IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

APRIL 2019 Vol. 19, No. 4; p. 37-48

INSIDE

RELIAS MEDIA

HEAL: An NIH Moonshot Against Addiction and Pain

Multi-institute, $850 million effort to fight the opioid epidemic

By Gary Evans, Medical Writer

The national opioid epidemic is a public health emergency, killing some 50,000 people annually even as new and more powerful synthetic drugs enter the illicit market. In addition to 2 million people addicted, some 25 million in the United States live with chronic pain.

The National Institutes of Health (NIH) is taking up this formidable research challenge with $850 million in federal funding, leveraging expertise from a wide variety of centers and institutes for the HEAL (Helping to End Addiction Long-term) initiative.

Although the backstage work has been going on for some time, on March 5, 2019, HEAL held the first meeting of its Multi-Disciplinary Working Group.

"This is an all-consuming effort across NIH, as well it should be," NIH Director **Francis Collins**, MD, PhD, told the group. "This is a national crisis that deserves every bit of energy we can put into it. We'll be in an all-hands-on-deck approach. This working group is a critical part of how we hope in the next few months to make major investments of about $850 million to try to be sure we're bringing all the best ideas, both to the treatment and prevention of addiction, and to the development of other approaches to manage chronic pain that are not addictive."

> "THIS IS A NATIONAL CRISIS THAT DESERVES EVERY BIT OF ENERGY WE CAN PUT INTO IT. WE'LL BE IN AN ALL-HANDS-ON-DECK APPROACH."

The funding issue has some controversial origins, as Collins explained it was decided that no pharmaceutical company funds will be used in the HEAL initiative.

Financial Disclosure: Author **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Editor **Jesse Saffron**, Editorial Group Manager **Terrey L. Hatcher**, and Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Nurse Planner **Kay Ball** is a consultant for Ethicon USA and Mobile Instrument Service and Repair.

IRB ADVISOR

IRB Advisor, *ISSN 1535-2064*, is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *IRB Advisor*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.
GST Registration Number: R128870672.

SUBSCRIBER INFORMATION:
Customer Service: (800) 688-2421.
ReliasMediaSupport@reliasmedia.com.
ReliasMedia.com

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, $377. 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@reliasmedia.com or (866) 213-0844.

ACCREDITATION: Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [1.5] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

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.

AUTHOR: Melinda Young
MEDICAL WRITER: Gary Evans
EDITOR: Jill Drachenberg
EDITOR: Jesse Saffron
EDITORIAL GROUP MANAGER: Terrey L. Hatcher
ACCREDITATIONS MANAGER: Amy M. Johnson, MSN, RN, CPNr

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

The NIH Foundation Board and others "were concerned given the fact that [drug] industry played some role in the opioid crisis, that now receiving money from industry to develop alternatives might present a reputational risk," Collins said. "We'll fund this by NIH contributions. What we're asking from industry is identification of assets, promising compounds, devices, data sets, that could be contributed to this kind of partnership effort in an open access way."

The HEAL working group started by bearing witness to the staggering human loss that is occurring daily, as family advocate **Jessica Hulsey Nickel**, founder of the Addiction Policy Forum, urged the NIH to help destigmatize the disease and find desperately needed cures and treatments.

"We believe working with scientists and researchers, following the science, is incredibly important," she said. "We're mired in myth and misconception with this disease."

The working group consists of external experts in addiction and pain who have been asked to give their input and guidance on the HEAL research.

"I don't have to tell this audience how severe this crisis is; however you choose to display the facts, comparing it from 1999 to 2016 is breathtaking," Collins said. "There are hot spots in certain areas like the Appalachian area and the Southwest, but there is no part of the country not touched by this."

HEAL will build around established NIH research tracks, including essential neurological science on the brain and its complex paths to pain and addiction.

"We believe that science has a lot to contribute to this national public health crisis," Collins said. "We want to bring the best addiction [research] strategies as well as enhancing pain management for people with chronic pain. So, those are both included within this enterprise, which has involved vast numbers of hours and lots of senior leaders and people all the way across the country helping us. The goals are scientific solutions to the opioid crisis."

HEAL's 26 Research Projects

Currently, the HEAL project involves 12 institutes and centers and 26 research projects.

"These cover the gamut from prevention research, basic and translational research, clinical trials, and all the way to implementation science on multiple things such as criminal justice, healthcare, etc.," he said.

Researchers will look at expanding therapeutic options, looking for more user-friendly formulations of existing medications.

