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Research Trust Issues Affect Vaccine Rollout

Equity is a challenge

By Melinda Young

The first month of the COVID-19 vaccine rollout among frontline healthcare workers was a reality check to the human research world after many people said no to the vaccine.

There are several reasons for vaccine hesitancy, including distrust in the accelerated vaccine development process.

"I think, hopefully, that this will be a wake-up call," says **Stephen B. Thomas**, PhD, founding director of the Maryland Center for Health Equity and professor of health policy and management at the University of Maryland. "We spend a lot of time asking people to accept the science, helping people to understand the regulatory oversight that goes into it."

> "IN THE END, IT WILL BE ABOUT AMERICANS TAKING THE VACCINE BECAUSE THEY BELIEVE THE PANDEMIC IS REAL, AND IT IS THEIR LIFE AND SAFETY ISSUES AND CONCERNS."

A major reason the vaccine has not been embraced by some communities is because there is no foundation of trust. Generations of medical and research abuses among vulnerable populations and communities of color have taken a toll that is seen in the halting rollout of the COVID-19 vaccines.

"When there's a history among communities of color of abuse, misuse, and misinformation, we argue for the research community to prove yourself trustworthy before you ask for trust," says **Rueben C. Warren**, DDS, MPH, DrPH, MDiv, professor of bioethics and director of the National Center for Bioethics in Research and Health Care at Tuskegee University. "There are incidences across history in this country where the trust

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has been repeatedly violated. The most onerous example is the U.S. Public Health Service syphilis study at Tuskegee."

Many Americans, including Black Americans, may be skeptical of the COVID-19 vaccines because of the term "Operation Warp Speed," Warren notes.

Operation Warp Speed is a "terrible" name for the vaccination program, said **Michael Osterholm**, PhD, a member of President Biden's COVID-19 Advisory Board. Osterholm also is the director of the Center for Infectious Disease Research and Policy at the University of Minnesota. He spoke about the vaccine distribution process in a web interview on Jan. 11. *(The interview is available at: https://wapo.st/39xyWSz.)*

"There were no safety steps shortened in this process," Osterholm noted.

But the quick development of the vaccines and the unfortunate name of the program have led communities to think the political thumb was on the scale in developing the vaccine, he said.

"We can make all the vaccine available, and the new administration can do everything it possibly can," Osterholm says. "In the end, it will be about Americans taking the vaccine because they believe the pandemic is real, and it is their life and safety issues and concerns."

Research organizations and IRBs will remain involved, even as the vaccines become ubiquitous in the United States.

"The first [vaccine] clinical trials will continue," said **Kathleen M. Neuzil**, MD, MPH, FIDSA, fellow with the Infectious Diseases Society of America (IDSA), and director of the Center for Vaccine Development and Global Health and Myron M. Levine professor in vaccinology at the University of Maryland School of Medicine. She spoke at IDSA's virtual COVID-19 vaccine briefing on Dec. 3, 2020.[1]

"The FDA says they should continue the trials for a minimum of two years," said Neuzil, co-director of the COVID-19 Prevention Network. "If there is any safety signal, those people will be five to six months ahead of where we are."

Researchers will collect safety information for at least two years, she added.

The research community knows the vaccine clinical trials will be more difficult over time as the vaccine is rolled out to the public, said **C. Buddy Creech**, MD, MPH, FPIDS, IDSA member and director of the Vanderbilt Vaccine Research Program in Nashville, TN. Creech is a principal investigator for Phase III trials for the Moderna and Johnson & Johnson COVID-19 vaccines. He also spoke at the Dec. 3 vaccine briefing.

"The design might have to be modified over time, where we compare one vaccine to another, focus on subpopulations," he said. "Focusing on different groups will be a challenge for us going forward."

There also is the question of ensuring equity as the public health community rolls out the vaccine to millions of people. The research community will deal with continued enrollment for the dozens of vaccine trials underway, but have not yet been approved by any government.

