recently to streamline its processes, decrease approval time, and improve IRB member training.

Hand-in-hand with the IRB consolidating its four panels into one, 40-member IRB that meets weekly, the IRB office has created a 67-page IRB Member Handbook that provides comprehensive training material for new members. It also serves as a resource for experienced members.

"The reason we created the handbook is because we had six new members come on, and we saw the need — especially for non-scientists," says **Meghan Wright**, MEd, IRB training manager. Wright is the lead author of a poster on the handbook resource.[1]

"We don't have constant turnover, but we felt it was a good investment to train members," Wright adds. "We also give it to current members to use as a resource during reviews."

The IRB's mission to improve processes began with the handbook, which Wright began to write in the summer of 2015. It also includes this past summer's consolidation.

With a goal of increasing consistency and decreasing time to approval, the IRB office took its three biomedical panels and one social-behavioral panel and combined them into one IRB that can handle all studies. The IRB membership was cut by 40%, and a chair and vice-chair were selected to head the new 40-member IRB. The chair and vice-chair attend each of the weekly meetings, but other members attend about one meeting per month, Wright explains.

When studies are submitted, the IRB staff pre-screen them and assign them to primary and secondary reviewers, based on their expertise.

"If we get social-behavioral research, it's assigned to a social-behavioral reviewer, but the study also can have the benefit of having biomedical members reviewing it at the meeting," Wright says.

The new member handbook resource is divided into three sections, including member information, a guide to reviewing a submission, and guidance for full board meetings. *(See samples from IRB Member Handbook, page 19.)*

For example, meeting guidance covers details about how an IRB member can make a motion, detailing the motions for approval, approval with conditions, and table. It notes that motions for disapproval, suspension, and termination are rarely used. It also discusses how to amend a motion and withdraw a motion. Details also outline the four voting options of "yes," "no," "abstain," and "recuse."

Wright wrote the book over several months, with editing assistance from IRB staff.

"I did research online, although there wasn't a lot available for public use," she says. "One university had a full training guide, but it didn't have the content I sought."

Wright pulled from various internal and external sources and created the guide in a PowerPoint, eventually merging into one PDF document.

The handbook is available in print and PDF format, listed on the IRB members' private folder. It's not available to the public. The PDF version has links to the IRB's electronic system.

The PowerPoint version makes it easy to create visual items and charts, she notes.

"We give all new members an electronic copy and a bound copy, so they can take notes on it," Wright says.

"I used to be a teacher, and I know that sometimes if a resource is too content-heavy or overwhelming, it won't be used at all," Wright says. "So I made this user-friendly and visually appealing."

The PDF also has color-coded charts and flowcharts, including a page that helps new members navigate the electronic submission system. Key words are outlined in color rectangles.

"The goal was to make it visually easy to read as a reference," Wright says. "We picked up the relevant things like reporting, consent waivers, compliance, HIPAA, and FDA, and also created some flowcharts for subparts."

When various human research protection regulatory changes occur, the handbook also will be updated, she adds.

Results of an IRB member survey suggest the handbook has been a success. About 86% of members said they used the handbook while completing a study review, and about half of the IRB members said they had referenced the handbook in an IRB meeting. All of those surveyed said they liked the handbook's format and layout, and 92% of members said they found the most useful section to be the one about reviewing a submission.[1] ■

REFERENCE

1. Wright M, Davison C. IRB member comprehensive handbook resource. Abstract submitted to PRIM&R's 2016 Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA. Poster 13.

VCU IRB's Member Handbook Covers What They Need to Know

The Virginia Commonwealth University IRB office created the IRB Member Handbook for training new members and to serve as a resource to all members.

The following are some highlights from the 67-page handbook:

• **Reviewing a submission.** This section covers various types of reviews, including initial review, expedited review, full board, continuing review, and amendment.

