IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

NOVEMBER 2016 Vol. 16, No. 11; p. 121-132

INSIDE

AHC Media

New NIH/FDA Rules Will Bring Greater Transparency to CTs

The big stick is withholding grant funds

By Melinda Young, Editor

The new rules published this fall by the NIH and FDA about reporting clinical trial results will expand transparency in research and give the world more knowledge about the effectiveness of investigational and new drugs and devices, FDA and NIH officials say.

Researchers and sponsors will have to submit their findings, whether or not they are going to be published, to ClinicalTrials.gov. Failing to provide findings could result in enforcement action, including the loss of federal grants, federal officials say.

"Clinical trials are vital for medical advancement, and increasing knowledge about clinical trials is good for trials, the patients, and for science," said **Francis S. Collins**, MD, PhD, NIH director.

This requirement is important because of its focus on the people who volunteer to participate in clinical trials, said **Robert Califf**, MD, FDA commissioner of food and drugs.

"ClinicalTrials.gov contains information from thousands of people around the world," Califf said. Califf and Collins were among a handful of government officials who spoke at a news teleconference in September about the change.

> RESEARCHERS AND SPONSORS WILL HAVE TO SUBMIT THEIR FINDINGS, WHETHER OR NOT THEY ARE GOING TO BE PUBLISHED, TO CLINICALTRIALS.GOV.

The NIH final rule, titled, *Clinical Trials Registration and Results Information Submission*, published in the *Federal Register* on Sept. 21, 2016, is effective Jan. 18, 2017. Organizations have 90 days after the deadline to come into compliance. The FDA is changing Section 801, also known as the FDAAA 801, and NIH also has issued the *NIH*

Financial Disclosure: Editor **Melinda Young**, Managing Editor **Jill Drachenberg**, Associate Managing Editor **Dana Spector**, Physician Reviewer **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.

AHC Media 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 #CEP14749, 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.

EDITOR: Melinda Young.
MANAGING EDITOR: Jill Drachenberg, (404) 262-5508 (Jill.Drachenberg@AHCMedia.com).
ASSOCIATE MANAGING EDITOR: Dana Spector
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger.

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

Policy on the Dissemination of NIH-Funded Clinical Trial Information with a Jan 18, 2017, deadline. *(For more information, see article on the changes, page 124.)*

"The new requirements outlined in the final rule are expected to provide greater transparency, not only of the information in clinical trials, but also about which trials are being done, what their designs are, and how they're being analyzed," Califf said. "The final rule expands and provides clarity to the statutes and requirements, allowing the FDA to ensure more efficient and effective compliance and enforcement activities related to the requirements for registration and reporting of certain clinical trial information."

Rule Expands Results Information

While the NIH final rule expands submission of results information, it does not specify that such results need to be written in layperson language, which is what the European Union and many bioethicists promote. *(See article on lay summaries in study results in the October 2016 issue of* IRB Advisor.*)*

"The law said there could be lay summaries," says **Kathy Lynn Hudson**, PhD, NIH deputy director for science, outreach, and policy.

Researchers and sponsors could add material to make their results more useful to participants, and ClinicalTrials.gov is being enhanced to make it easier to conduct searches, but what is required in the final rule is scientific information, Hudson says.

From a researcher's perspective, a layperson mandate would set a very high bar, says **Jennifer Grandis**, MD, an American Cancer Society Clinical Research Professor, associate vice chancellor of clinical and translational research, director of the Clinical and Translational Science Institute, and a professor of otolaryngology at the University of California, San Francisco.

"Those are two different issues: One is making sure all data are available, and the second is making it understandable, in a format that everyone can understand," Grandis says. "My instinct about what is lay language and what a true layperson thinks is lay language are not the same, and it's not a trivial difference."

Researchers have to write a lay abstract for every NIH grant, so they're accustomed to writing for nonscientists. However, even these lay abstracts do not go far enough, according to what Grandis has heard from lay cancer survivors. "They will say that the lay abstract is not intelligible."

One Important Goal

The NIH final rule accomplishes one important goal, which is related to the spirit of making research data available to the public, but it's not the complete answer for the public and research participants, she notes.

"Whether ClinicalTrials.gov changes from being a repository of information to a repository of information that is accessible to individuals who are not in science and medicine is an entirely different conversation," Grandis says.

Part of the impetus for ClinicalTrials.gov and its recent change is to help the research community understand how well devices and drugs perform, Collins says.

