IRB ADVISOR

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INSIDE

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Social-behavioral IRBs Gear Up for Common Rule Changes

Expect huge drop in continuing review

By Melinda Young, Author

Barring a last-minute reprieve, the new Common Rule — with all of its complex changes — will begin Jan. 19, 2018.

And at a least a few IRBs are ready.

"The new Common Rule has material implications, including changes to training and education of IRB staff and members of the research community," says **Jennifer Graf**, manager of the human research protection program and research integrity at Cambridge Health Alliance in Cambridge, MA.

(Note: At press time, HHS submitted a delay in Common Rule implementation. For more information, see story on page 15.)

"THE NEW COMMON RULE HAS MATERIAL IMPLICATIONS, INCLUDING CHANGES TO TRAINING AND EDUCATION OF IRB STAFF AND MEMBERS OF THE RESEARCH COMMUNITY."

"Cambridge Health has taken the position that the start of every IRB meeting has dedicated time to go over various elements of the revised Common Rule," Graf says. "So, we're ready, and our IRB members and IRB office staff are prepared."

Various organizations had asked the Office for Human Research Protections (OHRP) for a delay in the new Common Rule implementation. Since this delay had not occurred by the end of 2017, some IRBs proceeded with changes to their policies and procedures.

For example, the University of Wisconsin-Madison's educational and

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social-behavioral science (Ed/SBS) IRB implemented a new policy in October 2017, based on the Common Rule changes.

"As of Oct. 2, 2017, our new campus policy is that if a study meets these six criteria, they can meet the exception for continuing reviews," says **Casey Pellien**, CIP, Ed/SBS IRB director at the University of Wisconsin-Madison.

The six criteria are as follows:

- the study involves only one site;
- the study does not involve drugs, biologics, or medical devices;
- it is not federally funded;
- it is not regulated by the Veterans Administration;
- it does not enroll prisoners;
- it is eligible for expedited review, or it involves data analysis.

"We did this change in continuing review in anticipation for the new Common Rule," Pellien says. "We were granted that ability."

These are a few of the changes from the Common Rule regulations, published on Jan. 18, 2017:

- consent forms should provide clearer information about a project's scope, risks, and benefits;
- many multisite studies will use a single IRB review, rather than separate IRB reviews per site;
- researchers can rely on broad consent for future research involving studies on stored identifiable data or identifiable biospecimens;
- new exempt categories of research are based on the level of risk they pose to participants, and there's a new exemption for secondary research that involves identifiable private information, related to HIPAA rule protection;
- continuing review is no longer required for ongoing research studies in cases where the review does not contribute to protecting subjects.

"The new Common Rule offers greater flexibility for the application of regulations," Graf says. "One of the major impacts is the elimination of continuing review."

While the flexibility is welcome, the changes also present a challenge to IRBs. "Continuing review enables institutions to easily keep track of minimal-risk research," Graf notes.

"Many institutions use the continuing review process to satisfy various institutional policies, like getting annual conflicts of interest disclosures," she explains. "When the continuing review is eliminated, there is a need for new, reliable procedures — like having an annual check to keep track of the minimal-risk research that's going on."

IRBs might also want updates on adverse events, complaints, staffing, and retraining.

"With the elimination of continuing review, there will be a ripple effect in staffing and retraining," Graf says. "Under current regulations, you might have multiple staff who process continuing reviews. With the continuing review elimination, it's reasonable to infer there will be a shift in staff and resources."

For instance, IRB workflow might shift to auditing and monitoring roles.

"This presents challenges because the skill set and temperament needed to be a successful auditor or monitor differs from the skills needed in an office administration support role," Graf says. "It's not a one-on-one transfer, and IRBs might have to let some people go, and other people might not have an interest in being retrained."

It's possible the change will result in a 90% reduction in continuing review, Graf says.

"There could be an increased emphasis on field audits," she says.

"I think that with the elimination of continuing review, there will be a genuine need for robust monitoring and auditing."

This is a potentially positive change, Graf says.

"I think the continuing review in its current form doesn't necessarily optimize what the goals are: the protection of human subjects," Graf adds. "The protection of the safety and welfare of participants is better served by field auditing and monitoring than by continuing review information."

Adding additional exemption categories might affect social-behavioral and education research IRBs the most. A new exempt category involves research with benign behavioral interventions — but the exemption is not applicable for research involving deceit.

Another new exempt category involves storage or maintenance of identifiable private information or specimens for potential secondary research use. It's exempt if an IRB conducts a limited review.