The handbook notes that when an IRB member is a primary or secondary reviewer for an initial submission to the full board, they should use the Guiding Your Review template, and do the following:

- read the consent document, but do not take notes or make revisions,

- read the protocol summary,

- read the full protocol and supporting material carefully, taking notes as needed,

- re-read the consent document and make suggested changes or corrections, and

- re-read other submitted documents and make suggested changes or corrections.

The Guiding Your Review template has 53 questions, including the following:

- **Introduction, Background, Aims:** "Are there adequate preliminary data to justify the research?"

- **Scientific Design:** "Are the objectives likely to be achievable within a given period of time?"

- **Inclusion/Exclusion Criteria:** "Is the choice of subjects appropriate to the question being asked?"

- **Recruitment of Subjects:** "Are there acceptable methods for screening subjects before recruitment?"

- **Research Procedures:** "Is there a clear differentiation between research procedures and standard care?"

- **Drugs, Biologics, Devices:** "Are the drug or device safety and efficacy data sufficient to warrant the proposed phase of testing?"

- **Data Analysis and Statistical Analysis:** "Are the plans for data and analysis defined and justified, including stopping rules and end points?"

- **Potential Risks, Discomforts and Benefits for Subject:** "If there is no direct benefit to participants, is there mention of the benefits to future subjects of knowledge to be gained?"

- **Privacy and Confidentiality:** "Are there adequate provisions to protect the privacy and ensure the confidentiality of the research subjects?"

• **Reports:** This section covers unanticipated problems (UPs) and how to review reports of UPs, as well as protocol deviations and violations, noncompliance. The following is a sample item:

- Protocol Deviation is any change to the IRB-approved protocol taken without prior IRB review to eliminate an apparent immediate hazard to research participants;

- Protocol Violation is an accidental or unintentional change to the IRB-approved protocol that harmed participants or others, or that indicates participants or others may be at increased risk of harm. ■

'Reimagining' the IRB Model for the 21st Century

The IRB model created to protect human research subjects more than a half-century ago is in danger of being outstripped by technology-driven research and other forces. It must be "reimagined" for the 21st century to provide safe and ethical oversight of rapidly expanding research agenda, the authors of a recently published report argue.[1]

IRBs are facing an evolution of research methods and practices made possible to some extent by rapidly emerging new technology. As this trend continues, the authors question whether the ethical principles outlined in the landmark Belmont Report[2] are still being met.

"The ethical principles of the Belmont Report have stood the test of time, generally speaking," says co-author **Camille Nebeker**, EdD, MS, a research ethicist and educator at the Center for Wireless and Population Health Systems at the Qualcomm Institute in San Diego. "Our paper prompts reflection on whether we need to reconsider our existing structures to be more responsive to how research is presenting in today's world."

For example, Nebeker cites a study she conducted with her colleagues of active and sedentary behavior. The research subjects were asked to wear an outward-facing camera to determine how often and under what circumstances they sit or stand.

"While people who are not research participants can use a GoPro or smart-

phone to record their physical surroundings, download a fitness tracking app, and trace their location, the IRB initially denied approval of the study, citing risks to privacy," she says. "The use of a wearable camera was problematic [because] it would capture images of people who were not participants. The current federal regulations do not address the potential protections for people who, by virtue of their proximity to a research participant, become part of the research data set."

In this case the question arises: Does the ethical principle of "respect for persons" transcend the needs of bystanders and communities involved in research?

There are some 6,000 IRBs nationally tasked with protecting human research subjects, but they are working within a system that is "deeply and inherently flawed," Nebeker and colleagues note. Among the evidence cited for this claim is a 2013 study that examined 104 protocols of 20 IRBs at 10 large medical institutions.[3] The authors found that data monitoring and protection of vulnerable populations were rarely discussed, and 50% of the reviews did not compare risks and benefits. We asked Nebeker whether such findings may reflect practices at IRBs in nationally.