"These include formulas for longer duration, more powerful overdose-reversers, new approaches to reduce respiratory depression, immunotherapies for opioids to prevent relapses and overdose, and new targets, new approaches for treating opioid use disorder," Collins said.

There is a need for new prevention and treatment strategies, particularly for adolescents who may transition into opioid use disorder after a period of experimentation.

"How do we prevent that?" Collins said. "We talk about people who are clearly falling into the addiction zone, but what about people who aren't quite in that place? They are going through misuse or

have low-severity disorders. They may be at risk for getting further down that path. We haven't done a lot to figure out what those interventions ought to be."

There also are open research questions about optimal addiction treatment length, he added.

"Here is a big one," Collins says. "How long should medication treatment of opioid use disorder be sustained? We don't really have rigorous data to know. Again, it's probably different from person to person. My gosh, if we have 2 million people [addicted] and don't even know how long to recommend treatment, we really have a big evidence gap."

Complicating treatment is the fact that people with pain and addiction may also have common mental disorders.

"Estimates are that 40% of people with opioid use disorder have a diagnosable mental disorder," Collins said. "We have not done enough to understand the intersections there."

Another issue is the criminal justice system, which often is a lost moment for intervention, he says. Likewise, using behavioral health interventions to complement medications may be another avenue for research gains.

A challenge in pain management research is understanding the origins of chronic pain. One ongoing NIH project is researching how acute pain morphs into chronic pain.

"Why is it that some people who had a knee replacement several months later tell you they are doing well, and others end up in a chronic pain situation that's hard to break?" Collins asked. "What happens? What's the signature? What can we do to block that transition? Once it happens, it's hard to turn it back."

More targets for safe and effective pain treatment are needed, with the appropriate therapeutic developments to follow, he says.

"We need to engineer preclinical screening platforms to assist in identifying targets," he said. "We don't know yet how best to put that into place in terms of coming up with therapeutics that work."

If that aspect can be uncovered, it can be translated not only to new drugs but devices for pain treatment.

"That is also a significant part of HEAL's interests," he said. "We have to think — as far as interventions — not just drugs, not just devices, but also nonpharmacological and nondevice approaches involving complementary integrative health."

To expedite the myriad HEAL trials, the NIH has established the EPPIC-Net (Early Phase Pain Investigation Clinical Network), which will "support exploratory clinical trials of investigational drugs and biologics, investigational devices, natural products, and surgical procedures for the treatment of pain."[1]

The Abyss of Pain

One of the more disturbing aspects of the opioid crisis are babies born with the addiction. HEAL research will address this problem and look for research solutions, Collins says.

"This is a heartbreaking situation. How do we best manage newborns with neonatal opioid withdrawal syndrome?" he says. "Those babies are, as you know, found in every neonatal ICU these days. What are the long-term consequences? We know far too little about this."

Families deal with this condition and so many other tragic consequences when they are "drowning" in the loss that comes with addiction, Nickel told the NIH panel.

"We work really hard to make sure that we reach people having their darkest day, in crisis, figuring out how to help a loved one or help themselves, and not always knowing where to go," she said.

Through her personal testimony and the pictures and words of families and victims, Nickel opened wide a door to pain.

"I lost both my parents to heroin use disorder and got involved to change what happens when this disease hits your family," she said. "Because it is isolating, stigmatizing, and difficult to navigate."

The central vision of the Addiction Policy Forum is to bring the condition fully into the realm of disease, with clinical approaches and interventions devoid of shame.

"What we've learned in working with patients and families, it's not only that we have to educate," she said. "We have to uneducate and re-educate."

Many people think addiction is a "moral failing" that can be fixed in a 28-day stay at a fancy spa, she noted.

"Dismantling some of the myths and then following up with the real information is so important," she said. "Addiction is a brain disease — a brain disorder."

The support group runs a 24/7 telehealth center manned by licensed workers.

"Half of the country does not believe addiction is a health condition," she said. "How do we make sure we change those minds?"

The key is integrating addiction more into mainstream medicine so these patients will be treated socially much like those with diabetes or undergoing hemodialysis.

"What we really want is what

other diseases have, right?" she says. "Take, for example, cancer. We would like to have individualized care, not one-size-fits-all. We would like to be able to find the doctors and specialists that can treat our illness."

More medications should be developed in addition to creating strategies that could treat addiction like a chronic condition, she said.