"Even after licensed products

are approved, clinical trials can help us learn of their effectiveness," he says. "We can learn even more from clinical trials that indicate a product or device that is not effective or safe."

ClinicalTrials.gov now has registration information for more than 224,000 studies that take place in all 50 states and 192 countries, Collins says.

"Not all of these are subject to the final rule," he notes. "There are more than 50,000 unique visitors who access ClinicalTrials.gov every day, learning about trials open for recruitment, identifying new studies, new therapies, or looking for results of studies that have been completed."

While the website has improved research transparency and accessibility, it hasn't gone far enough because of the lack of study results, Collins says. "We in the research community have a disappointing track record in making those results accessible."

For instance, a 2014 analysis of 400 clinical trials found that, within four years of completing the study, 30% had not shared results through publications or through reporting in ClinicalTrials.gov, Collins says.

"That's clearly unacceptable," he says. "A more recent study found that 51 of U.S. academic medical centers found that 43% of their studies were unpublished two years after the trials were completed."

Key Elements

The final rule's key elements, according to Collins, include:

- providing a checklist of which elements are subject to the regulations and who is responsible for submitting the required information,
- expanding the scope of trials for which summary information must be submitted to include drug, biological, and device products that have not yet been approved, licensed, or cleared by the FDA, and
- requiring additional registration and summary information data elements to be submitted to ClinicalTrials.gov, including the rates, ethnicity, and the full protocol.

In order for a study to be registered on ClinicalTrials.gov, researchers will have to include information about whether the study has had IRB approval, says **Deborah Zarin**, MD, director of ClinicalTrials.gov.

> "YOU'RE NOT ALLOWED TO GO INTO RECRUITING STATUS UNLESS YOU TELL WHETHER OR NOT YOU HAVE IRB APPROVAL, AND YOU HAVE TO PROVIDE US WITH EVIDENCE OF THAT."

"You're not allowed to go into recruiting status unless you tell whether or not you have IRB approval," Zarin says. "And you have to provide us with evidence of that."

The National Library of Medicine, which operates the clinical trials registry and results data bank, is gearing up for an increased volume of submissions, Collins says.

"The National Library of Medicine is continuously making improvements," he says. "All of our efforts are made at ensuring society gains from knowledge gained from participation."

Collins and Califf say they expect research organizations to comply with the new rule, both because they also care about greater transparency and because there are severe penalties, including withholding of grant funding for new projects to noncomplying institutions and publishing the names of noncompliant institutions.

"I really believe it won't take much to get people to comply with this once they realize how serious it is," Califf says. "I know the press will be on top of this."

While the agencies do not have extra resources for monitoring compliance of the rule, they expect the fear of taking a hit to one's reputation will do much of the job for them. "No one wants to be on the wall of shame," Collins says.

"We have a clear expectation of compliance with the appropriate clout behind it," Collins adds. "I don't think we'll have a very large challenge here with people out of compliance."

Research institutions and investigators will want to comply with the rule, but logistically it will be challenging, Grandis says.

"It's simply more things one has to do," she says. "Whose responsibility is it for doing it? How do they do it?"

Also, for studies that are published, it won't be as simple as linking the published report to the ClinicalTrials.gov website. All of the study information will have to be uploaded separately into each of the fields.

"It's really important to get the public the information, but there are so many consequences and requirements," Grandis says. "We'll comply and do the best we can, but it's not clearly obvious how one does this." ■

Highlights from Final Rule on Clinical Trial Results Submissions

Federal regulators outline the final rule

The NIH published the final rule, "Clinical Trials Registration and Results Information Submission," on Sept. 21, 2016, with an effective date of Jan. 18, 2017.

Rule Highlights

The following are some of the rule's highlights:

• **How does registration work?** Studies are registered at ClinicalTrials.gov within 21 days of enrolling the first human subject.

• **Which trials are covered?** All interventional clinical trials, involving FDA-regulated products, with one or more arms and with pre-specified outcome measures are subject to the rule. Expanded access use is not applicable.

• **Who submits information?** One person, such as a principal investigator, is named the responsible party.

• **How are results submitted?** Results are placed in a tabular format summarizing participant flow, demographic and baseline characteristics, primary and secondary outcomes, adverse event information, and any scientifically appropriate statistical tests. Plus, there must be a full protocol and statistical analysis plan. The results information must be submitted within one year of the study's completion date.