"I would say that paper documents concerns that have been anecdotal — that is, within institutions and between investigators," she says. "Researchers talk amongst each other about the inconsistent actions, unpredictability, and strategies used to 'get through' the IRB. I've also been in conversations with colleagues where they ask whether what appears to be administrative in nature and holds up the approval of their studies actually impacts human research protections."

Other articles and books have raised similar concerns, she notes, citing Carl Schneider's *The Censor's Hand* and Robert Klitzman's *The Ethics Police?*

"A paper[4] we published in 2015 documented the inconsistencies with reviewing technology-support research within my own institution, which has five IRBs at present," she says. "I don't fault the IRB analysts, coordinators, members, or directors — they are trying to do a good job. I've served on an IRB as either a member or as an institutional ex-officio for over 20 years, so I empathize with both sides of the issues. The existing structures do not have the agility needed to be responsive or, perhaps, those operationalizing the regulations are more focused on protecting institutions and risk management?"

Nebeker and colleagues say that "the time has come to reimagine and, ultimately, work toward redesigning our human research protections system so that it is responsive to both the evolution of general research practices and new forms of research enabled by technological advances."

To address such issues and reimagine the IRB for the 21st century, the authors participated in a 2015 workshop comprised of 11 researchers and IRB professionals drawn from academic and research institutions in San Diego. Using a "design thinking" brainstorming method to generate ideas and solutions, they proposed several avenues for exploration.

For example, they proposed creation of informed consent protocols that would allow real-time feedback from participants, an approach which suggests that consent should be more of an ongoing process than a single decision point in the research protocol.

"Yes, ideally the consent process is bidirectional, ongoing and participant-centered," Nebeker says. "Most people who have little or no formal training in academic research are not familiar with the scientific method and, subsequently, may not understand many of the required elements of what is relayed via the consent document or conversations. As we move into electronic delivery of informed consent using tablets and smartphones with no face-to-face component, it will be important to offer avenues of communications to participants and utilize the consent process to assist in developing a relationship with the participant rather than documenting a legal transaction. Ideally, we will work toward the democratization of research where the participants are more involved at study onset and have a voice each step of the way."

Another idea is to empower researchers to protect participants, scaling back the role of the IRB. Researchers would post study plans and risk assessments and get review and feedback from peers in the research community. "In this scenario, responsibility for ethical conduct during the study would be shared by both the researchers and the peers who agreed that the plan would adequately protect participants," the authors wrote.

"A form of this idea is actually being pilot-tested in a project that we call the Connected and Open Research Ethics, or CORE initiative," Nebeker says. "We have designed and deployed CORE using a participatory research methodology that involves IRBs and researchers in shaping a web-based research ethics community resource. The idea is to have stakeholders in the mHealth and digital medicine ecosystem convene in the CORE community to share ideas, questions, and resources." ■

REFERENCES

1. Bloss C, Nebeker C, Bietz M, et al. Reimagining Human Research Protections for 21st Century Science.

J Med Internet Res 2016;18(12): https://www.jmir.org/2016/12/e329.
2. Zucker B. The Belmont Report. In: Wiley Encyclopedia of Clinical Trials. New York, NY: John Wiley & Sons; Dec 14, 2007.
3. Nebeker C, Linares-Orozco R, Crist K. A Multi-Case Study of Research Using Mobile Imaging, Sensing and Tracking Technologies to Objectively Measure Behavior: Ethical Issues and Insights to Guide Responsible Research Practice. *J Research Admin* 2015;46:118-137.
4. Lidz C, Garverich S. What the ANPRM missed: additional needs for IRB reform. *J Law Med Ethics* 2013;41(2):390-396.

The Ethical Question of Denying Children Antibiotics

As IRB members are no doubt aware, public health officials are warning that the overuse and misuse of antibiotics has selected out resistant strains of bacteria all over the globe. As the drugs kill off susceptible strains, those with innate or acquired resistance emerge and proliferate.