"You know, you don't go to someone's schizophrenia graduation ceremony," Nickel said. "Or you don't say, 'Oh, I'm so sorry you were diagnosed with diabetes — so glad you're going in for 30 days and that that will be cured.'"

More than anything, addiction is almost inseparable from stigma. "It is not just in the media and movies," she said. "It's in medicine as well. It's in child welfare systems, criminal justice systems. It's in our homes, schools, churches, our communities. Stigma keeps us from coming out of the shadows and asking for help, from intervening early."

To change this, the NIH can help explain how addiction is a health condition, detailing how it affects the brain and how treatment works and recovery is possible, she urged.

"As you all know, the numbers are still going in the wrong direction for overdose deaths — 192 people a day," she said. "But we don't always dig down. These are real families and loved ones, real adolescents and adults, siblings and sons and daughters." ■

REFERENCE

1. National Institutes of Health. Pain-related Clinical Trial Networks. Available at: https://bit.ly/2Oe4xxL.

Gene Therapy Studies on the Rise Due to Market Demands

NIH proposed streamlining changes

By Melinda Young, Author

Gene therapy applications are increasing across the globe due to increases in life-threatening and chronic illnesses and developed nations' moving to accelerate commercialization of gene therapy.

The market's growth raises the prospect of IRBs overseeing gene therapy clinical trials. It also means that research organizations, both large and small, should be prepared for such trials and develop or have access to an institutional biosafety committee (IBC).

"A subsection of clinical research specifically defines how clinical research needs to be done when it comes to these molecules," says **Daniel Kavanagh**, PhD, senior scientific advisor, gene therapy, at WIRB-Copernicus Group (WCG) of Princeton, NJ.

"Any research that involves National Institutes of Health [NIH] funding or is conducted by people who voluntarily wish to submit to the guidelines must be approved by the IBC if the research involves recombinant DNA or RNA technology," Kavanagh says.

There are more than 1,000 studies underway that fall under the NIH's definition of human gene transfer. There are five current products, with more predicted to be on the market within the next few years, he says. The following are the latest gene therapies to receive FDA approval:

- **Kymriah:** Gene therapy for pediatric and young adult patients with acute lymphoblastic leukemia, approved Aug. 30, 2017 *(http://bit.ly/2VkYJVo)*;
- **Yescarta:** Gene therapy for treating adult patients with relapsed or refractory large B-cell lymphoma, approved Oct. 18, 2017 *(http://bit.ly/2Ei9alG)*;
- **Luxturna:** Gene therapy to treat children and adults who have an inherited form of vision loss, approved Dec. 19, 2017. *(http://bit.ly/2EDyqEf)*

For years, IRBs have reviewed studies using small molecules or biologics that do not contain DNA, he notes.

"But if these become a clinical trial where the investigational product incorporates genetically modified DNA or RNA into the product and it's introduced into a human subject, then it becomes human gene transfer research and a new set of oversight kicks in," Kavanagh says.

In most cases, the research institution needs to have an IBC.

"There are 1,300 IBCs registered with the NIH," he says. "If people don't comply, the NIH can withdraw their funding and make them ineligible for future funding."

Even when multisite clinical trials

use a central IRB for review, they must each have their own IBC for these studies.

"We're starting a multicentered trial where there are 50 sites for one trial, and all 50 sites will require their own IBC," Kavanagh says. "There will be one multicentered trial with a single protocol, but 50 sites and IBCs."

In August 2018, the NIH released a proposal to amend its guidelines to streamline oversight for human gene transfer clinical research protocols. The change would eliminate recombinant DNA advisory committee (RAC) review and reporting requirements to NIH for human gene transfer protocols and modify the roles and responsibilities of institutions, IBCs, the RAC, and NIH. *(Find more information at: http://bit.ly/2BVsCUS.)*

The proposed change received dozens of public comments. Commenters included Paul Gelsinger, father of Jesse Gelsinger, who died during a gene therapy trial in 1999. Gelsinger wrote in opposition to the proposed change, stating, "So, if you believe that the system has fixed the financial conflicts of interest issues in clinical research, especially the overhyped gene technologies, think again." *(The comment can be viewed at: http://bit.ly/2T4JnaO.)*

The proposed change was not finalized by the end of February 2019.

While the changes, if finalized, would affect some IBC responsibilities, they would not change the IBC structure with regard to including community members and how they are required for each research institution that conducts a gene therapy clinical trial.