• **What else is required?** The final rule also requires submission of adverse events' number and frequency, by arm or comparison group. It requires three tables of adverse event information, including one that summarizes all serious adverse events, another summarizing other AEs that happened with a frequency of 5% or more in any arm of the clinical trial, and a third that summarizes the all-cause mortality data by arm or group. The AE tables must include information about the events that occurred, whether they were anticipated, and it requires submission of the time frame for AE data collection.

ALL INTERVENTIONAL CLINICAL TRIALS, INVOLVING FDA-REGULATED PRODUCTS, WITH ONE OR MORE ARMS AND WITH PRE-SPECIFIED OUTCOME MEASURES ARE SUBJECT TO THE RULE. EXPANDED ACCESS USE IS NOT APPLICABLE.

• **What types of descriptions of results are submitted?** The final rule does not require the submission of technical or non-technical narrative summaries of study results. NIH says in the final rule that summaries can lead to biased reporting, so they prefer results information to be presented in a tabular format.

• **Why make the change?** NIH lists the benefits as follows:

- The changes in submissions to ClinicalTrials.gov will help people find trials in which to enroll and ensure their participation is honored and trust enhanced by creating a public record of the trial and results.

- Requiring publication of the results fulfills an obligation to trial participants from the research team.

- It furthers the goal of ensuring research participation leads to accountability via the public reporting of information.

- Having results available will assist people in making more informed decisions about participating in clinical trials.

• **What are the penalties of noncompliance?** The following are the listed penalties:

- NIH will publicly post notices of noncompliance in the data bank.

- NIH will require report forms under certain grants to include a certification that required registration and results information submission are complete.

- Federal agencies will need to verify compliance before future funding or continuation of funding.

- The FDA has the authority to sanction responsible parties who fail to comply with the act.

- Committing a prohibited act could subject the violator to criminal and/or civil penalties, including financial penalties.

For more information on the rule, visit: http://bit.ly/2cEpSMx. ■

Historical Exposé on Sugar Industry Funding Research has Relevant Lessons for Current IRBs

Conflict of interest policies much stronger, but vigilance warranted

A recently published study[1] linking secret funding by the sugar industry to bias in research studies published in the 1960s is less a historical curiosity than a clear warning to IRBs to remain vigilant about conflicts of interest.

"The purpose of IRBs is to protect patients and human subjects in research. Industry-sponsored research deserves more than the usual level of scrutiny to ensure that subjects are not at risk," says **Marion Nestle**, PhD, MPH, an author and professor in the department of nutrition and food studies at New York University in New York City.

Though the influence of industry funding on research outcomes has long been a subject of concern for IRBs, it is exceedingly rare to find such a "smoking gun" linking an undisclosed funding source to skewed research outcomes, says Nestle, who wrote a commentary accompanying the study. *(For more information, see related story on page 126.)*

"I think the public and policymakers need to view any industry-funded research that could be averse to the industry's bottom line with extreme skepticism," says **Stanton A. Glantz**, PhD, co-author of the study and professor at the Phillip R. Lee Institute for Health Policy Studies at the University of California, San Francisco. "There is a difference between work that is funded by the NIH or the American Heart Association. It is being supported by organizations that have a fundamental interest in getting the answer correct. [Industry] has a fundamental interest in maximizing profits."

Glantz and colleagues analyzed historical documents and reports by the Sugar Research Foundation (SRF) — now the Sugar Association — related to publication of articles in the 1960s in the *New England Journal of Medicine*. Like other medical journals at the time, the prestigious publication did not have stringent disclosure and conflict of interest policies. Though full disclosure is now a given for research enterprises and journal publications, IRBs should not become complacent just because it is more difficult for industry to secretly fund research under current requirements.

"I THINK THE PUBLIC AND POLICYMAKERS NEED TO VIEW ANY INDUSTRY-FUNDED RESEARCH THAT COULD BE AVERSE TO THE INDUSTRY'S BOTTOM LINE WITH EXTREME SKEPTICISM."

"It's harder now, but the whole disclosure issue really relies on people to be honest," Glantz says. "Medical journals today almost uniformly require disclosure of who funded the study, and many require disclosure of any active involvement the funding agency had in preparing in the manuscript. Some journals even require disclosure of any other interests you have that could be viewed as a conflict."

Pay for Play?

