IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

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INSIDE

IRBs Have Less Than a Year to Prepare for NIH Policy

To be or not to be an IRB of record

By Melinda Young, Editor

Ready or not, IRBs across the United States have only 10 months remaining to change the way they handle reviews of multisite research that is funded by the National Institutes of Health (NIH).

IRBs will need to become either a relying IRB or a single IRB of record for those nonexempt human subjects research protocols after May 25, 2017, according to the *Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research*, published June 21, 2016.

NIH received 167 comments on its draft proposal of Dec. 3, 2014, including many with concerns about how this would be a complicated and difficult-to-implement unfunded mandate. Some commenters suggested NIH continue with a voluntary single IRB model with incentives, or base the use of a single IRB model on evidence-based practice.

"There's a lot of emphasis these days on evidence-based medicine, and we forget the fact that the phrase really means something," says **Alexander M. Capron**, JD, former board chair of the Public Responsibility in Medicine and Research (PRIM&R) and professor at the University of Southern California in Los Angeles. Last year, Capron had written a comment to NIH on behalf of PRIM&R. His letter suggested NIH not pursue the single IRB policy as it was described in the draft policy, published in December 2014.

> "THERE'S A LOT OF EMPHASIS THESE DAYS ON EVIDENCE-BASED MEDICINE, AND WE FORGET THE FACT THAT THE PHRASE REALLY MEANS SOMETHING."

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NIH has made sweeping statements about its single IRB policy and its benefits to research organizations, but there are no data backing up those claims, Capron says.

"What we have are anecdotes and impressions about this change, but we don't have data," he says.

There's also the possibility that this change will result in a large growth of commercial IRBs, consolidation, and closing of smaller, institutional IRBs, Capron says.

It's even possible that some small research sites will stop being research sites because they might not feel equipped to make judgments about IRB of record agreements and they're concerned about their own liability under a relying IRB arrangement, he adds. "It's not just they get out of the IRB business, but they get out of the research business, and if that happens, it could change the extent to which patients, who are seen at those institutions, come into the process of developing and testing drugs and devices."

NIH's final policy on requiring a single IRB of record answered a few commenter concerns, but left others in limbo.

"One of my biggest remaining concerns is this model they've implemented takes you down the path of using 20, 50, potentially 100 different central IRBs," says **David L. Wynes**, PhD, vice president for research administration at Emory University in Atlanta.

"It's simply the logistics," Wynes says. "What this means is we have to have a mechanism for tracking these 20 to 100 IRBs."

NIH's new policy states that its goal is to "enhance and streamline the IRB review process in the context of multisite research so that research can proceed as effectively and expeditiously as possible."

The final policy also addresses IRBs' and other commenters' concerns about a burdensome implementation, saying that any challenges associated with implementation will be short-lived. "Once the transition to the new way of operating is made, the benefits of widespread use of sIRBs [selected IRBs of record] will outweigh any costs and, ultimately, reduce burdens to the research process," the NIH final policy says.

"I've been a proponent of using a central IRB for many years, but my feeling is you should use as few as possible because you have to set up these complex relationships," Wynes says. "And NIH policy is set on getting approval and not on other parts of the relationship, which are extremely complicated and involved."

IRBs and institutions will have to review their operational structure and the potential costs of becoming an IRB of record before deciding how they should proceed, notes **Karen Hansen**, director of the institutional review office of the Fred Hutchinson Cancer Center in Seattle.

Fred Hutchinson has established many IRB-of-record agreements and currently has more than 100 sites that rely on the organization for IRB reviews, but getting to this point has taken decades, Hansen says. *(See story on preparing for single IRB of record change, page 90.)*

"Institutions have to make a decision on how they want to approach the potential of increasing demands for a single IRB in multisite trials, as required by the new policies," Hansen says. "I think people have to look at how many multisite trials they currently engage in and how many in the future they

might be engaging in."

'Significant Investment with Unknown Payoff'

Use of single IRBs of record can be effective, but this will depend on whether the IRB of record is well-prepared for its role, notes **David Borasky**, MPH, CIP, vice president of quality management at Copernicus Group, a WIRB-Copernicus Group (WCG) company in Princeton, NJ.