"We believe a lot of protocols we see will fall under the exempt category," Pellien says. "So I think we'll move away from approving a lot of protocols through expedited review to a lot of protocols being exempted."

The new Common Rule says that activities that do not meet the definition of research include the following:

- "scholarly and journalist activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship);"
- "public health surveillance activities authorized by a public health authority to assess onsets of disease outbreaks or conditions of public health importance;"
- "certain criminal justice and intelligence activities."

Consent changes might have more of an effect on medical review boards.

"For social and behavioral research, we request consent forms be no more than two pages," Pellien says. "In the new Common Rule, new information has to be at the top of the consent form. Well, we've been doing that for years."

The IRB requires informed consent for every study, even if it's secondary data or exempt research, Pellien says.

"Even with exempt research, we require them to have some sort of consent process," she adds. "They either have a signed consent process, or we require a waiver of signed consent."

Whenever there's interaction with subjects, there must be some sort of consent document.

The new Common Rule also changes the definition of "human subject:" "Human subject means a living individual whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens." ■

Preparing for the Transition to a Single IRB Policy

Exceptions include 'compelling justification' for multiple IRBs

One of the more sweeping changes in the revised Common Rule is the single IRB policy, which is designed to reduce unnecessary and duplicative review by several IRBs over a multisite human research trial.

However, there will be exceptions to this requirement when the regulations become effective, and there has been some confusion about the difference between a single and a "common" IRB. To address these and other issues, the National Institutes of Health (NIH) recently held a webinar meeting to explain this new approach.

To be compatible with the final revised Common Rule, the requirement to use single IRBs for multisite studies was to go into effect in 2020. However, the rule has been subject to delays and its fate is in question in the current antiregulatory political climate. On Jan. 4, 2018, HHS submitted a notice of "Delay of the Revisions to the Federal Policy for the Protection of Human Subjects." The implementation of the rule is delayed until July 19. *(The notice can be found at: http://bit.ly/2DmNtmT.)*

The single IRB policy has become a major theme of the rule revisions, and would likely remain an important aspect in the finalized version.

"All NIH-funded multisite domestic studies involving nonexempt human subjects research are expected to use a single IRB," said **Deysi Duque**, PhD, with the NIH Office of Extramural Research. "Sites must

be conducting the same protocol. It applies to all human subjects, not just clinical trials. It applies to all new and recompeting applications and proposals currently being funded. Also, for research funded through grants and development contracts."

Exceptions to the Rule

The single IRB rule does not apply to foreign sites and institutional training, she said, noting there are three types of exceptions. These include "policy-based" exceptions, when federal, state, tribal, local laws, regulations, and policies require local review.

"For example, tribal regulations and policies are given specific consideration in order to ensure the importance of their role is recognized," Duque said. "They do not require NIH exceptions review committee approval."

There also are "time-limited" exceptions, typically when ancillary studies are part of ongoing or parent studies. "These exceptions do not require a single IRB until the parent study is expected to comply with the single IRB policy," she said. "This is to ease some concerns about ongoing research without a single IRB."

The third exception is when there is "compelling justification" for local IRB review, which must be approved by an NIH exceptions review committee, Duque said.

"With the compelling justification exception, you want to identify the sites that are impacted and provide the justification," said **Petrice Brown-Longenecker**, PhD, an extramural Human Research Protection Officer at the NIH. "When you create your budget, you want to budget as if there was no compelling justification exception because you have not been granted one yet. The compelling justification exception must be approved by NIH. Once it has been approved by NIH and granted the award, the budget can then be adjusted."

Single or Central?

Two terms that have been used interchangeably and with some confusion are a "single" IRB and a "central" IRB, Brown-Longenecker said.

> "THE CENTRAL IRB IS USUALLY CREATED SPECIFICALLY FOR THE STUDY AS OPPOSED TO A SINGLE IRB, WHICH IS AN EXISTING IRB THAT HAS AGREED TO BE THE IRB OF RECORD."

"A single IRB is typically selected on a study-by-study basis," she said. "It's usually an existing IRB at an institution that agrees to serve as the IRB of record for a particular study."

Conversely, a central IRB is typically "set up or created" to review all sites that are participating in a study, she noted.

"The central IRB is usually created specifically for the study as opposed to a single IRB, which is an existing IRB that has agreed to be the IRB of record," she said. "So, unless the funding opportunity announcement or contract solicitation that you are applying to specifies the creation of a central IRB, you do not have to create one."