The investigators essentially found that the SRF paid researchers at Harvard to do a literature review that ultimately minimized the role of sugar as a risk factor for coronary heart disease (CHD). By all appearances, the study fulfilled the expectations of a predetermined conclusion. For example, in correspondence with the SRF, the Harvard researchers explained a delay in completing the review paper due to the need to "rework a section in rebuttal" every time research raised concerns about sugar consumption and public health, the authors report.

"The SRF set the review's objective, contributed articles for inclusion, and received drafts," the authors found. "The SRF's funding and role was not disclosed. Together with other recent analyses of sugar industry documents, our findings suggest the industry-sponsored a research program in the 1960s and 1970s that successfully cast doubt about the hazards of sucrose while promoting fat as the dietary culprit in CHD."

No Rules

In response to the investigative report, the Sugar Association posted

a comment on its website that stated in part, "We acknowledge that the Sugar Research Foundation should have exercised greater transparency in all of its research activities, however, when the studies in question were published, funding disclosures and transparency standards were not the norm they are today. Beyond this, it is challenging for us to comment on events that allegedly occurred 60 years ago, and on documents we have never seen. Generally speaking, it is not only unfortunate but a disservice that industry-funded research is branded as tainted. What is often missing from the dialogue is that industry-funded research has been informative in addressing key issues."

Glantz found the defense somewhat disingenuous, as practices like that of the sugar group in the 1960s ultimately led to the disclosure reforms in place today.

"What they did for a journal paper in the '60s was a clear violation of current ethics," he says. "The reason we have heard comments like, 'well, they didn't break the rules' is because there weren't any rules. The reason we now have all of these rules is because back in the '60s there was this expectation that forthright, honest people would disclose this information. So while they didn't break any rules, the reason we have the rules that they didn't break is that there were a lot of people misbehaving the way they did."

The Sugar Association accused the researchers of trying to "reframe historical occurrences to conveniently align with the currently trending anti-sugar narrative, particularly when the last several decades of research have concluded that sugar does not have a unique role in heart disease."

The investigators concede in the paper that "the contribution of dietary sugars to CHD is still debated," but also note that the sugar industry "steadfastly denies that there is a relationship between added sugar consumption" and heart disease.

"All you have to do is look at the Sugar Association's website to see how active they are," says **Cristin E. Kearns**, DDS, MBA, the lead author of the paper and a professor at the Phillip R. Lee Institute for Health Policy Studies. "They submit comments on anything to do with sugar and health going on at the federal level. So they are actively out trying to shape the debates."

The historical findings about undisclosed industry funding of research in the 1960s could well apply to other groups as well.

"The sugar industry was not the only active trade group back during that time," Kearns says. "That's one of the limitations of our study — we only looked at this one. Certainly, other food industries, including the corn and wheat industries, all had an interest in this debate going back that far. It's important to look at those industries as well."

The trend of funding favorable research is certainly not limited to the food industry, as similar patterns are seen for a wide variety of groups trying to protect and expand their market share for a particular commodity, Glantz adds.

"It's beyond dispute," he says. "The petrol, chemical, and coal industries do it around global warming. Pharma often tries to shade the results of the work they fund. It is a broad problem. That's why you see this consistent pattern in areas related to public health and public policy. Businesses support and promote work that supports their political, economic, and ideological positons, which may or may not have anything to do with public health." ■

REFERENCES

1. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents [published online September 12, 2016]. *JAMA Intern Med* doi:10.1001/jamainternmed.2016.5394.

Big Sugar's Smoking Gun

'Science is not supposed to work this way'

Though the influence of industry funding on research outcomes has long been a subject of concern for IRBs, it is unusual to find a "smoking gun" strongly linking an undisclosed funding source to biased research outcomes, says **Marion Nestle**, PhD, MPH, an author and professor in the department of nutrition and food studies at New York University in New York City.

A recently published study,[1] which found that the sugar lobby secretly funded studies in the 1960s that apparently "cherry picked" data to downplay the role of sugar in coronary heart disease (CHD), has the documentation and granular detail to meet the smoking gun test, she noted in a commentary[2] accompanying the study.

"From a deep dive into archival documents from the 1950s and 1960s, they have produced compelling evidence that a sugar trade association not only paid for, but also initiated and influenced, research expressly to exonerate sugar as a major risk factor for CHD," Nestle wrote in the commentary. "Although studies at that time indicated a relationship between high-sugar diets and CHD risk, the Sugar Association preferred scientists and policymakers to focus on the role of dietary fat and cholesterol. The association paid the equivalent of more than $48,000 in today's dollars to three nutrition professors — at Harvard, no less — to publish a research review that would refute evidence linking sugars to CHD."