In comments submitted to NIH after the draft policy was published, WCG raised concern about the lack of a description of characteristics necessary for a central IRB. In the final policy, NIH committed to issuing guidance by May 2017, which may include how single IRBs are selected, Borasky says.

"We're hoping the guidance will reflect our concerns and the concerns of other commenters," he says.

IRBs that plan to serve as the IRB of record will need to prepare for this role through an investment in resources, new policies and procedures, and other changes, Borasky suggests.

"It'll be a significant investment with an unknown payoff," he adds.

IRBs of record will have both direct and indirect costs associated with this role, and there will need to be a mechanism for recouping that expense, Wynes says.

"If you are charging for these additional costs, you will have to document it," he adds. "Somebody has to pay the direct cost, and there has to be a mechanism for charging this cost to the grant."

One concern some commenters, including Wynes, had after the draft policy was published was that it did not clarify which multisite studies would need an IRB of record. The final policy answered this question by saying that only multisite studies in which more than one institution was following the same protocol would need the central IRB, Wynes says.

"If two places are working on a grant together, they could be doing completely different things," he explains. "And so NIH changed that in the final policy."

Twenty-three Qualifying Words

Another concern NIH has already attempted to address involves the development of a template for IRB reliance agreements, Capron says.

NIH recently published a 19-page template with a long title: *National Center for Advancing Translational Sciences Streamlined Multisite Accelerated Resources for Trials Institutional Review Board (SMART IRB) Reliance Master Common Reciprocal Institutional Review Board Authorization Agreement*. The template is available online at http://bit.ly/29GXyeA.

NIH's New IRB of Record Policy Guidance Coming Soon

Here's what is left to be addressed

The *Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* acknowledges that additional guidance is needed and will be issued before May 25, 2017, when the policy becomes effective.

The following are some of the topics NIH says will be addressed in future guidance:

- how costs associated with single IRBs may be charged as direct vs. indirect costs,
- considerations in the selection of the sIRB,
- the content of the single IRB plan that must be submitted with applications and proposals,
- process for applicants/offerors to submit a request for an exception and process for NIH review of the request for exception,
- roles and responsibilities of the single IRB and participating sites,
- model authorization agreement that lays out the roles and responsibilities of each signatory,
- models for gathering and evaluating information from all the reliant sites about community attitudes and the acceptability of proposed research, and
- a model communication plan that identifies when and which documents are to be completed and shared with those involved so each may fulfill their responsibilities. ■

While this is a good-faith effort on NIH's behalf, it demonstrates the complexities of this change to a single IRB of record, Capron notes.

"That agreement has a name with 23 qualifying words," he says. "So institutions entering into an agreement like this are going to be faced with a lot to consider, including a lot of issues about responsibility between the reviewing IRB and the IRB that cedes its authority to that IRB."

For institutional IRBs that would like to see central IRB models could look at what many independent IRBs already are doing for many industry studies. *(See story on specific policy concerns, below.)*

"By and large, more and more institutions for industry-sponsored research have decided it's in their best interest as good research partners to allow reliance on a single IRB," Borasky says.

"We work hard with institutions to include the specific language they want in the informed consent," he adds.

That's one example of how an IRB of record must communicate with the relying institutions. The central IRB also should know all of its partners' state laws and requirements, Borasky adds.

The change might result in more institutions relying on independent IRBs.

As NIH releases guidance to help IRBs adjust to this change, the human research protections world will learn more about what the change will mean for the industry as well as for individual IRBs and institutions. But for now, there are more questions than answers, some say.

"This is flying in the fog without instruments, as far as I am concerned," Capron says.

Editor's note: The Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research is available at: http://bit.ly/29xH0Yw. ■

Will NIH Answer Concerns from IRBs, Others?

Many questions remain

The NIH's nearly 6,000-word final policy requiring the use of a single IRB for NIH-funded, multisite research leaves IRBs and research organizations with many unanswered questions, according to the comments the organization received since the Dec. 3, 2014, draft policy was published.

Some of the remaining questions include the following:

• Will there be criteria or a template for sites serving as single IRB of record?