Research institutions can start their own IBCs or contract for IBC services. Kavanagh offers the following advice on how to form an IBC:

• **Select IBC members.** IBCs need a minimum of five members, including science experts, at least two community members, and a chair. If human gene transfer occurs at the institution, the IBC must have a gene transfer expert as a voting or ad hoc member.

> "IF PEOPLE DON'T COMPLY, THE NIH CAN WITHDRAW THEIR FUNDING AND MAKE THEM INELIGIBLE FOR FUTURE FUNDING."

IBCs should include, in addition to science and gene therapy experts, members who can represent the community's interests.

"The NIH is serious about the requirement of community involvement," Kavanagh says. "The community members on the committee must not be affiliated with the research site."

Community members could include people who work in the biotech industry, so long as they are not affiliated with the research institution. The goal is to find people who represent the interests and concerns of the community, he adds.

This likely is easy to do in large cities but more challenging in rural states and regions.

"Each IBC can only oversee the interests of the local community for which it is registered; a general standard is within a radius of 50 miles," Kavanagh says. "So, there have to be a lot of individual IBCs registered across the country."

One strategy for finding IBC members is to create a professional network that can be accessed when starting an IBC or replacing members on one, he suggests.

"I'm always collecting cards from people around the country at conferences, keeping those networks active," he says.

"If someone were setting up their own IBC from scratch, they'd have to pick up the phone book and guess who would be interested," he adds. "The goal is to find members who are competent to advise the institution on safety and community standards."

• **Follow NIH rules.** Current guidelines are flexible for IBCs, Kavanagh notes.

"There is a large self-assessment tool that NIH has published, which provides a lot of details and points to the IBC in terms of their operation," he says. "The real purpose is to make sure the work is done safely."

The rules also ensure trials follow proper technical equipment training, waste disposal, and NIH requirements.

IBCs must make their meeting minutes available and detailed in how the board made its decisions.

"A typical IBC at a major university meets once or twice a month, while an IBC at a hospital with only one gene therapy clinical trial might meet once a year," Kavanagh says.

The IBC's role is to assess the facility in which the work will be performed. It includes a biosafety professional, who is knowledgeable about the various biosafety levels and infectious agents, and the types of protective measures needed for each level.

For example, a biosafety level 4 would be for biodefense and high-

security studies that involve toxins or bioagents. Protective measures for these studies would include following best practices in room airflow, biosafety cabinets, wearing personal protective equipment, and other measures, he says.

WCG provides services at biosafety levels 1 or 2, Kavanagh notes.

"We send in consultants to do IBC inspections at the site, which is a big part of the review," Kavanagh says. "An IBC has these boots on the ground and needs to look at facilities, looking at where the garbage and sharps are disposed, and the personnel training and certification."

These are very different from the IRB's review and involvement, he notes.

"It's a facility-specific review of safety capabilities of the site, and every new protocol has to address the new agent," he adds. "If I have a recombinant DNA molecule that's one kind of potential hazard, or if I have live virus, that's a different hazard, and a different assessment is required."

• **Work with IRBs.** "It's at the discretion of the institution, but it's certainly useful to have somebody from the IRB attend the IBC meeting," Kavanagh says. "You want communication between the biosafety, human subjects protection, occupational health, and animal protection committees."

The institution needs a plan to coordinate between those four branches, he says.

"The IRB is focused on the human subject who is enrolled in the study; the IBC is focused on safety of the subject and the protection of everyone around that person, including the community, family, lab workers, physicians, and others," he explains. "It's a complementary set of roles."

The IRB assesses risks and benefits, and IBCs have experts that can shed light on certain risks. It would help IRBs in making their decisions if members can ask the IBC experts about particular agents and the risks they pose to research participants.

IRB and IBC chairs could hold a monthly meeting to discuss studies.

"The current NIH guidelines require IBCs to review informed consent," Kavanagh says. "Last year, the NIH director proposed some streamlining, which may — if implemented — remove the requirement for the IBC to review the informed consent form."

This second review by the IBC is a best practice, he adds.

"It's up to the institution who reviews the informed consent document first, but my company provides a parallel IRB and IBC review of informed consent," Kavanagh says. ■

Central and Local IRBs: Can This Marriage Be Saved?

Collaboration on key issues will be important

As the new normal becomes single IRB review for multisite studies, some researchers are wary that this system may undermine the vital role of local IRBs to protect research subjects in their community.