The historical investigation documents the influence of the industry on the results of a subsequent study, suggesting the authors at the time knew what they were being paid to produce.

"The investigators knew what the funder expected, and produced it," Nestle wrote. "Whether they did this deliberately, unconsciously, or because they genuinely believed saturated fat to be the greater threat is unknown. But science is not supposed to work this way. The documents make this review seem more about public relations than science."

The study serves as more than a historical cautionary tale, as Nestle cites current efforts of industry to influence research findings as reported by journalists.[3,4] *IRB Advisor* asked Nestle to discuss the issue, and her answers are as follows:

IRB Advisor: You mention that industry attempts to influence research are not ancient industry, but are indeed ongoing. Do more rigorous requirements for disclosure for conflict of interest make it much less likely that something as blatant as this historical example could occur today?

Nestle: The disclosure requirements help, but there is considerable evidence that they are not always adhered to. In any case, disclosure is necessary but not sufficient for addressing real conflicts of interest, particularly because the influence of industry funding on investigators is usually unconscious, unintentional, and unrecognized.

IRB Advisor: You have certainly written a lot of books on the food industry. Were you surprised at the degree of sophistication the sugar industry seems to have put into spinning the research findings in the 1960s?

"SCIENCE IS NOT SUPPOSED TO WORK THIS WAY. THE DOCUMENTS MAKE THIS REVIEW SEEM MORE ABOUT PUBLIC RELATIONS THAN SCIENCE."

Nestle: No. The big surprise was the documentation. That is hard to come by. We suspect that corporations funding research do so for a purpose and want to ensure that their purpose is achieved, but finding documentation for corporate involvement is rare. We now know from recent examples in which reporters obtained emails that funding sources attempt to manipulate investigators, and the example in 1967 suggests that these kinds of relationships have gone on for a long time.

IRB Advisor: There has been some debate about the influence of big pharma on research and actually some pushback that industry has been unfairly vilified. Do you think there is just too much conflict of interest for an industry to be involved in research that could translate to lost profits?

Nestle: I have just reviewed the literature on drug industry funding of research and can say that this topic has been studied extensively for more than 40 years. Drug industry-funded research comes out with results that favor the benefits and lack of harm of the sponsor's patented, branded drug. The purposes and lack of controls in that research have also been well-documented. Experts concerned about the conflicts of interest in this research — and the potential harm to patients — believe that this research is unethical and deserves intense criticism. ■

REFERENCES

1. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents [published online September 12, 2016]. *JAMA Intern Med* doi:10.1001/jamainternmed.2016.5394.
2. Nestle, M. Food Industry Funding of Nutrition Research: The Relevance of History for Current Debates: Invited Commentary. *JAMA Intern Med* September 12, 2016 doi:10.1001/jamainternmed.2016.5400.
3. O'Connor A. Coca-Cola funds scientists who shift blame for obesity away from bad diets. *New York Times*, August 9, 2015. http://nyti.ms/1f2lI1J.
4. Choi CAP. Exclusive: how candy makers shape nutrition science. Associated Press, *The Big Story*, June 2, 2016. http://apne.ws/1UhbJmR.

BEAM Program Provides a Buddy Mentoring Approach

Outreach to really young talent

Many IRB leaders struggle with attracting young professionals to the human research protection field, but few would dream of heading to elementary schools to groom the next generation of IRB members or experts.

Yet that's exactly the approach taken by **Armida Ayala**, PHD, MHA, director of the Kaiser Permanente Southern California IRB in Pasadena.

Ayala started a mentoring program at the IRB in 2013 called the Bridge Expose Advance Mentoring Program (BEAM). It was designed to select youth and young adults for mentoring in the enterprise of advancing human research ethics. The program has trained more than 25 young people and resulted in two people becoming members of the IRB, three hired as employees, and 14 still being mentored.

"For example, I work with our internal outreach program, and I had been mentoring and evaluating young girls from ages 10 years old," Ayala says. "Some have been participating in research, so we picked some from that pool and trained one to be a board member."

A young woman who now is an IRB member had begun as a participant in a study. She graduated from the University of California, Los Angeles (UCLA) while still a teenager. "We're looking for talent, so we follow these kids since they were little," Ayala says. "We have a program of mothers and daughters learning together, and we meet them at age 10 and follow them until they're 23."