Some of the basic single IRB models include an existing IRB that is participating in the study or was awarded funding for the multisite study.

"Or, the investigator can decide to use an independent or unaffiliated IRB," Brown-Longenecker said. "We typically refer to these as commercial IRBs. Please note that the single IRB of record that's chosen does not have to be the parent site. It can be any of the sites or a commercial IRB, as we've mentioned. It's really the best IRB for the study. NIH will not select the IRB for the award unless it's a cooperative agreement or a contract that is determined to do so."

The single IRB selected must be registered with OHRP and must have membership for the study.

"When choosing the single IRB of record, it's important to keep in mind the type of study and the sites that are conducting the research," she said. "So again, the NIH isn't usually going to select the IRB — it's the best IRB for the study. And how do you know which is the best IRB? That's a study-by-study decision. But we suggest that participating sites work together ahead of time to determine the best IRB for the study. Make sure that all reliance agreements and communication plans are in place and up to date, either while you are writing the application or soon after the 'just-in-time' area of award." ■

Identifying Key Personality Traits Affected by Parkinson's Disease, Deep Brain Stimulation

Novel study asks which personality characteristics are most important

Parkinson's disease, and deep brain stimulation (DBS) procedures sometimes used to treat it can alter personality, including key traits that make a person, in essence, who they are.

While many patients and families report positive changes, there is a need to better identify exactly what personality characteristics may be affected and to what degree personality is altered. Knowing such information could help clinicians and researchers to provide more concise informed consent, says **Cynthia Kubu**, PhD, a neuropsychologist in the Cleveland Clinic's Center for Neurological Restoration.

Kubu recently received a $1.6 million grant over four years to study patients' and family members' perspectives regarding personality changes in Parkinson's disease and DBS. The study is funded by the NIH's Brain Research through Advancing Innovative Neurotechnology (BRAIN) initiative. The project is now in its fifth year, studying brain disorders like Alzheimer's, autism, epilepsy, schizophrenia, and traumatic brain injury. A central question is how these conditions affect the brain in terms of altering personality, an area Kubu is keenly interested in as a neuropsychologist.

"What I tend to hear most often from my patients and their family members in the context of Parkinson's disease — before they have even had the DBS — is that there are no significant [personality] changes. Or they will say he is more withdrawn, more anxious, quieter. There are dimensions of neurological disorders in which personality changes are much more dramatic. That's because they affect different parts of the brain. In which case, they may be more irritable or short-tempered or inappropriate, but that is a different kind of disorder. This grant is focusing only on patients with Parkinson's disease."

The study's data could be applicable to other conditions, as Kubu tries to discern whether existing measures capture personality characteristics most valued by patients and families.

"We are going to compare — measure, essentially — what the patient and the family members think are most important personality characteristics, and have them kind of rate those and then see how well they are correlated with existing personality measures," she says. The extent to which the most common existing personality measures really reflect patients' and families' values are most important, she adds.

Kubu is recruiting 150 patients with Parkinson's disease. Each patient will have a family member or a close friend who will participate in the study essentially as an observer of personality changes.

"So, we will have 300 people total enrolled in the study," she says. "Fifty of those will be within a few years of the diagnosis of Parkinson's disease; 50 will be five to seven years from their diagnosis of Parkinson's; and 50 will be those scheduled to have DBS. We will talk to those 50 patients as well their family member or close friend, before surgery, six months after surgery, and 12 months after surgery."

'What Trait Would You Least Like to Lose?'

We asked Kubu to provide more detail on this cutting-edge research, particularly as patients and loved ones try to assess whether the subject's sense of humor, for example, has been affected by the disease and/or the intervention.

IRB Advisor: Can you tell us a little about your background that has led you to this path of research?

Kubu: I am first and foremost a clinician — a neuropsychologist. Neuropsychology is the study of the brain and behavior, and we know certain parts of the brain are important for certain thinking skills. Some parts are important to memory, attention, language, but also aspects of our mood and personality — kind of who we are. Throughout my 25-year career, I've worked primarily with functional neurosurgery teams. In the last 18 years, I've worked primarily with deep brain stimulation [DBS] teams. My job is to see these patients before they go to have a deep brain surgery. Most people think Parkinson's disease is mostly a movement disorder — tremors, rigidity, trouble walking, and balance problems. But we know there are a number of non-motor symptoms that can occur with Parkinson's disease as well, including changes in thinking, mood, or personality.

IRB Advisor: What is involved in DBS?