NIH could help research institutions with this policy change by providing a "set of template documents that specify criteria for IRBs to participate in the reliance program," wrote **Elliott M. Antman**, MD, FAHA, immediate past president of the American Heart Association, in a comment dated Jan. 20, 2015.

Antman refers to a sample template on the Clinical and Translational Science Awards (CTSA) program site at http://bit.ly/29xNGAt. The Master Reciprocal Common IRB Reliance Agreement (MRA) contains explanations for the following three elements:

- common language and regulatory interpretation, including "uncheck the box" on the Federalwide Assurance (FWA); harmonization of subject injury language; insurance coverage, and privacy compliance requirements,

- common processes and consistent approach, including identifying the reviewing IRB; defining chain of responsibility and communication; quality assurance mechanisms; aligning certification and continuing education requirements; controlling study activation; unanticipated problems, serious adverse events, and deviations; and requesting and agreeing to IRB reliance, and

- common standard operating procedures (SOPs), including reliance agreement policy; audit SOP; SOP for reporting serious adverse events and unanticipated problems; SOP for data protection and incident responses; SOP for managing conflicts of interest, and SOP for training.

The Society or Clinical Research Sites (SCRS) also called for NIH to establish criteria for evaluation of central IRBs when selecting a single IRB for a specific multicenter clinical trial.

According to SCRS' comment, dated Jan. 29, 2015, NIH should do following:

- investigate compliance history of the single IRB,

- review qualifications of board members, including therapeutic expertise,

- request references and review organization's history of working with

institutions and/or sponsors,

- evaluate IRB's ability to step seamlessly into the process (including state laws and local considerations),

- determine scope and associated costs of services provided,

- establish communication process between institution, investigator, and IRB, and

- assess operational processes (frequency of board meetings, document management, capacity, turnaround time, quality assurance processes), and inquire about technology used by the central IRB and compatibility with existing systems.

• Will NIH provide templates and details for addressing local contextual issues?

As institutional comments noted, there is need for additional details and template forms for information about local contextual issues, including investigator competence, site suitability, state laws, and community standards. "In addition, provide details about when ad hoc members or consultants would be necessary to review local contextual issues," wrote several IRB and research officials at Tufts University and Tufts Medical Center of Boston, in a comment letter dated Jan. 14, 2015.

• How will research institutions and IRBs handle the differences between institutions' electronic data systems and technologies?

Many IRB software systems are part of larger human research protection programs, including investigational drug pharmacy, biosafety program, radiation safety, and other offices, notes **David L. Wynes**, PhD, vice president for research administration at Emory University in Atlanta.

"Every time an external central IRB is used, the automated notification and information-sharing system is disrupted," Wynes wrote in a comment letter dated Jan. 21, 2015.

"This not only increases the risk of noncompliance with institutional, regulatory, and sponsor requirement but also forces investigators to enter information into independent systems for these other units," he wrote. "These systems can be adjusted via programming special workflows for a limited number of central or commercial IRBs and we have implemented these workflows to rely on WIRB and NCI's [National Cancer Institute's] CIRB, for example."

"FROM LOOKING AT THE COMMENTS ON THE DRAFT POLICY, INSTITUTIONS ARE WELL AWARE THIS WILL BE A VERY CHALLENGING POLICY FOR THEM TO IMPLEMENT IF THEY WANT TO BE A SINGLE IRB."

But it's not feasible to program unique workflows for a large number of new central IRBs, and this issue is not resolved in NIH's final policy, Wynes says of the policy published June 21, 2016.

"The NIH policy is set on getting approval of protocols and not on the other parts of the relationship, which are extremely complicated and involved," he says. "I think they have underestimated and not given appropriate weight to the importance of these other issues and the complexities that come with doing this with 20 to 100 IRBs; if I can do it with five IRBs, great, but that's not the model that's been put forward."

• How will NIH ensure central IRBs can effectively report noncompliance and unanticipated problems?

IRBs might find it challenging to manage multisite research, and this raises questions about how well they'll handle noncompliance and unanticipated problems reporting, according to a comment dated Jan. 29, 2015, by the WIRB-Copernicus Group (WCG).

"Administrative processes must be flexible enough to accommodate the unique needs of each institution," according to the comment. "For example, consent forms and other study materials will also need to reflect local differences, including site-specific legal and institutional requirements."