"We need those second-generation vaccines," Neuzil said. "We've seen an uptick in interest in being in a clinical trial."

The first two vaccines showed such great results (95% effective at preventing COVID-19) that people have reason to believe future vaccines also will be highly effective, she explained.

"We have to be careful with the rollout," Neuzil noted.

Since few COVID-19 vaccine doses were available to the public, it was ethical to continue with placebo-controlled vaccine trials. But the risk-benefit balance could shift once the emergency use authorization (EUA) vaccines are more plentiful.

"I see these trials continuing for the next month or two, and then there would have to be another reassessment," Neuzil said. "It's better to be right than consistent. This is a constantly changing field."

Pfizer/BioNTech, which developed the first COVID-19 vaccine to receive an EUA, and Moderna, which received the second vaccine EUA, have methodically communicated with study participants about the fast-track process of making the vaccines available to the public. "They sent letters, saying, 'We're going forward and have filed an EUA. We understand and have an obligation to provide vaccine to the placebo group,'" she added.

The vaccine trial participants are the real heroes, she said. "We all in society owe a huge debt of gratitude to these people who have stepped forward and taken the new vaccines," Neuzil said. "We owe the placebo group careful consideration, and at the right time, we should make sure they also have access and opportunity to get the vaccine."

Physicians and researchers also have to build public confidence in these new vaccines.

The vaccine rollout, which began with hospital and nursing home staff, faces the tricky dual challenge of ensuring supply and demand.

"We want citizens to say, 'Someone like me participated in these trials,' whether that is someone with diabetes, ethnic minority," Creech said. "When we introduce these vaccines for frontline healthcare workers, they need to know what to expect. We have a lot of work to do to educate healthcare workers in the community."

These concerns were not addressed adequately, judging by reports of vaccine hesitancy among healthcare workers in the first phase of the vaccine rollout. In late December 2020 and early January, media reports indicated many healthcare workers were choosing not to receive the vaccine. For instance, 40% of staff at a Chicago hospital, serving a predominantly African American community, said they would not take a vaccine.[2]

Worse, at the end of December 2020, Ohio Gov. Mike DeWine said 60% of nursing home employees were opting out of receiving the vaccine. Nursing homes were not mandating vaccination, even though nursing homes and long-term care facilities accounted for more than half of Ohio's COVID-19 deaths.[3] California also saw large numbers of frontline workers refusing to take the vaccine.[4]

The groundwork for reducing vaccine hesitancy among Black Americans and other minorities can start with research sites and IRBs. The contemporary IRB's process of informed consent exists because of a research atrocity, the U.S. Public Health Service syphilis study at Tuskegee, Thomas and Warren say.

"What made it so egregious is in the early days, there was no treatment for syphilis, but in the 1950s, they had penicillin, and then denied the men treatment," Thomas explains. "Tuskegee needs to be contextualized; it should not be used as a blunt instrument. Yes, the Tuskegee syphilis study is the longest nontherapeutic experiment on humans, but it's the aftermath that led to human subjects protection we have now."

The Belmont principles of beneficence, nonmaleficence, and respect for autonomy stemmed from the Tuskegee men's sacrifice. "The lesson to Tuskegee should be that Black people are not denied access to the vaccine and need easy access to the vaccine," Thomas says.

Black Americans also need assurances that any long-term health consequences of the vaccine are monitored and healthcare will be equitably available, Warren says. *(See*

article in this issue about building trust in minority communities.)

Ensuring equity in vaccine distribution will not be easy due to the need for concerted and well-planned education and outreach about the vaccine. It is important to help people understand that Operation Warp Speed did not mean researchers and IRBs were cutting corners on vaccine research, Thomas notes.

"'Warp speed' meant that we'll pay companies billions of dollars before they do anything; we paid them in advance," he explains. "We created a market for the product before we saw it, and we paid them to develop it, which is something we've never done like that before."