In an attempt to answer and resolve these issues, researchers asked central IRBs about their perceived needs for local knowledge and input.[1] In a description that suggests single and local IRBs are going to have to work together through better and worse, lead author **Robert Klitzman**, MD, tells *IRB Advisor*, "It's like a marriage."

Klitzman, a psychiatrist and director of the Master of Science in Bioethics Program at Columbia University in New York City, says, "It's sort of a division of labor, and these kinds of things need to be worked out. There are still issues — if something goes wrong, who is responsible? There are levels of trust, and local IRBs may feel it is important that certain local information be communicated to the single IRB."

In the study, Klitzman and colleagues interviewed IRB members from boards that have served as central IRBs for multisite studies. Local knowledge identified as potentially important to single IRBs included culture and linguistics issues, geography, socioeconomics, and researchers.

"Such knowledge can potentially be obtained through local sites, but single IRBs may be unaware of potentially relevant local information, and lack of informal relationships may impede single IRBs' reviews and interactions with researchers," the authors noted. "While a recent, commonly used, standardized single IRB form asks

three basic questions about local information, our findings suggest potential needs for additional information and, thus, have important implications for practice, policy, and research."

Q&A

IRB Advisor asked Klitzman to comment on these findings in further detail in the following interview, which has been edited for length and clarity.

IRB Advisor: The move to single IRB oversight of multisite studies has not been universally embraced, with some seeing it as trading off one set of problems for another. Do you think it was a mistake to adopt a single IRB system?

Klitzman: I wouldn't say it was a mistake. I do think there are a lot of details about how it is actually going to work that have not yet been thought out. It's one thing to say there will be single IRBs that use local IRBs. What are the unintended consequences that have not been thought through? What are the kinds of details that need to go along with that? The single IRB policy was made from sort of a 30,000-foot level. There are a lot of issues about how all of this is going to play out on the ground.

IRB Advisor: In the context of institutional challenges, you note that single IRBs will need the requisite organizational skills and resources to manage research across multiple sites. You suggest those that decide to do it for the first time may face a learning curve.

Klitzman: When you decide to become the single IRB, you may need someone to manage 60 IRBs in 30 different states. That's a different experience [from a local IRB]. An IRB administrator who is just used to looking at reviews and protocols may not have the experience to deal with all these different IRBs and make spreadsheets to keep track of them. People are trainable, but you need someone who is good at that kind of management.

IRB Advisor: You found that issues that single IRBs should be aware of are cultural restrictions and language barriers in research subjects, which will be better known by the local IRB.

Klitzman: I think it is important to drill down. What percentage of potential participants is English not their primary language? Someone at the single IRB may not think of that — 3% of the population speaks Vietnamese.

IRB Advisor: You also raise questions about the cost of living and ability to get to clinic sites in various locales reporting to a single IRB.

Klitzman: In some places, it is a three-hour drive to a hospital. Somebody else in the same study might just take the subway. That is a big burden to participants. Those are relevant concerns.

IRB Advisor: What can local IRBs tell central IRBs about researchers they may not have worked with before?

Klitzman: Local IRBs know if a researcher has some problems, has been overextended, or they have to keep an eye on him. It is not bad intentions, necessarily. Maybe he is busy in China half the time and is just not around.

IRB Advisor: What about the challenges for local IRBs in this new system?

Klitzman: There are still going to be local human subject programs and there will be challenges. For example, local institutions will have to come up with reliance agreements to work with the single IRBs, and that poses a number of challenges because they are giving up certain responsibilities and functions to the single IRB. Local IRBs and local human subject protection programs will presumably retain several important functions, such as conflicts of interest assessments, monitoring and management, responsible conduct of research, research integrity, and compliance issues. ■

REFERENCE

1. Klitzman R, Pivovarova E, Murray A, et al. Local Knowledge and Single IRBs for Multisite Studies: Challenges and Solutions. *Ethics Human Research* 2019;(41)1: 22-31.

Remember IRB Review Criteria When Updating Application Design

The IRB had been working with application materials that had not been updated in years and were less flexible than current regulations allow.

One of the IRB's basic jobs is to make sure criteria are met, but the application's old design made IRB reviewers' work more challenging, says **Robert S. Bienkowski**, PhD, CIP, CHRC, director of the office of research compliance at Central Michigan University.

"We found the old application material to be repetitive in different sections. Information was scattered all over the place, so the reviewer had to piece information together," says **Deborah Geasler**, CIM, IRB coordinator at Central Michigan University.