BEAM involves mentors from the IRB, who are paired with the young prospects for a six-month period. It is intensive, with the chief purpose of placing young people in research protection jobs, Ayala says.

"We can be mentoring them for a while, as we did with a young woman I recently recruited," Ayala says. "She just got accepted at the university and is getting a master's degree in social sciences."

BEAM IS ABOUT IDENTIFYING YOUNG MENTEES' CHARACTER AND WORKING WITH THEM ON THE SKILLS NECESSARY TO DISCUSS ETHICAL ISSUES AND TO ASK QUESTIONS.

Ayala asked the woman if she would be interested in being trained to be an IRB member, and she agreed. "She's a featured poster child for that strategy — she's done a tremendous job."

Another strategy is to seek out talented young people at local universities and invite them to learn more about the IRB. "We focus on activities like leadership training and career guidance," Ayala says.

Young people mentored through BEAM sometimes are asked to use an app at via.org where they can take a survey about themselves to learn their top five strengths, she says.

"What the app does is give you a free survey to identify your strengths with exercises about doing the right thing," Ayala says.

BEAM has leadership and character training specifically designed for the program. For instance, participants receive books about research ethics, including *The Immortal Life of Henrietta Lacks*, written by Rebecca Skloot.

"We give them these things to inspire them and to show how leaders have made ethical decisions in the past," Ayala says. "Then we work on character development activities and give them training on how to handle various situations."

For example, there is a character strength exercise with three-to-five-minute discussions. The idea is to encourage people to speak up when they have a question or comment. They can practice talking, using a speaker cone as a visual aid, and they also can go to their mentors for guidance, she says.

BEAM is about identifying young mentees' character and working with them on the skills necessary to discuss ethical issues and to ask questions, she says.

It's necessary for IRBs to do what they can to recruit and mentor younger IRB professionals, as many IRB directors and leaders will retire in coming years, Ayala says.

"I want to bring in young people and train them because they're the next generation," she says. ■

Establishing Trust in Partnerships is Key to Centralized IRB Review

A central IRB model can be efficient

As IRBs begin to increase their reliance on central IRBs or form relationships as the IRB of record, the most important action they can take is to build close relationships and trust with research organizations and researchers, experts say.

"The key is close relationships with the people you're working with and establishing a trusting relationship with your research staff," says **Cherie Bilbie**, MS, CCRP, CIP, director of the human research protection program at Hartford HealthCare in Hartford, CT.

Having templates in place and being well-organized can help build trust, she notes.

"For instance, we have some local partners in Connecticut," she says.

"We have a template agreement in place, and within that written agreement are steps built into who is responsible for what," Bilbie says. "We have expectations on each side of the fence outlined so everyone knows their part."

A large hospital system, Hartford has formed partnerships with a number of smaller healthcare institutions throughout Connecticut. The partnerships resulted in Hartford HealthCare taking on primary IRB review duties, bringing in the smaller hospitals' IRB staff when possible, Bilbie says.

"Originally, there were four functioning IRBs within a health system," she says. "But it made sense for us to transfer oversight and take over that function for them."

The health system has a tertiary care teaching hospital, four community acute care hospitals, two regional behavioral health centers, a home care system, and other healthcare organizations. When hospitals were brought into the health system, the organization established a centralized IRB, applying one set of standard operating procedures and decreasing duplicative reviews.

One of the challenges involves electronic records and connecting other organizations to that record.

> "THE KEY IS CLOSE RELATIONSHIPS WITH THE PEOPLE YOU'RE WORKING WITH AND ESTABLISHING A TRUSTING RELATIONSHIP WITH YOUR RESEARCH STAFF."

This works well when a health system brings hospitals on board. For instance, the Hartford HealthCare IRB has access to all research records in which its institutions are involved, Bilbie notes.

"It works for us because it allows the project to enter our tracking system," Bilbie says. "What our study teams do is rely on our electronic IRB system as a document repository, and it gives us access to all of the approved documents that we're accepting, and it allows the study team to access those documents."

The IRB can track financial conflicts of interest, training requirements, and other items to be monitored.

"We won't accept the review until we check it to make sure everybody is up to date on their requirements," Bilbie says. "Our internal system allows us to have a gatekeeper."

Even when a health system's IRB is relying on another institution, monitoring should still take place, she notes.

"You still have an element of responsibility for what's going on in your shop, so even if the study team is not submitting progress reports to your office, you need to do your own post-approval monitoring," Bilbie says. "We have one full-time person to do post-approval monitoring."