As a result, the short-lived miracle of the antibiotic era — which essentially began with the use of penicillin in WWII — is at risk of coming to an end. Once-treatable infections are progressing to severe illness, and the use of antibiotics preventively prior to medical care is imperiled. Thus, clinical trials are examining whether antibiotics can be used less often for shorter durations without sacrificing clinical effect.

For example, the NIH's National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring a clinical trial at five medical centers, enrolling some 400 children to determine whether the standard 10-day course of antibiotics for community-acquired pneumonia (CAP) could be reduced to five days but still provide effective treatment. One of the safeguards in place is that the duration would be shortened only for those showing improvement after the first few days of treatment. Most frequently caused by *Streptococcus pneumoniae*, CAP typically is treated with a 10-day regimen of amoxicillin.

Children age six months to six years will be studied in the Short Course vs. Standard Course Outpatient Therapy of CAP in Children (SCOUT-CAP) trial. As an additional safeguard, participants in the study must have been initially treated in outpatient clinics, urgent care facilities, and EDs for CAP and have clinically improved prior to enrollment. The trial is being conducted in part through the NIAID-funded Antibacterial Resistance Leadership Group (ARLG), which is targeting a broad array of clinical research to preserve antibiotic efficacy. Participating research institutions include Duke University, Vanderbilt University, Cincinnati Children's Hospital Medical Center, Children's Hospital of Philadelphia, and Children's Hospital of Pittsburgh.

Estimated to run through March 2019, the clinical trial will evaluate short courses of the oral antibiotics amoxicillin, amoxicillin-clavulanate combination, and cefdinir. The research subjects will be split into equal groups undergoing five-day and 10-day treatment. **C. Buddy Creech**, MD, MPH, one of the principal investigators and a pediatric infectious diseases physician at Vanderbilt, agreed to field a few questions on the SCOUT-CAP trial for *IRB Advisor*.

IRB Advisor: Can you comment on the primary ethical issues raised by this type of study — for example, obtaining informed consent to treat the five-day group that will receive only half the currently recommended antibiotic duration?

Creech: The most important ethical portion of this study is that the children who will be enrolled must already be showing signs of recovery, including no fever for at least 24 hours before they switch to potentially receiving placebo. Realistically, new data from a large CDC-sponsored study[1] suggest that the vast majority of community-acquired pneumonia in children is actually due to viruses. Therefore, the antibiotics they are receiving may not have much of an impact at all. The other important consideration is that if we can shorten therapy, and therefore decrease the likelihood of rash, diarrhea, and stomach upset that comes with antibiotic use, we would make a significant impact on medical care for pneumonia.

IRB Advisor: Can you comment more on the safeguards in place to ensure longer treatment for those in this group that do not clear the infection after five days?

Creech: The first safeguard is that if children are not better by day five when we seek to enroll them, they simply will not be in the study. Therefore, all children must be significantly improved — including no fever — before they can even be considered for the study. Second, we are asking parents to keep a daily diary that will help them gauge symptoms such as cough, fever, and fussiness. If any of these increase

or if any children appear to get worse, we have created ways to get them back to their pediatrician to consider other treatments. We've also built safeguards into the study so that if multiple children seem to get worse during day 5-10, we can ask an independent group of physicians to review their records to see if we need to change, or even stop, the study.

IRB Advisor: Related to that question, can you elaborate on the provision that calls for enrolling research subjects who were initially treated in outpatient clinics and other settings?

Creech: For children, one of the most reliable signs of ongoing infection is fever. Therefore, fever must be gone for at least 24 hours or we will not enroll the child. The child must also have a normal rate of breathing and look well overall.

IRB Advisor: Did the IRB(s) involved comment on or stipulate that these types of measures must be place for the trial to proceed?

Creech: The IRBs at five institutions, the NIH, the FDA, and an independent Safety Monitoring Committee (SMC) reviewed the protocol. Each of the measures we instituted were decided upon upfront and no additional modifications were needed before proceeding with the trial.