NIH's final policy doesn't address these and other questions IRBs and research organizations have, says **David Borasky**, MPH, CIP, vice president of quality management at Copernicus Group, a WCG company in Princeton, NJ.

"It will be interesting to see what it looks like when NIH's guidance comes out," Borasky says. "From looking at the comments on the draft policy, institutions are well aware this will be a very challenging policy for them to implement if they want to be a single IRB."

Even with nearly a year to get ready, it will be challenging for most IRBs to prepare. "In my own opinion, I don't think a guidance document will solve these issues, although it will be nice if NIH puts out a list of recommendations for a single IRB," Borasky says. ■

Smoothing the Path for an IRB of Record

Start with a conversation

As increasing numbers of IRBs are entering into central IRB agreements, there are steps they can take to better prepare, including building trust with other research organizations and IRBs, experts say.

"It's about having some good conversations about processes," says **Karen Hansen**, director of the institutional review office at Fred Hutchinson Cancer Center in Seattle.

Fred Hutchinson has more than 100 sites that rely on the research organization for IRB review of one or more protocols. The organization has formed these types of cooperative agreements since the 1980s, Hansen says.

"There have been many investigators who ask our IRB to be the IRB of record," Hansen says. "I require the PI [principal investigator] to talk with the PI at the other organization, and that PI needs to talk with his IRB office before I enter into a conversation with the other IRB."

Those initial conversations are a first step to creating a new IRB reliance agreement.

"I let other organizations know there is no pressure on our IRB office's part for them to rely on us," Hansen says. "I try to approach it with no pressure on our part, saying, 'I'm here to talk with you about it. Here's how our process works. Just let me know what you decide.'"

This method appears to work: "We've received good feedback from people as to their receptivity to it," Hansen says.

If an organization is relying on the Fred Hutchinson IRB, a local context reviewer is identified from the relying organization to provide input when the protocol is reviewed. He or she completes a local context reviewer form that describes confidentiality issues and confirms that there are no conflicts of interest with the protocol they are reviewing. The form also has questions about subject selection, the consent process, privacy and confidentiality, and other considerations, including the following:

> "THE PROTOCOL AND APPLICATION THEY HAVE IS BUILT UNIQUELY FOR THEM. THE IRB APPLICATION AND CONSENT IS CUSTOMIZED TO ACCOMMODATE THEIR MODEL CONSENT, WHICH IS USED AT THE OTHER ORGANIZATION."

- Do you find the selection and recruitment methods acceptable in the context of your local area?
- Is the participant compensation consistent with local laws and your institution's policies?
- Are the provisions for privacy and confidentiality consistent with local laws and your institution's policies?
- Have there been any recent events in the local community that may have created positive/negative attitudes toward human subjects research?
- Given the nature of this particular research study, are there any additional factors (community attitudes, ethnic diversity, language, etc.) that may contribute to the acceptability of this research in your area?

"The conversation with the other organization includes discussing how their IRB director or chair or another committee member can serve as a local context research reviewer," Hansen says. "We ask someone from that organization to evaluate the protocol from their organization's perspective, and that person is identified as being the local context reviewer."

Local context questions include subject selection, recruitment process, and whether these processes comply with federal, state, and local laws and regulations, Hansen says.

"Are they acceptable in the context of your area?" she explains. "We ask about privacy and confidentiality, and they complete the four-page form, sign it, and turn it in to be uploaded for our IRB to review."

To make it easier for relying organizations to use Fred Hutchinson's protocol application, the process includes reminders and prompts. "We have some state laws related to research and human subjects, so we have those built into our policies," Hansen says. "Every state might have different laws and requirements, and we really value our local research reviewer's input."

In some cases, a coordinating

center will turn in an application for a site outside of the state of Washington, and study coordinators build unique consents that accommodate the consent documents that use that application, she adds.

"The protocol and application they have is built uniquely for them," she says. "The IRB application and consent is customized to accommodate their model consent, which is used at the other organization."

The organizations that rely on another IRB for a full convened board review should keep in mind that they still will need to do a number of tasks including looking at the informed consent document, maintaining records, have an administrative review of the file, and have the IRB chair sign off on files included in the cooperative agreement, Hansen notes.