Kubu: Deep brain stimulation is a procedure in which a tiny hole is drilled into the skull and an electrode is implanted deep in the brain with a connecting cable to something like a pulse generator — it's kind of like a cardiac pacemaker that's placed in the chest. You control the stimulation of that electrode to maximize benefit and minimize harm or side effects. The procedure is highly effective in treating the motor symptoms of Parkinson's disease.

[For the most part], it doesn't really impact their thinking or the non-motor symptoms. My job with the deep brain stimulation team is to kind of help identify what are the potential risks to these people that go on to have an elective surgical procedure designed to improve their quality of life. That's where the ethics comes in because it is related essentially to informed consent. The concern I have after seeing thousands of these patients is that the existing measures to look at personality may not capture what is most important to patients and their family members. From the IOM patient-centered care ethical mandate, and from a clinician's perspective, that is probably what is most important — what is most meaningful to the patient.

IRB Advisor: So, you want to better identify and measure personality changes associated with Parkinson's disease and DBS?

Kubu: The goal of this study is really to identify the personality characteristics of the patients and, in a separate interview, what their families and friends think are the most important things that really define who the patient is. Then, to see if there are changes associated with Parkinson's disease and deep brain stimulation on the characteristics that are identified. That feeds into an informed consent issue that is relevant to ethics.

Furthermore, we know from some of the literature, there are some people who think it is bizarre to have an implant in the brain. Some of the literature in the philosophy realm or bioethics has questioned this [in terms of] your surrounding identity. If you've got this implant [in your brain], are you really you? There are a few isolated case studies in which patients did show some pretty dramatic changes as the result of stimulation, and that was quickly addressed. The vast majority of people, though, really don't observe changes — at least, that's been my clinical experience.

IRB Advisor: How do the data to date inform this topic?

Kubu: What we can say is that some pilot data suggest patients and family members attribute more negative changes to the Parkinson's disease. Then, after DBS, the majority say they haven't observed any changes, or if there are changes they tend to be positive and more like who [the patient] was before the disease. In terms of the [personality characteristics] that are most important from the patient and family perspective, about 75% of the patients said they did not see any changes in their personality related to the DBS, and 25% said they are more like they used to be. And that helps in terms of the informed consent decision-making. I think what is unique is that this is very much from the patients' and the family's perspective, which is what matters the most.

IRB Advisor: Just to clarify, the NIH grant you received will be used to try and improve the informed consent process and/or review different measures of personality and possibly develop new ones?

Kubu: That is really the issue. My goal is really empirical nueroethics — to use the data to help other DBS teams identify what are personality and meaningful changes that occur in the context of Parkinson's disease and/or with DBS. That can help better inform clinicians when they go through potential risks, benefits, and side effects, so that there are data to guide that and it also can be used to develop measures that more clearly and accurately reflect patients' values, which is also ethics and then informed consent specifically regarding deep brain stimulations.

IRB Advisor: So, patients and families may ask if the subject will lose a sense of humor or no longer appreciate some aspect of life that is currently vital?

Kubu: That is the question we are trying to answer. I don't think there are really very many measures of sense of humor in terms of a personality scale. We are trying to identify what are those big buckets of things that people think are most important. I don't think it is necessarily going to be how smart you are. It's going to be, for example, how you interact with other people because I think we are inter-relational beings. What are the things that you never want to see that person lose? It could be sense of humor.

We are going to parse out the things that people value most in the humanity of their loved ones. I think some of the same things are going to bubble up to the top. Then, we can start to look at a couple of things. For example, we can design measures that reflect those measures if they don't already exist. Or, identify personality measures that do reflect those values. Then we can start to look at what are the underlying neuroanatomical correlates as well. Can we use those data to help other patient populations? ■

IRBs, Researchers Gain Much by Adding Statistical Reviewer

It didn't slow IRB process

After an incident involving a protocol modification, the Northwell Health IRB of New Hyde Park, NY, found that the board needed certain expertise that it had been lacking.

An investigator submitted a modification that included changes to the study design. The IRB sent the modification to an expert who found a problem with the study design and thought the revised study could expose research participants to risk, recalls **Hallie Kassan**, MS, CIP, director of the human research protection program at Northwell Health.

The IRB suspended the study, believing it no longer met criteria for approval.[1]

"The study sounded fine as written, but when you studied the numbers you could see it wasn't a proper design," Kassan says. "We put the study on hold until the design was revised."