Hartford HealthCare has set up a System Central IRB with its own federalwide assurance to serve as a central IRB for individual committees from three partner institutions. "We put in place an authorization agreement with each of these hospitals," she says. "It has worked smoothly."

The central IRB format has made the IRB work much more efficiently, eliminating about 100 duplicative reviews so far, Bilbie says.

"We had some learning curves because we were bringing on the electronic system at the same time," she adds. "But we did a lot of volume assessment before we made the move, so we knew what we would be taking on if we needed to make adjustments." ■

IRBs Should Ensure that Proposed Studies Include Whether Research is 'Reproducible'

Surprising amount of past research cannot be replicated

An emerging body of research reveals that past studies — some of which may form the basis of current policies and recommendations — cannot be replicated by investigators today. This lack of "reproducible" research may undermine current studies based on prior findings, particularly as investigators look at the risk-benefit ratio for people participating in a clinical trial, says **Barbara K. Redman**, PhD, MBE, of the division of medical ethics at New York University Langone Medical Center.

"Having served on an IRB myself for three years, if you are looking at the risk-benefit ratio, you are assuming that the studies on which they are basing it are valid," she says. "Now we are finding they might not be. A percentage of them might not be, and that might vary by field. I think this strains IRBs in trying to fulfill their requirements."

The lead author of a recently published paper[1] on the issue, Redman cites studies that estimate anywhere from 22% to almost half of published results in biomedical research actually can be validated.[2,3]

"[Reproducibility] varies across fields, but let me just stop and say when scientists are working at the edge of new innovations or new fields, frequently things are not reproducible," she says. "That is just part of the process, as you might well imagine, and it is a normal process to some extent to have non-reproducibility."

Thus, it is more of an issue of degree than kind, as the large proportion of studies that lack reproducibility has underscored the scale of the problem even to those who first questioned such findings.

"It is contested, though I don't see as many people contesting it now," Redman says. "I think they are shocked, to tell you the truth. This particularly has been a political issue because pharmaceutical companies depend on academic and other research to get a basic idea of [product efficacy], but when [subsequent researchers] go back and try to reproduce those studies, they can't."

IRBs should "require that research protocols contain explicit probability statements about likely risks and benefits, based on a comprehensive review of prior studies and meta-analyses addressing reproducibility … Such estimates are essential for IRB judgment about minimizing risk, for determining an appropriate risk-benefit ratio for presentation as a part of the informed consent process, and in seeking to facilitate the informed choices of potential research subjects," Redman wrote in the paper.

For their part, investigators should include assessments of past studies in terms of reproducibility and perceived risk. As such requirements are hardwired into IRB and investigator protocols and policies, more research should become reproducible, she notes. As it stands, unreproducible research may pose a risk to research participants, particularly those from vulnerable populations.

As defined in the paper, reproducibility is an "umbrella term" that includes whether an original study can be repeated and yield the same results. Other nuances to the concept are "replicability" and "validation," but all terms generally reflect the enduring quality of data to provide a jumping-off point for subsequent research.

"We are trying to dig into all of the reasons that something might not be reproducible, and those factors vary dramatically," Redman says.

Among the common reasons cited are unrecognized study variables, poor study design, inadequate documentation of findings, and overstatement of the benefits of the research.

"Lack of reproducibility by independent investigators may signal that research misconduct took place and that, as a result of fraudulent data, current research participants and subsequent patients could be harmed if research and medical practices are based on such data," Redman wrote.

In addition to ethical issues, there are now regulatory incentives to address reproducibility, she says.

Though the study was published before it was issued, recent final guidelines by the Department of Health and Human Services on clinical trials emphasize that, "the public availability of results information helps investigators design trials and IRBs review proposed trials, by allowing them to weigh the proposed study's risks and benefits against a more complete evidence base than is currently available through the scientific literature."[4]

Redman sees that as a strong endorsement of ensuring reproducibility in clinical trials, though she concedes IRBs may not currently be geared up to

address the issue.

"That is the crux of it," Redman says. "These regulations will go into effect in January 2017 and be enforced three months thereafter. I think there is no question that it will be a catch-up situation for IRBs. The first thing to do is to be sure that all trials are registered. [Then] an IRB could look on ClinicalTrials.gov for a particular kind of proposal, see all of the studies that have been done, and figure out whether they have been reproduced. Some people say this is more than an IRB ought to do. Our response is that it is central to their ethical role, which is to control harms and to figure out if the risk-benefit ratio is OK."