"Make sure you have the resources and are willing to accommodate different workflows," she advises. "Identify the main person you'll work with on these agreements and arrangements, and then follow through, maintaining a good dialogue after the study is approved and activated." ■

Internet Research and the IRB: Change is the Constant

High risk, great reward in the world of Big Data

Like a geologist identifying strata of rock, **Elizabeth Buchanan**, PhD, describes three distinct eras of the internet as a way of coming to grips with its profound implications for human research: the Old Ways, Social Media, and Big Data.

Unlike our traditional view of geology with eons of shifting lands and tides, we are witnessing rapid change as new ways to manipulate and aggregate internet and digital data threaten to outpace our understanding of their research implications. By way of example, Buchanan cites the 2013 internet research guidelines[1] by the Secretary's Advisory Committee on Human Research Protections (SACHRP), which were issued amid ongoing data changes that continue to escalate.

"Many IRBs drafted their guidelines around those," says Buchanan, interim IRB research administrator at the University of Wisconsin-Stout in Menomonie. "But even in a three-year time span — the SACHRP document took a couple of years to write, so it started probably in 2011 and then was actually published in 2013 — a lot had changed. Right as we think we have this figured out, here comes big data. We are again rethinking some of these data concepts and what these issues mean. Because we are not just seeing new forms of data — we are seeing all new methodologies and technologies that did not exist five years ago. The sophistication of these technologies just keep increasing so we are continually seeing [change]."

Buchanan froze this blur to a snapshot recently in Long Beach, CA, at the annual conference of the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In addressing the rapid evolution of the internet and its implications for human research, she traces cyber history back to the old days when there was the relative anonymity and perception of control and ownership over sites we visited and data we downloaded.

Today, all bets are off. Ninety percent of the data in the world was created in the last two years, she estimates. The 10-year labor of decoding the human genome can now be done in roughly a week, she adds. *IRB Advisor* recently reached Buchanan at a conference in Dublin, Ireland, and asked her about her AAHRP presentation and the implications for a rapidly changing future.

IRB Advisor: Can you talk a little about how we have moved from this era of internet anonymity to one of identifiability?

Buchanan: I started doing this work in the mid-1990s and at that point there were many avenues and opportunities to remain anonymous to some degree in online experiences. And that's not that long of a time — we are talking 15 to 20 years here — when what I call the "second phase" of social media really took hold. That was 2005 to 2006. If you think about the nature of social media, you can't be anonymous. The whole point of social media is its interconnectedness, interrelations, and [showing] one's presence and persona. So the whole idea is to be visible.

That is where the shift comes from anonymity — and let me say that some hardcore computer scientists would say, "We never had anonymity," but that's a different conversation. For our purposes, this shift is really significant and it pushed us into this third phase of big data.

IRB Advisor: You note in your presentation that big data research relies on algorithms and predictive analytics, but there have been a few public surprises and attendant outrage with the way the numbers can be crunched. We have recently seen dating site details about people released, with the researchers arguing it is already public data. Researchers have also shown that internet search patterns can reveal people with disease by their queries about symptoms.

Buchanan: We are starting to see big data now take this kind of next step. I think that people initially thought with big data that these data sets were so huge, and you needed such powerful computing and skill to be able to drill down to an individual level, that we didn't have to worry about it from a human subject perspective. We are starting to rethink that and starting to see the human subjects' research level [can be revealed] even in these massive data sets.

We shouldn't be quite so surprised anymore. Think of the analogy of when [a retail business] has a data breach. We're like, "Oh, no!" We get upset for a minute and then we go right back to doing the exact thing — our online shopping habits don't change. So I think the public needs to realize that this is the new reality. The researchers, on the other hand, need to really respect the privilege that we have in engaging in research. I think it's vastly important we that we use these data in responsible ways. There's something like 5 quintillion bytes of data right now, and I know that's a lot of data. We want to really think carefully about the research questions that we are asking and the methods that we are using to answer them. It really comes down to making sure our methods and our ethics are intact.

IRB Advisor: Is informed consent possible in such a research environment?