Influencers in the research and public health community need to let people know the actual research followed protocols and went through the same oversight and review as every other research study. "We put all this effort into getting a scientifically valid vaccine," Thomas says. ■

REFERENCES

1. Infectious Diseases Society of America. IDSA media briefing: COVID-19 vaccine progress report. Dec. 3, 2020. https://bit.ly/2LQPvkk
2. Hopkins CD, Valentine A. Some health care workers are hesitant about getting COVID-19 vaccines. NPR. Jan. 1, 2021. http://n.pr/38oVVjr
3. Ingles J. Ohio governor says 60% of nursing home workers declined COVID-19 vaccine. WOSU Public Media .Dec. 31, 2020. http://bit.ly/3q12i2j
4. Mosley T. California frontline workers are hesitant on COVID-19 vaccine, complicating state's recovery. WBUR. Jan. 1, 2021. http://wbur.fm/3hUxJbE

Research World Can Help Build Trust Among Minorities

Context helps in understanding

By Melinda Young

The COVID-19 vaccine rollout has raised issues about trust among many Americans who are hesitant or unwilling to take the vaccine. The issue of trust is especially problematic among minority communities that have been harmed in historic medical and research incidences.

People also are skeptical of a vaccine that was developed in record time, considering most vaccines take 10-15 years to make it to market.[1]

Although data from the first COVID-19 vaccine research suggests there are few serious adverse reactions to the vaccines, there are no long-term data. This is not reassuring to many people who are worried about receiving a novel vaccine, says **Rueben C. Warren**, DDS, MPH, DrPH, MDiv, professor of bioethics and director of the National Center for Bioethics in Research and Health Care at Tuskegee University.

If researchers and IRBs want to ensure more equity and diversity in clinical trials, and gain trust among Black Americans and other minority communities, they need to listen to the people they want to engage in clinical trials — and not just when they are ready to start a research project.

"You have to build trustworthy relationships before you ask something of the community," Warren says. "You do that first by engaging people from that community. That's not an automatic approval, but that's a good start."

The context of the vaccine rollout and the research ethics breaches that preceded this once-in-a-century public health crisis are important to note when trying to understand vaccine hesitancy.

"I believe in vaccines. I believe in vaccinations. Science has made it clear that people need vaccinations, but that's a different proposition in the context of how this vaccine has been communicated to the general public," Warren says.

Researchers and public health officials tried to share their confidence in the first vaccines among the public.

"We want there to be a great deal of confidence in this process. We want citizens to have confidence in taking the vaccine," said **C. Buddy Creech**, MD, MPH, FPIDS, member of the Infectious Diseases Society of America (IDSA), and director of the Vanderbilt Vaccine Research Program of Nashville, TN. Creech is a principal investigator for Phase III trials for the Moderna and Johnson & Johnson COVID-19 vaccines. He spoke at IDSA's virtual COVID-19 vaccine briefing on Dec. 3, 2020.[2]

It is not a quick and easy task to educate people about the safety of the

vaccines, especially among those with longstanding mistrust of research and the medical industry.

"We have to listen to people and their legitimate concerns, and see that hesitancy among African Americans has been earned," says **Stephen B. Thomas**, PhD, founding director of the Maryland Center for Health Equity and professor of health policy and management at the University of Maryland.

Warren suggests pharmaceutical companies provide uninsured research participants with five years of access to healthcare providers in a follow-up to their participation in the COVID-19 vaccine trials. This also could be a tactic for any investigators seeking to enroll underrepresented minorities, including people who are uninsured and are low income.

"Most studies say if there's a problem directly related to the trial then we'll take care of it and provide appropriate care," Warren says. "But if you ask low-income populations of people of color, who are uninsured, and ask them to take the risk, then what happens in two to five years from now if there are problems indirectly related to the vaccine, and they don't have insurance?"