Investigators sometimes wondered why the IRB application asked particular questions, so the IRB asked reviewers to link their comments to specific regulatory criteria, says **Katherine Rosier**, PhD, chair of the IRB and professor of sociology at Central Michigan University.

"This was difficult for reviewers to do," Rosier notes. "We were getting better at it, but this led us to consider reorganizing the application in such a way that it had a checklist of each of the 111 criteria."

The process of revising the IRB application took about a year and a half. The new application is organized in criteria headings, based on federal regulations under 45 CFR § 46.111. *(The regulations can be viewed at: http://bit.ly/2tIlxT9.)*

If there is a request for information that is not common to all applications, such as enrolling children, it is handled through a hyperlink to a specific form.[1] *(See checklist of 111 criteria, below.)*

The revised application served as an educational tool for researchers, and it helped reviewers focus on the 111 criteria and avoid bringing extraneous questions into their review, Geasler says. It has tightened up the review process, decreasing the amount of time spent from study submission to IRB approval.[1]

"The total review time from submission to approval was cut to one-third of what it was, although we can't make a causal argument that it was only the change in the application form that led to that decrease," Rosier says.

EXPEDITED REVIEW WORKSHEET INCLUDES 111-CRITERIA CHECKLIST

The IRB at Central Michigan University revised its IRB application to make it more efficient and more closely aligned with federal regulations under 45 CFR § 46.111. *(View the regulations at: http://bit.ly/2tIlxT9.)*

The expedited review of new application worksheet includes checklist questions based on 111 criteria. In the IRB application, the cover page explains how each of the seven criteria under 45 CFR § 46.111 must be satisfied before the IRB will approve the research. The title page also asks investigators to list the project's title, principal investigator's name, department, college, mailing address, phone, and email. The form also asks investigators to checkmark which government agency funded or supported the work.

For each checklist item, there is a question of "Is Criterion met?" Options are "yes," "conditional," and "no."

In using the "conditional" response, a reviewer would add a suggestion such as "insert the following language…," according to explanatory comments by **Robert S. Bienkowski**, PhD, CIP, CHRC, director of the office of research compliance, Central Michigan University.

The following are some checklist items, shared by Central Michigan University IRB:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject;
- Informed consent will be appropriately documented;
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. ■

Other factors possibly contributing to the decrease in review time are changes in the board's membership, reviewers' experience, and IRB leadership, she adds.

One of the unexpected benefits of the application revision process was that the IRB added IT representatives to the board, Geasler says.

Investigators can work upfront with the IRB IT members as they prepare application materials, which helps them establish appropriate data security protections, she says.

"It's been a win-win, and the information technology crew now better understands research on campus," Geasler adds. "They're a tremendous addition to our board."

Another positive outcome is that IRB reviewers and investigators say they find the new application to be a great improvement to the IRB review process, Rosier says.

"Our reviewers are finding the review of the application easier because our investigators are now used to the forms and they know ahead of time what's expected of them," Geasler says. "Applications are becoming better written, which makes the review process easier for our reviewers."

It has had a big impact on reviews overall, she adds.

"We're finding that when a protocol is deferred for additional information, we can get it through the approval process in about two reviews, versus three or four reviews as it was with the old application materials," Geasler explains.

From a quality improvement perspective, the new application form and checklist make it easier to assess whether a new IRB reviewer understands what is required and includes appropriate responses, Bienkowski notes.

"It has highlighted some cases where reviewers did not understand conditional approval and requirements for modifications; we have addressed that with several tutorials," he says.

Investigators and IRB reviewers were offered an opportunity to submit comments on the new application form as it was being developed, Rosier says.

"The comments we received were uniformly positive from both," she says.

From Rosier's perspective as the IRB chair, the application and accompanying worksheet are a major improvement, she adds.

This process was part of the institution's continuous quality improvement, Bienkowski says.

"We are very conscious of an obligation to not only adhere to regulations, but to also not settle for what we've been doing and always be thinking about how to improve things," he explains. "This is part of our process of introspection: What are we doing? How can we do it? And how can we better protect human subjects?" ■

REFERENCE

1. Geasler D, Rosier K, Bienkowski RS. Reimagining the application form. Poster presented at PRIM&R's Advancing Ethical Research Conference, Nov. 14-17, 2018, San Diego. Poster:51.