Buchanan: I think there are many levels and it is complicated. That's why we are having this discussion everywhere for IRBs.

> WE'RE ABLE TO DO THINGS IN A DAY NOW THAT WOULD HAVE TAKEN YEARS NOT TO TOO LONG AGO. THERE ARE TREMENDOUS WAYS IN WHICH THIS IS GOING TO BE BENEFICIAL TO SOCIETY.

We're participants first and foremost in these other tools — in Facebook, and using Google and Bing as search engines. So at the first level we are participating, consenting to those terms. It's only at the second level that the research consent becomes a consideration. So we are getting to this point [where researchers may say,] "Well, it's already public data. Facebook, Google or Bing has already collected it according to their terms."

And yet it is not necessarily [public] in terms of research. I think that's where we are really conflating the two and saying, "Because you consented to use some product, that automatically transfers to consent in a research project to use those data." That's kind of a high-risk assumption. I think you have to look at it on a case-by-case basis. I couldn't say all internet research should have consent waived, but I think there are many times where obtaining documents and consent might be truly impractical. But I can't say, simply, "Because you are doing internet research, you can't possibly get consent." I don't think that is true, either.

IRB Advisor: Is the primary role of the IRB in this type of research as a watchdog, assuring the protocol is ethical and if informed consent is waived, the subjects cannot later be identified?

Buchanan: Our role is to ensure that, first and foremost, persons are protected, and that we are sure that the research is scientifically valid and generalizable and contributes to some knowledge base. So with that, I think it is going to be harder and harder for IRBs to serve in that role when we are not talking about the human subject in the traditional regulatory sense or even in the philosophical sense of a human subject. We are talking about a "data subject," something that exists external to us that we partially created based on our data inputs and outputs every day. But it is also based on these other operations and machinations that are always going on behind the scenes in third-party software.

So there is only so much the IRB can control in all of the things that are happening in this concept of the data subject. As we look more and more at this kind of research, which is in every discipline now, I think IRBs have a role in really reminding individuals and researchers about the basic ethical principles. Our traditional research ethics principles — all the issues with trust and

dignity, because so much of what is happening is seemingly out of our control. A good majority of U.S. IRBs have or rely on some form of internet research guidance. *(See editor's note below for resources.)*

IRB Advisor: This is starting to sound like *Future Shock*, the book by the late futurist Alvin Toffler that predicted change would occur faster than our ability to adapt.

Buchanan: I think we are very unsure of what we all want this to look like. Right now, I am in Dublin for a research ethics workshop and they are facing this whole new slate of EU regulations around data privacy. They are having a very different conversation than we are having in the states. We hear about being globally connected — the global web — and yet we have very different philosophical approaches to privacy. We have very different political approaches to how we enact these laws. So it continues to be really challenging. The best approach we find [may be] best practices for like cases and continuing to talk to each other. I think one of the worst things that can happen is that we get so scared and so shocked that we just stop doing this. I don't think that can happen at this point. The cat's out of the bag. I think it would be dangerous to try to shut down a lot of these new forms of research.

IRB Advisor: Of course, with all the risks comes the potential for great reward if this data can be harnessed and used ethically.

Buchanan: I think we have a lot of opportunities in science and medicine right now with these forms of data and the power of big data for computing. We're able to do things in a day now that would have taken years not to too long ago. There are tremendous ways in which this is going to be beneficial to society.

We are in some growing pains right now. Think about our own lifetimes. I was not born a digital native. I grew up and learned how to use a computer when I went to college. It's very different now, and I think societally and culturally we are kind of learning what it means to have a generation that grew up digitally — to experience life in a very different way than what a large portion of our society has grown up with. There are going to be a more of these "shock" cases that will continue to pop up, but I hope we can continue doing the best we can as educators for ethical research.

Editor's note: Buchanan has compiled a list of IRB internet human research policies from a wide variety of institutions at: http://bit.ly/29sz45Y. ■

REFERENCE

1. SACHRP. Considerations and Recommendations Concerning Internet Research and Human Subjects Research Regulations, with Revisions. Final document approved at SACHRP meeting March 12-13, 2013: http://bit.ly/29CoDyi.