Bottom-line protections for research subjects essentially assume that a new study is based on valid, reproducible research — which, unfortunately, may not be the case. As the issue is addressed and rectified, IRBs must make good faith efforts to do what they can to seek evidence of reproducibility and point out when it is lacking.

"We understand that IRBs may have difficulty fulfilling this right now, but they need to work on it," Redman says. ■

REFERENCES

1. Redman BK, Caplan AL. Limited Reproducibility of Research Findings: Implications for the Welfare of Research Participants and Considerations for Institutional Review Boards. *IRB: Ethics & Human Research* 2016 July-August 2016;8-10.
2. Ioannidis J. How not to be wrong. *New Scientist* 2014;22:32-33.
3. Ioannidis J. Improving validation practices in "omics" research. *Science* 2011;334:1230-1232.
4. HHS. 42 CFR Part 11. Clinical Trials Registration and Results Information Submission; Final Rule. *Fed Reg* 2016; 81:(183):64,982-65,157.

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. 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. **Which of the following information is not included in the final rule of the Clinical Trials Registry and Results Information Submission?**

   A. Provide a checklist of which elements are subject to the regulations and who is responsible for submitting the required information.
   B. Expand the scope of trials for which summary information must be submitted to include drug, biological, and device products that have not yet been approved, licensed, or cleared by the FDA.
   C. Monitor compliance at all levels of clinical trial work, including detailed reports of investigator infractions.
   D. Require additional registration and summary information data elements to be submitted to ClinicalTrials.gov, including rates, ethnicity, and full protocol.

2. **Which of the following is a penalty for researchers or organizations that do not comply with the NIH's final rule that requires research results be submitted to ClinicalTrials.gov?**

   A. NIH will publicly post notices of noncompliance in the data bank.
   B. NIH will require report forms under certain grants to include a certification that required registration and results information submission are complete.
   C. Federal agencies will need to verify compliance before future funding or continuation of funding.
   D. All of the above.

3. **The authors of a study on the health effects of sugar in the 1960s broke established requirements for disclosure of conflict of interest that were already in place at the *New England Journal of Medicine*.**

   A. True
   B. False

4. **According to Barbara K. Redman, PhD, MBE, IRBs should require that research protocols contain explicit probability statements about likely risks and benefits, based on:**

   A. approval and registration in the new HHS reproducibility module.
   B. a statistically significant survey of experts in the field.
   C. a comprehensive review of prior studies.
   D. good faith estimates by the researchers.

IRB ADVISOR

United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
IRB Advisor	1 5 3 5 _ 2 0 6 4	10/1/16
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$419.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta
Fulton County, GA 30326-1180

Contact Person: Regenia Sims
Telephone: 404-262-5473

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
AHC Media LLC, David Fournier, President and CEO
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

Editor *(Name and complete mailing address)*
Jill Drachenberg, same as above

Managing Editor *(Name and complete mailing address)*
Dana Spector, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180
David Fournier	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180
~~Bethany Schilling~~	~~950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180~~
Lone Peak Capital Group, LLC	79 West Paces Ferry Road, Suite 200-A, Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☒ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526,** October 1999 *(See Instructions on Reverse)*

13. Publication Title: IRB Advisor			14. Issue Date for Circulation Data Below: September 2016	
15.	Extent and Nature of Circulation		Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a.	Total Number of Copies *(Net press run)*		258	236
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	159	156
	(2)	Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	28	2
	(4)	Other Classes Mailed Through the USPS	43	52
c.	Total Paid and/or Requested Circulation *(Sum of 15b. (1), (2),(3),and (4))*		230	210
d. Free Distribution by Mail *(Samples, complimentary, and other free)*	(1)	Outside-County as Stated on Form 3541	11	11
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e.	Free Distribution Outside the Mail *(Carriers or other means)*		5	5
f.	Total Free Distribution *(Sum of 15d. and 15e.)*		16	16
g.	Total Distribution *(Sum of 15c. and 15f)*		246	226
h.	Copies not Distributed		12	10
i.	Total *(Sum of 15g. and h.)*		258	236
j.	Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*		93%	93%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2016 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: *David R. Fournier* Publisher & CEO — Date: 09/12/2016

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or, if the publication is not published during October, the first issue printed after October.
6. In item 16, indicate the date of the issue in which this Statement of Ownership will be published.
7. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of Periodicals authorization.

PS Form **3526,** October 1999 *(Reverse)*