Study Investigates Reasons Why People Do Not Enroll in Clinical Trials

Hint: It's not lack of interest

A new study of cancer clinical trial participation breaks down and analyzes the reasons why only a small fraction of adult cancer patients participate in research.

The study found that a main reason why so few people participate is because there is no trial for more than half of cancer patients for their particular type and stage of cancer.[1]

"Going back to studies in the 1990s and early 2000s, researchers frequently cite the statistic that less than 5% of adult cancer patients participate in clinical trials," says **Joseph Unger**, PhD, health services researcher and biostatistician at Fred Hutchinson Cancer Research Center in Seattle.

"But, in fact, when patients are offered to participate in a trial, about half choose to do so," he adds. "This leaves a very different impression about the role of patients in clinical trial participation, indicating that they are much more willing to participate than is commonly assumed."

Other systemic, structural reasons why people fail to participate have to do with clinical trial locations and the cost of travel, as well as the fact that cancer patients often are ineligible for trial enrollment.

"Many patients cannot travel to where the trials are available because of the constraints like taking time off work, family constraints, and child care," he says.

Traveling for clinical trials also is expensive with travel costs, housing/hotels — sometimes for long periods of time — and other costs related to living in one place and maintaining a residence in another place, he adds.

Unger and co-investigators decided to assess barriers to cancer clinical trial participation because of the issue's importance, he says.

"Patient participation in clinical trials is the backbone of clinical cancer research," Unger explains.

"A great deal of attention and research has been paid to the reasons why patients don't participate in trials," he adds. "Although this research is important, it leaves the impression that patients themselves are the main barrier to trial participation, when, in fact, many structural and clinical barriers get in the way long before patients are offered the option of a trial."

The study's findings confirm this: "Nearly 56% of patients didn't have a trial available to them at their institution, and nearly 22% were deemed ineligible for an available trial," he says. "Together, these structural and clinical factors alone are the main reasons why more than three out of four cancer patients don't participate in trials."

Similar structural barriers likely affect clinical trial participation in noncancer clinical trials, he says.

"It's very likely that similar patterns exist for clinical trials in other diseases, since the factors underlying structural barriers, such as the absence of a locally available trial, and clinical barriers — especially not meeting the trial inclusion criteria — are not specific to cancer," Unger explains.

The solution to breaking down structural barriers is for research institutions to find better ways to connect patients to trials, he says. Strategies can include making trials available at many more sites or providing more sites with the necessary resources to participate.

"IRBs could also focus on whether exclusion criteria for trials are adequately justified by concerns about patient safety, and whether some criteria could be modified or removed to make trial participation more inclusive," Unger says.

Another strategy would be to reimburse patients for the costs of participating in trials, which is vitally important if the goal is to reduce income disparities in clinical trial participation. The current reality is that patients with greater financial means are more likely to be able to travel far distances to receive care in a trial, he adds.

"Overall, we need better ways to both bring the trials to the patients or the patients to the trials," Unger says. ■

REFERENCE

1. Unger JM, Vaidya R, Hershman DL, et al. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst.* 2019 Mar 1;111(3):245-255. doi: 10.1093/jnci/djy221.

Complex Research Ethics Question? Consultants Offer Their Expertise

A public health researcher was unclear on the ethical implications of a "secret shopper" concept — in this case, to see how many local stores failed to ask children under 18 for identification before selling them cigarettes. Another researcher wanted to recruit adolescents with chronic illness for a study through social media but was unclear how to go about ethically obtaining parental consent.

These are two recent issues handled by the research ethics consultation (REC) service at Johns Hopkins. The REC serves as a resource to help answer investigators' ethical questions. "We have created a place to come talk about research ethics that's different from the IRB. It is an educational opportunity," says **Holly Taylor**, PhD, MPH, PhD program director and core faculty at the Johns Hopkins Berman Institute of Bioethics in Baltimore.

Taylor is lead author of a recent paper on a national REC collaborative.[1] Based on data collected on more than 350 consultations, the authors concluded that REC can assist investigators:

- before and after regulatory review;
- when facing challenging or novel ethical issues;
- navigating informed consent and risk/benefit analysis;
- overcoming study hurdles;
- mediating conflicts within a team;
- directly engaging with research participants.

"What researchers really want is the opportunity to talk to a person about their work," says Taylor. "That's really the reason we were created — to meet the investigator where they are."