Report: NIH Clinical Center Riddled With Research Problems

Actions being taken after scathing independent panel report

The National Institutes of Health Clinical Center — one of the most prestigious research institutions in the world — has been rocked by an independent panel report that found glaring errors in research oversight and safety.

Among the panel's recommendations in a recent report[1] was for the NIH to establish an Office of Research Support and Compliance (ORSC) and "evaluate institutional review board activities and other human subjects protections activities and ensure consistent standards are met."

IRB Advisor asked the Clinical Center in Bethesda, MD, for comment on this aspect of the report, and after repeated inquiries over several weeks was emailed a statement that was attributed to the NIH rather than a specific individual.

"In developing its report and recommendations, the working group of the Advisory Committee to the Director did not identify any documented problems with the NIH Human Research Protection Program, i.e., with IRB review and oversight of clinical trials at NIH, nor did it identify areas of oversight inconsistency or lapses in common issues like informed consent and conflict of interest," according to the statement. "[The report] directs NIH to refine its approach to regulatory support services and compliance quality assurance so that there is a greater uniformity and transparency across the 20 NIH Institutes and Centers that conduct human

participant research. NIH agrees with this recommendation and is grateful for the fresh, independent, and outside perspective of the committee. We are currently working hard to stand up a new office at NIH, the ORSC."

The problems at the NIH center began in May 2015, when an FDA inspection found drug-processing problems in the pharmacy department and the Intravenous Admixture Unit (IVAU). In the preceding month, two vials of drugs used in research were found to have fungal contamination. Moreover, some of the contaminated drugs were administered to patients, though no infections resulted.

As the center looked into the causes of the problem, it became evident that they reflected larger, troubling issues within the institution and the work culture. Thus, NIH Director **Francis Collins**, MD, PhD, charged an independent panel to conduct an investigation.

"It was deeply disturbing to me when I learned last May of serious deficiencies in the hospital Pharmaceutical Development Section identified by the FDA," Collins said in a statement posted on the NIH Clinical Center website. "Fortunately, there was no evidence then, and there is no evidence to this date, that any patients were harmed by these problems, but it was incumbent on NIH to act swiftly. While the immediate deficiencies identified by FDA have since been addressed, it became clear to me while addressing these issues that a broader review of hospital operations was needed by outside experts in hospital management and administration, patient safety, and clinical laboratory quality and safety regulations."

The recently released[1] working group's findings included the following:

- absence of a readily apparent and anonymous avenue to escalate concerns within NIH beyond immediate supervisors,
- failure of supervisors to appropriately address and escalate important deficiencies that were reported by staff,
- evolution of a culture and practice in which patient safety gradually, and unintentionally, became subservient to research demands,
- insufficient expertise in regulatory affairs, compounded by misunderstandings about how to comply with regulations for a federal research institution conducting clinical operations,
- fragmentation of authority and responsibility for clinical operations, driven by a unique decentralized structure, authority, and funding for intramural clinical research, resulting in accountability and quality assurance gaps that could compromise patient safety,
- inadequate independent oversight of safety and regulatory compliance within NIH, and
- insufficient regular monitoring and metrics for identifying and tracking needed steps for improvement.

"PROMOTION OF PATIENT SAFETY AND ADHERENCE TO THE HIGHEST STANDARDS OF PRACTICE MUST BE VIEWED AS AN ESSENTIAL, NON-NEGOTIABLE MANDATE, NOT SIMPLY AN EXERCISE TO SATISFY INTERNAL AND EXTERNAL REGULATORS."

Patient Safety Failure

Among the most damning findings in the working group report was a "failure to prioritize patient safety," which should be the prime directive of any research activity.

"[P]atient safety was occasionally put at risk, perhaps as a result of a well-intended, single-minded focus on research with an unintended but concerning concomitant inattention to safety," the working group report concluded. "In some instances, regulatory compliance and quality assurance was not viewed as a principal priority of the [Clinical Center]. NIH should ensure that the staff views the needs of research participants rather than researchers as their ultimate priority, and commensurately consider patient safety in all activities. Promotion of patient safety and adherence to the highest standards of practice must be viewed as an essential, non-negotiable mandate, not simply an exercise to satisfy internal and external regulators."