IRB Advisor: Will the use of previously treated patients make it more difficult to ultimately extrapolate your findings to inform antibiotic therapy for untreated cases of CAP in pediatric patients?

Creech: This study will be the first of hopefully many studies evaluating the best management of children with pneumonia. We hope to develop robust prediction models to help determine, at the time of diagnosis, which children are more likely to have bacterial versus viral pneumonia — and, therefore, who needs antibiotics and who does not.

IRB Advisor: Stepping back for a second, we know antibiotic resistance has become a major public health threat, but can you comment generally on why this particular area of research is important?

Creech: For years, we have given strict instructions to parents, "make sure your child takes all of the prescription," and yet for many infections we don't actually know the precise length of treatment needed to make sure children recover well. Many are based on years of experience; others are based on ensuring that we treat until the child is better, and then for a short period after.

Over time, though, we have learned that even short courses of antibiotics can have important effects on the types of germs that children carry on their skin, in their noses and throats, and in their GI tract. As a result, the field is moving toward making certain that we treat children with the most precise antibiotic for the shortest amount of time. This study will help us make certain that shorter duration of therapy — only five days for children that are already getting better — will be just as good as a full 10 days.

IRB Advisor: It seems you will need to draw a bright line marking when it is safe to end therapy if the traditional patterns of antibiotic overkill are to be reversed. Is there a gray area there that might end up showing, for example, seven days of therapy gives you the most bang for the buck in terms of balancing patient safety versus antibiotic resistance?

Creech: We deliberately chose five days for a couple of reasons. First, it usually takes children a few days to recover from pneumonia, so anything shorter than five days might be a bit too short. Second, shortening to only seven days is already done by some pediatricians with good results. Therefore, we thought this study would be a good chance to move that to five days. [Previous research] suggests that in this age group, five days of amoxicillin is just as good as 10 days, while three days was not. We wanted to extend those observations to the United States by enrolling children receiving other antibiotics, and enrolling a much larger number of children. ■

REFERENCE

1. Jain S, Williams DJ, Arnold SR, et al, for the CDC EPIC Study Team. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children. *N Engl J Med* 2015;372:835-845.

'Serious Noncompliance' the Leading Incident Reported to OHRP

IRBs and research institutions may be concerned that reporting incidents of noncompliance to the HHS Office for Human Research Protections (OHRP) could be a red flag to prompt an investigation, but the reverse is actually true.

IRBs that do good-faith reporting are less likely to be targeted for a "not-for-cause evaluation," says **Kristina Borror**, PhD, director of the Division of Compliance Oversight at OHRP.

"Institutions are selected for not-for-cause evaluation based on a range of considerations, and if an institution has a history of a relatively low level of reporting to OHRP under the requirements of HHS regulations, they will be more likely to be selected," she tells *IRB Advisor*. "Reporting incidents is important not only because the regulations require it, but also to foster a partnership with OHRP to assist in responding to and preventing incidents."

Borror and colleagues recently published a review and analysis[1] of 6,511 incident reports from institutions conducting research between January 1, 2008, and December 31, 2014. The incident type most frequently reported was "serious noncompliance," which often involved changes to the research protocol without IRB approval and breakdowns of the informed consent process. Overall, there were 2,943 instances of serious noncompliance and 583 instances of continuing noncompliance.

"Protocol changes without IRB review and approval included study interventions not administered as required by [the] protocol, compensating subjects more than allowed in the protocol, and failure to follow inclusion or exclusion criteria," the OHRP authors reported. "Noncompliance related to informed consent included failure to obtain informed consent prior to inclusion in research, failure of the informed consent document to include all the risks of the research, and failure of the subject to sign the consent form prior to participation in research."

These findings may help IRBs avoid common compliance pitfalls going forward.

"The paper points out many of the types of reportable incidents as well as some specific examples," Borror says. "Institutions also can glean examples of types of corrective actions to consider when addressing an incident, particularly noncompliance — the most common type of incident reported to OHRP."