That near-miss highlighted the need for the IRB to have a professionally trained eye look at studies' statistical designs when they pose greater than minimal risk, she adds.

The IRB decided to assign a statistical IRB reviewer to all studies that were investigator-initiated and greater than minimal risk. The IRB also created a two-page statistical reviewer checklist. The reviewers can have valuable effect on the 46.111 approval criteria, specifically numbers one and two.[1]

Adding a statistician to the IRB seemed like a good solution. But would it cause IRB review delays?

"We were interested in whether the addition of statistical reviewers on a consistent basis would lead to additional delays," says **Jon Newlin**, CIP, assistant director of human research protection program at Northwell Health.

"We looked at data where there were no scientific reviewers, and we looked at it after the change, and what we found reassured us," Newlin says.

> "WHEN STUDIES WERE DEFERRED AFTER THE CHANGE, IT WAS FOR REASONS THAT MAY INCLUDE STATISTICAL ISSUES, BUT THEY WERE NOT THE SOLE REASON."

Adding a statistical reviewer did not increase the rate of study deferrals.[1] "When studies were deferred after the change, it was for reasons that may include statistical issues, but they were not the sole reason," Newlin says. "The studies would have been delayed, anyway."

Finding statistical reviewers proved to be easy, as IRB chair Martin Lesser is an associate vice president of the biostatistics unit and could refer experts from his office, Kassan notes.

"Within the organization, we have a research institute, and because of that they created a biostatistics unit," she says.

When the IRB rolled out this change, IRB leaders met with the biostatistics unit and discussed the human subjects research criteria for approval and how these apply to the biostatistics issue, Newlin explains.

"We talked about issues one and two, and built the checklist around the kinds of things that might impact one and two in the criteria," he says. "For instance, the example we gave was having a sample size larger than needed to meet study objectives."

Additional examples of statistical problems that could affect the criteria for approval are included in the statistical reviewer checklist. The following are some sample items:

- deficiencies in randomization, study design structure, clearly defined aims, etc. may result in the inability to achieve meaningful results;
- inappropriate or lacking power or precision analysis could decrease the likelihood of developing knowledge to the point that risks no longer are reasonable.

The statistical reviewer checklist also includes reviewer tips, such as the following:

- "If the PI refused to adopt a suggested change, would you assess that the study does not meet the criteria for approval? If not, then the recommendation should be a suggestion instead of a requirement."
- "Will risks to subjects be reduced by the suggested change? If so, and the change will not make the study undoable, then the change is required by criterion 1."

Since adding the role of statistical reviewer, the IRB has had positive outcomes. "We have this extra level of review with additional feedback," Kassan says. "It will ultimately protect our participants and ensure there are better study results that come out of our studies."

Performing a statistical review of investigator-initiated studies that are greater than minimal risk has improved the research and ensured that participants' time on studies has value, she adds.

The IRB's statistical reviewers undergo the same human research protection training as all IRB members, including a general orientation and CITI-training, Newlin says.

During IRB meetings, the board encourages statistical reviewers to voice their opinions during discussions of protocols.

"We ask them if they have any comments, and they are specifically given the floor," Kassan says.

While not all of the statistical reviewers' comments might pertain directly to criteria for approval, those that do affect the criteria can affect the study's status.

"What's interesting about having statistical reviewers on the IRB is they have a very unique expertise, and they are the only ones at the meeting with that expertise," Newlin says. "So we rely on the statistical reviewer to be the expert, and with any statistical issues that come up, you have to be careful they do relate to the criteria for approval."

Other IRB members might approve of a study, but if the statistical reviewer finds that the study's aims do not match the statistical analysis plan, then there's a problem noted.

"We incorporate statistical feedback in the IRB feedback letters, listed alongside all other referral issues," Newlin explains. "Sometimes the issues are significant, and we ask investigators to make an appointment with the biostatistics department service."

While investigators are not required to use the biostatistics service, it could be useful.

When a statistical reviewer finds a problem with a study, the IRB's action to suspend or deny the application is based on IRB criteria for approval. "We try to explain carefully in our letters why this is a question and how we can't find the criteria for approval to be met," Kassan says. ■

REFERENCE

1. Lesser M, Newlin J, Kassan H. Using statistical reviewers on an IRB. Poster presented at PRIM&R's 2017 Advancing Ethical Research Conference, held Nov. 5-8, 2017, in San Antonio.

Improve Staff Efficiency, Productivity With These Tips

Keep staff in the loop

Staff training that includes a thorough focus on each employee's job description and expectations, along with staff engagement, can be crucial to improving an IRB office's workflow and efficiency.