The panel also found a surprising "dearth of regulatory expertise," saying the NIH lacks knowledge on regulations that apply to research facilities.

"There is no central source of information about the regulatory requirements that pertain to intramural clinical activities," the panel found. "Because the Clinical Center is a federal facility, some

formal requirements for oversight and regulation that are in place at typical research hospitals are not mandatory for the [center] — and were not instituted."

Moreover, the investigation "brought to light serious failures in reporting and addressing known problems. Until the FDA intervened, leadership at the center and the NIH were not aware of issues in compliance, quality, and safety that spanned many years," the independent panel found.

The Clinical Center needs a sweeping culture change, one that would encourage information-sharing and reporting any concerns, the group recommended.

"Staff should feel safe reporting concerns, and information-sharing, including near-misses, should not in itself be an indication for a need for reprimand or any negative consequences," they noted. "Staff in the [pharmacy] raised concerns regularly, but these concerns apparently were never reported beyond the department, and there was no formal mechanism at the [Clinical Center] for staff to report concerns outside their chain of authority."

New Human Research Approach

In recommending the Clinical Center create the ORSC oversight branch, the panel advised the NIH to incorporate its existing Office of Human Subjects Research Protections (OHSRP) into this new office. The working group recommended that this new combined research support and compliance office should do the following:

- serve in a coordinating role for existing compliance activities (including but not limited to human subjects protections, lab safety, and FDA compliance), and it should be equipped to efficiently respond to data calls about compliance,
- ensure that all institutes have sufficient compliance support, including training, auditing, and compliance tracking that feeds into a common, NIH-wide system,
- report directly to NIH senior leadership to ensure that there are no barriers to identifying or remediating compliance gaps,
- establish improved systems to reduce burden and increase research quality and safety, so that compliance creates better results for research participants and researchers,
- establish overarching systems, and serve as a repository for documentation of best practices and checklists that are robust and do not rely on the initiative of specific individuals,
- increase tracking and evaluation of both standard hospital metrics and metrics that are germane to a research hospital,
- evaluate IRB activities and other human subjects protections activities and ensure consistent standards are met,
- be attentive to regulatory responsibilities for scientists, clinicians, and staff and seek mechanisms that promote standards, accountability, and performance without unduly increasing staff workload, and
- improve training programs and implement a centralized learning management system to track training for regulatory compliance and patient safety, and share training resources across units.

The NIH Clinical Center is in the process of considering and implementing the recommendations. ■

REFERENCES

1. The Clinical Center Working Group Report to the Advisory Committee to the Director, NIH. Reducing Risk and Promoting Patient Safety for NIH Intramural Clinical Research. Draft Report. April, 2016: http://bit.ly/29Qjm9a.

CME/CE OBJECTIVES

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

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

COMING IN FUTURE MONTHS

- Check out strategies for chairing IRB meetings
- Improve your pre-review process by following these best practices
- Urban health center solves dilemma with centralized review functions
- Educating IRB members, A through Z

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 "MyAHC" 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. In June 2016, the National Institutes of Health published a final policy that requires a central IRB to handle which type of human subjects research?

A. Exempt socio-behavioral studies
B. Nonexempt human subjects research protocols of studies funded by NIH
C. Continuing review and expedited review studies
D. Commercial clinical trials of devices and drugs

2. When organizations rely on a single IRB, it's important to have them complete a local context reviewer form, according to Karen Hansen of Fred Hutchinson Cancer Center in Seattle. Which of the following is not one of the items she recommends to include on this form?

A. Do you find the selection and recruitment methods acceptable in the context of your local area?
B. Is the participant compensation consistent with local laws and your institution's policies?
C. How many and what type of study subject complaints does your site typically have in a given year?
D. Are the provisions for privacy and confidentiality consistent with local laws and your institution's policies?

3. Elizabeth Buchanan, PhD, recommended that which of the following internet data categories should be considered with different ethical and security measures?

A. Data in use
B. Data at rest
C. Data in transit
D. All of the above

4. An independent panel report on research problems at the NIH Clinical Center recommended that the NIH evaluate IRB activities and other human subjects protections activities and ensure consistent standards are met.

A. True
B. False