Similarly, OHRP will use the findings to focus on the identified problems and improve reporting and feedback between the agency and IRBs and investigators.

"OHRP will use this information to develop educational materials to help institutions prevent and respond to incidents," Borror says.

The Department of Health and Human Services (HHS) regulations require that institutions have written procedures to ensure that incidents of noncompliance are promptly reported to OHRP. In general, according to Borror and colleagues, these incidents include the following:

- unanticipated problems involving risks to subjects or others,
- serious noncompliance with the protocol approved by the IRB, and
- suspension or termination of IRB approval.

"When reviewing an incident report, OHRP assesses most closely the adequacy of the actions taken by the institution to address the incident," the authors report. "Specifically, OHRP assesses whether the corrective actions will help ensure that the incident will not happen again with the investigator or protocol in question, with any other investigator or protocol, or with the IRB. Therefore, OHRP recommends that, when appropriate, corrective actions be applied to the entire institution."

Among the most common corrective action taken by reporting institutions was education of researchers, IRB members, and institution staff. OHRP received reports of 2,114 instances of corrective actions involving education from 2008 to 2014. In addition, corrective actions reported included restructuring the IRB, adding staff members or making staffing changes, adding an IRB, and adding a research compliance officer to the process. Policies and procedures were commonly corrected to ensure data encryption for research laptops and flash drives, and created checklists to confirm study compliance, they reported.

The OHRP authors also looked at how often the agency requests additional information after an IRB or institution reports incidents and corrective actions. Only 69 (3.8%) of 1,826 reports filed in 2013-2014 prompted OHRP requests for additional information.

"The conduct of human subjects research can be complicated and not necessarily under the control of the IRB," the OHRP authors stated. "During the conduct of research, it is not uncommon to find that, for one reason or another, the research must be suspended or terminated or the approved protocol has not been followed — that there is noncompliance or unanticipated problems that may need to be reported to the IRB, institutional officials, sponsors, and federal agencies. These occurrences or deviations can have a range of possible impacts depending on multiple factors such as the overall risk of the study and the nature and extent of the incidents. Once the causes of the problem are discovered, they must be assessed, and action must be taken to correct them and prevent such occurrences in the future." ■

REFERENCE

1. Ramnath K, Cheaves S, Buchanan L, et al. Incident Reports and Corrective Actions Received by OHRP. November-December 2016;38:6: http://bit.ly/2iAqqr8.

IRB ADVISOR

CME/CE 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 My Account to take a post-test.

3. Pass the online test 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, a credit letter will be emailed to you instantly.

5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE QUESTIONS

1. **What is one of the big IRB-related changes that is promoted by the 21st Century Cures Act, signed by President Obama in late 2016?**

   A. The Cures Act promotes a national database for collecting clinical trial adverse event findings both during research studies and post-approval.
   B. The Cures Act requires IRBs to designate one member as a liaison to a national central IRB or to the funding source.
   C. The Cures Act encourages the shifting of research protection away from local IRB review toward national or central IRB review.
   D. All of the above.

2. **Historical accounts of the biggest human research scandals of the past two centuries primarily involved which populations?**

   A. Female
   B. Children
   C. Vulnerable
   D. White male

3. **Researchers projecting future changes for IRBs proposed creation of informed consent protocols that would:**

   A. automatically lapse at a certain point during the trial.
   B. allow real-time feedback from participants.
   C. include an "opt-out" provision for granting DNA data storage.
   D. use a tiered process based on participants' cognitive function.

4. **Which of the following safeguards is in the research protocol of a clinical trial to determine whether the standard 10-day course of antibiotics for community-acquired pneumonia (CAP) in children could be reduced to five days?**

   A. The participants must have been initially treated for CAP and have clinically improved.
   B. They must have no fever for at least 24 hours prior to enrollment.
   C. They must show signs of recovery before they are switched to receiving placebo.
   D. All of the above.