Consistency also is key. One person should not receive more training than another person, says **Angela Brown**, REEGT, IRB Panel A administrator in the office of research subjects protection at Virginia Commonwealth University (VCU) of Richmond, VA.

The change has resulted in a 13% decrease in time to approval, and there's a 3% increase in general satisfaction of the IRB.[1]

Brown offers the following suggestions for how IRBs can improve their staff training and education:

• **Discuss with staff their perceived strengths.** When the VCU IRB changed from having four separate medical IRBs that each met monthly to having one IRB that meets each week, the staff administrators for each board were suddenly working together. Their jobs and responsibilities were adjusted, as well.

"We met with our director to determine our strengths and weaknesses," Brown says.

The director asked:

- Did we prefer one study over another?

- How did we prepare for a meeting?

- What work do we like to do best?

• **Modify job descriptions.** As job descriptions were modified to fit the new, more collaborative IRB administrator model, there was a

focus on improving training of how to write minutes and becoming more proficient, Brown says.

IRB leaders consulted with staff to learn more about their strengths.[1]

"There were different goals set for us individually," she says. "Management rewrote our job descriptions and told us what we needed to be doing."

• Engage staff to identify ways to modify workflow. Managers and staff looked at each person's strengths and role for meetings.

"Before we switched to a single board review, we had worked independently," Brown says. "Now the three of us work well together as a team, and it's a team effort."

Administrators helped their teammates manage the new workflow and tasks. "We were overwhelmed in the beginning — it's a fairly busy office," she says.

For instance, when there were four IRBs, administrators would take more time — maybe a week — to turn around meeting minutes. With the new, weekly meeting schedule, they are supposed to have their meeting minutes completed the next day, Brown explains.

"Now there are three of us writing up 12 submissions," she says. "Management wanted the minutes done in a day; investigators are anxious to get started, and we don't send out letters until the minutes are done."

Other workflow changes include:

- IRB staff use new review checklists, tracking documents, and templates to assist with study reviews;
- new workflow deadlines;
- the IRB office meets weekly to discuss meeting agendas prior to the IRB meeting.[1]

The workflow is more manageable for investigators, and the time to review turnaround is faster.

"We're not just getting our minutes done faster, but we're getting approval letters out to investigators more quickly, so they can make the study changes needed and get it back to us," Brown says. "That was really what was the deciding factor to get everything reduced, getting research approved faster."

"WE'RE NOT JUST GETTING OUR MINUTES DONE FASTER, BUT WE'RE GETTING APPROVAL LETTERS OUT TO INVESTIGATORS MORE QUICKLY, SO THEY CAN MAKE THE STUDY CHANGES NEEDED AND GET IT BACK TO US."

Another workflow change involved the time to add studies to the agenda. Previously, investigators could submit a study at the beginning of the month and wait a few weeks to get it on the board agenda. Now, they don't have to wait more than a week, Brown says.

"The workflow is more manageable this way," she says. "In the beginning, it was more overwhelming because it was just trying to get through things in a faster period of time."

• Create comprehensive IRB minutes training with staff participation. "We had IRB minutes training that involved self-paced, once-a-week topics that lasted about six weeks," Brown says. "It was in Google Docs and had a quiz at the end."

The topics included:

- regulatory requirements of minutes;
- summarizing versus transcribing;
- organization of a discussion;
- clarifying panel decisions;
- drafting and editing;
- correcting mistakes and problems;
- revising;
- substantive versus administrative issues;
- documenting unspoken parts of an IRB discussion.

"These helped us complete the minutes more efficiently," Brown says. "We have a manager who looks at our minutes, and in the beginning there were changes sent back to us that needed to be made, and now, across the team, we usually don't have many revisions to make in our minutes."

• Collect IRB staff feedback on what's working. Managers met informally with administrators to see which changes worked and which did not.

"We didn't make a lot of changes once we started the process," Brown says. "We thought about changing things and having one administrator at each meeting, but we decided not to do that, so we have all three go to each meeting."

Managers had their own expectations of how administrators would handle their workflow, but they were open to adjusting these when something did not work well, she adds.

"In the end, all three of us came together as a team," Brown says. "If someone was not feeling well and couldn't make it to the meeting, someone would pick up their slack."

• Engage staff in a comprehensive training and

competency assessment process. "We had a 50-page training packet that covered a lot," Brown says. "They wanted to know that we understood FDA regulations and different types of studies."