The REC works independently from the institution's IRBs, although the IRBs occasionally reach out for help with challenging cases. Researchers typically seek help early in the process when thinking about recruitment or what populations to include. "The vast majority of consults we get are long before it gets to the IRB," says Taylor.

Most questions are about study design or informed consent. Sometimes, investigators are recruiting in a region with low literacy levels and need to determine how to obtain informed consent in this population, for instance.

Consultants at Johns Hopkins assess the satisfaction of participants by asking, "Did you get the information you wanted? Would you recommend it?"

"We would like to do a more robust evaluation in the future," says Taylor. "Perhaps it would be even more powerful if we as a group identified key outcome measures that consultants could collect across institutions."

The REC service emphasizes education, as opposed to helping investigators gain IRB approval or grant money. "My goal is to help them realize they already know the answer and I'm helping them get there. I'm interested in helping them build their ethics capacity," says Taylor.

Any and All Areas

Zubin Master, PhD, a consultant at the Mayo Clinic's biomedical ethics research program, authored a recent paper arguing that the scope of REC services should be expanded.[2] "There is a need for it. It's a necessary role. It can help solve issues that arise and prevent issues from escalating," says Master.

At the Mayo Clinic, the REC service handles a wide range of issues. These include authorship, mentorship, and conflicts of interests. At Albany (NY) Medical College, where Master was an associate professor at the Alden March Bioethics Institute, a REC was created by the bioethics department. "We did have people coming to us with these sorts of questions," says Master. "It could be a small chat around an issue, or something that took several days with lots of back and forth."

Scientists may primarily perform animal research but are now working with human embryos. They may find that their research integrity office lacks ethics expertise specific to this area. "They can call people like us," says Master. "We handle any and all areas surrounding research ethics."

Sometimes, the IRB turns to the REC service for assistance. "It might be over a consent form, unfamiliar research, or a vulnerable population is involved and they just want somebody to double-check something," says Master.

One issue is that struggling investigators do not always know REC exists at their institutions. Generally speaking, clinical ethics services are "much better embedded institutionally," says Master. "This is just anecdotal, but people we've asked are not necessarily even aware that research ethics consultation services exist."

Accessible to All

Not every institution offers an in-house REC — but that does not mean REC services aren't accessible to researchers. The national collaborative hosts a monthly call where a member of the group presents a case and how it was resolved. Any institution can participate in these calls.

"We offer consults to individuals at institutions that don't have a consult service," says Taylor. "Not every institution is going to have the expertise in-house, whether in the IRB or elsewhere."

However, the service doesn't need to be resource-intensive. Smaller institutions could conceivably start it up on their own. "If you can find a champion in the institution with research ethics expertise, and there always is, certainly, those people could start a research ethics consultation service," says Master. ■

REFERENCES

1. Porter KM, Danis M, Taylor HA. The emergence of clinical research ethics consultation: Insights from a national collaborative. *Am J Bioeth* 2018; 18:39-45.
2. Master Z, Martinson BC, Resnik DB. Expanding the scope of research ethics consultation services in safeguarding research integrity: Moving beyond the ethics of human subjects research. *Am J Bioeth* 2018; 18:55-57.

COMING IN FUTURE MONTHS

- What children really understand about research participation
- Best practices in electronic informed consent
- What is appropriate in pay-to-participate?
- Best practices in obtaining research participant feedback

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. Log onto ReliasMedia.com and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME/CE QUESTIONS

1. **What question did Francis Collins, MD, PhD, raise about newborns with neonatal opioid withdrawal syndrome?**

   a. "Can they breast-feed if the mother is opioid-free?"
   b. "Can they be weaned off opioids with surrogate drugs?"
   c. "Is it ethical to put them in controlled trials?"
   d. "What are the long-term consequences?"

2. **What percentage of people with opioid use disorder have another common diagnosable mental disorder?**

   a. 20%
   b. 30%
   c. 40%
   d. 50%

3. **What is the chief role of an institutional biosafety committee?**

   a. To review informed consent and human subject protection
   b. To review study's science and statistical analysis
   c. Review the safety of the subject and protection of the community, family, lab workers, physicians, and others
   d. Review of the investigators' conflicts of interest

4. **Federal regulations that outline how IRB application reviews should assess risks and benefits to subjects, subject selection, informed consent, data monitoring and collection, and other issues are in which of the following federal codes?**

   a. 45 CFR § 46.111
   b. 45 CFR § 46.212
   c. 45 CFR § 46.411
   d. 45 CFR § 46.464