The training and competency assessment process included information about humanitarian devices, informed consent, and reviewing the submission process. "We wanted to make sure all requirements were included with that submission."

A checklist helps them account for all items. Also, the competency training was based on the meeting minutes and the amount of time necessary to complete the work, Brown says.

"It also was preparing for minutes and our taking quizzes," she adds. ■

REFERENCE

1. Hicks S, Haywood N, Brown A. The professionalism of IRB staff members. Poster presented at PRIM&R's 2017 Advancing Ethical Research Conference, Nov. 5-8, 2017, San Antonio. Poster: 35.

Is It Safe? NIH Ends Moratorium on Enhancing Pandemic Pathogens

'Ethics involves inevitable uncertainty'

"Gain-of-function" research designed to make pathogens deadlier or more transmissible in order to develop treatments and countermeasures has been given a green light by the National Institutes of Health (NIH).

The NIH pulled the plug on such research on Oct. 17, 2014, after several incidents that could have led to public health threats, not the least of which were breaches in working with anthrax and bird flu in the prestigious labs at the CDC.

"During the funding pause, the U.S. government undertook a deliberative process to assess the potential benefits and risks associated with these types of studies," the NIH stated in a Dec. 19, 2017, announcement.[1] "The purpose of this guide notice is to notify applicants that in accordance with the December 2017 issuance of the Department of Health and Human Services' 'HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens,'[2] the National Institutes of Health is removing the funding pause on the provision of new or continuation funding for gain-of-function research projects."

The research could enhance pathogenicity and/or transmissibility of a potential pandemic threat. The pathogens likely targeted include MERS coronavirus or H5N1 avian influenza, both of which could cause considerable human suffering and mortality if they mutated to improve virulence or transmissibility. Enhancing these deadly pathogens in high containment labs could anticipate such a mutation in nature, allowing for the development for treatments and vaccines if the viruses eventually mutate in the wild or through the efforts of bioterrorists. Of course, the risks include an enhanced pathogen escaping the lab and the possibility that the methods used could fall into the hands of those wanting to weaponize the microorganisms.

One study reviewed a framework to access the ethics of such research, but concluded that "difficult judgments will need to be made. … There might not always be clear right answers regarding whether a given case of gain of function research should proceed (or be funded). Like risk-benefit assessment, ethics involves inevitable uncertainty."[3]

Safeguards

To prevent accidents and incidents and ensure the work is conducted under controlled conditions, HHS calls for the following criteria for research on a potential pandemic pathogen (PPP):

- the research has been evaluated by an independent expert review process (whether internal or external) and has been determined to be scientifically sound;
- the pathogen that is anticipated to be created, transferred, or used by the research must be reasonably judged to be a credible source of a potential future human pandemic;
- an assessment of the overall potential risks and benefits associated with the research determines that the potential risks as compared to the potential benefits to society are justified;
- there are no feasible, equally efficacious alternative methods to address the same question in a

manner that poses less risk than does the proposed approach;

• the investigator and the institution where the research would be conducted have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly, mitigate potential risks, and take corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches;

• the research results are anticipated to be responsibly communicated, in compliance with applicable laws, regulations, and policies, and any terms and conditions of funding, in order to realize their potential benefit;

• the research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing federal and institutional oversight of all aspects of the research throughout the course of the research;

• the research is ethically justifiable. Nonmaleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the ethical values that should be considered by a multidisciplinary review process in making decisions about whether to fund research involving PPPs.

Though this will probably be determined on a case-by-case basis, it remains to be seen if possible bioterror agents would be approved for enhancement. For example, smallpox has been eradicated from nature, and thus may not be "judged to be a credible source of a potential future human pandemic." However, frozen stores of smallpox — to which much of the Earth's population is now susceptible — are still held by the United States and Russia. In addition to smallpox, the Department of Homeland Security lists other agents that meet the "material threat determination" as threats to national security if weaponized. These pathogens include anthrax, glanders, melioidosis, botulism toxin, hemorrhagic fever, tularemia, MDR anthrax, typhus, and plague.[4] ■

REFERENCES

1. NIH. Announcing the Removal of the Funding Pause for Gain-of-Function Research Projects. Dec. 19, 2017. Available at: http://bit.ly/2z6aG5Q. Accessed Jan. 11, 2018.
2. HHS. Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens. 2017. Available at: http://bit.ly/2EoC41J. Accessed Jan. 11, 2018.
3. Selgelid MJ. Gain-of-Function Research: Ethical Analysis. *Sci Eng Ethics* 2016; 22(4): 923–964.
4. Trust for America's Health. Ready or Not? Protecting the Public's Health From Diseases, Disasters, and Bioterrorism. 2017. Available at: http://bit.ly/2FpqZif. Accessed Jan. 11, 2018.

Study: Pain Research Can Harm Participants

Researchers must pay greater attention to the rights of study participants in pain research, concludes a recent paper by the Ethics Committee of the Pain-Omics Group.[1]

"Patients in pain, particularly chronic pain, are vulnerable by virtue of being in pain and in their desire to be relieved of pain," says **David B. Waisel**, MD, senior associate in perioperative anesthesia at Children's Hospital Boston and associate professor of anesthesia at Harvard Medical School. Waisel authored a recent review which found multiple, continuing ethical issues involving research on patients in pain.[2]

"A narrow path permits providing good clinical care, doing good research, and protecting patients from a desperate headlong rush into research that may prove deleterious to them," says Waisel.

Widespread Ethical Issues

Some of the ethical issues Waisel found are widespread, but also are relevant to pain research. These include scientific misconduct, deception, placebo use, and genomics. Other ethical concerns are unique to pain research, such as research in neonatal pain management. "I approached this paper with the goal of including issues that were not commonly talked about," says Waisel. Some unique ethical concerns in pain research include the following:

• Some studies inadequately manage pain in neonates. "Relatively minor procedures in the neonate, such as heel pricks, can have lifelong consequences," says Waisel. "Too often, neonates do not receive pharmacologic or nonpharmacologic analgesia."

While there are a number of validated analgesic therapies, most studies assessing pain management in

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neonates do not use these validated therapies in the control group. "This exposes the neonate to unnecessary harm and possible long-term consequences," says Waisel.

This may be due to a misunderstanding that a new intervention must be compared to a placebo instead of to current therapies. "That is untrue, and, in fact, harmful to neonates," says Waisel.

• **Genetic pain research involving biobanking — the saving of a person's tissue — raises privacy concerns.** "This research is both incredibly valuable and very dangerous," says Waisel.

There is a debate about how to ensure proper informed consent regarding privacy, known and unknown long-term harms, and use of the tissue for future undefined studies. "There are no set answers for these questions, but researchers may prioritize the sacred trust of holding individuals' genomes," says Waisel.

• **Research fraud.** A major scientific misconduct case involving multimodal pain therapy was discovered in 2009.[3] Misconduct in pain research may lead to direct patient harm.

"Or there could be wider patient harm due to invalid data from inappropriate subject recruitment and data fabrication, falsification, or substandard research," says Waisel.

As with all research with human subjects, pain research by responsible investigators must ensure that participants are fully informed of the goals, procedures, and risks of the study before giving their consent. However, there's another important ethical consideration for participants who are in chronic, debilitating pain.

"Researchers have an added obligation that they are not providing consent in desperate situations," says **Robert Guerin**, PhD, a bioethics fellow at Cleveland (OH) Clinic and an adjunct instructor in bioethics at Case Western Reserve University.

Potential participants may feel they have no choice but to enroll in the study in order to relieve terrible pain. "Such desperate situations lead to vulnerabilities to coercive enrollment in clinical trials," says Guerin. He says pain researchers also have an ethical obligation to ensure that research subjects are not subject to stimuli that exceed a subject's tolerance limit; that subjects should be able to escape or terminate a painful stimulus at will; and that minimal intensity of noxious stimuli necessary to achieve the goals of the study must be established and not exceeded.

"This should be discussed during the informed consent process," says Guerin. "This ensures that patients are not subject to unnecessary harm during research."

Trust between investigators and study participants is important in all research with human subjects. Its importance is perhaps more pronounced in pain research. "Participants must feel no pressure to misrepresent their pain for the sake of continuing a trial, or for the sake of discontinuing a trial," says Guerin. ■

REFERENCES

1. Compagnone C, Schatman ME, Rauck RL, et al. Past, present, and future of informed consent in pain and genomics research: Challenges facing global medical community. *Pain Pract* 2017; 17(1):8-15.
2. Waisel DB. Ethics of research for patients in pain. *Curr Opin Anaesthesiol* 2017; 30(2):205-210.
3. Rittner HL, Kranke P, Schafer M. What can we learn from the Scott Reuben case? Scientific misconduct in anaesthesiology. *Anaesthesist* 2009; 58(12):1199-1209.