States could fix this problem by expanding Medicaid (not all states have expanded this program under the provisions of the Affordable Care Act). This would provide coverage to low-income people. But pharmaceutical companies and other research sponsors also could help by providing uninsured research participants with health coverage that can be used at federally qualified health centers (FQHCs), Warren says. This also could convince more people to take the vaccine because they would no longer have to shoulder all the possible long-term risks of receiving the COVID-19 vaccine.

"You have the vaccination, and we'll enroll you in a FQHC for the next five to 10 years," Warren says. "That's not an unreasonable proposition."

It is one way to obtain vaccine acceptance from people who have historic and well-founded distrust of the medical and research communities. "Don't try to convince me to do something when the risk is one-sided," Warren says. "It won't be that expensive because FQHCs have a strong tradition of treating low-income populations at better cost and more efficiently, and they're trusted."

"Helicopter research," in which investigators from wealthier areas collect data from lower-income areas and leave, does not work, he adds.

"How does the research community — both public and private — prove itself trustworthy in communities that have a history of trust problems?" Warren asks. "Health disparities are getting worse during the pandemic, so don't blame it all on history."

Vaccine researchers spent a lot of time thinking about how to build confidence in the vaccine among minority communities, Creech noted.

"As we recruit individuals in clinical trials, we recruit a diverse population," he said. "We're having multiple conversations every week to intentionally ensure diversity."

Research organizations also are removing barriers in clinical trials that hinder acceptance of new therapies as they emerge.

"One thing you'll see is individual states and jurisdictions thinking intentionally about how we identify those in our communities at higher risk," Creech said. "We think hard about ensuring equitable access to those vaccines as they become available." ■

REFERENCES

1. The College of Physicians of Philadelphia. Vaccine development, testing, and regulation. Updated Jan. 17, 2018. http://bit.ly/2LOWnyo
2. Infectious Diseases Society of America. IDSA media briefing: COVID-19 vaccine progress report. Dec. 3, 2020. https://bit.ly/2LQPvkk

Chief Ethical Considerations for Continued COVID-19 Vaccine Research

Is placebo arm still ethical for vaccines?

By Melinda Young

The COVID-19 pandemic has created more uncertainty in human research protections in 2021. IRBs will see more non-coronavirus studies come their way, but they also will have to navigate the many COVID-19 trials that continue to be a big part of the research picture.

One issue IRBs will face is whether the benefits continue to outweigh the risks for people who enroll in COVID-19 vaccine studies. Now that

highly effective vaccines have received emergency use authorizations (EUAs), is it ethical for people to enroll in vaccine trials in which they could be assigned to the control/placebo arm?

Ethical Questions

The authors of a new paper from the National Institutes of Health (NIH) asked these two questions:

- "First, if a vaccine candidate is found to be safe and efficacious in a placebo-controlled trial, should the researchers continue that trial as designed?"
- "Second, should researchers continue to test other vaccine candidates using placebo-controlled trials?"[1]

"The primary ethical considerations are to ensure that the trials continue to have sufficient social value and do not expose participants to excessive risks," says **David Wendler**, PhD, senior researcher and head of the section on research ethics in the department of bioethics at the NIH Clinical Center. Wendler is the principal author of the COVID-19 vaccine trial ethics paper.

"With respect to social value, the question is whether or not a placebo arm continues to be needed to collect valuable information that could not otherwise be obtained," Wendler says.

IRBs also might face a third question: Is it ethical to continue to enroll people in COVID-19 vaccine trials when highly effective and safe vaccines could be available to them within months?

"The important question is to evaluate the risks to the participants in comparison to what would happen to them otherwise," he adds. "If an individual is a candidate for obtaining the vaccine outside of research, then it would be important to assess how the risks and potential benefits of being in the trial compare to receiving the vaccine."

IRBs and researchers might consider the feasibility of completing a placebo-controlled trial once an efficacious vaccine is available outside of research.

"This will depend on how individuals react to the possibility of getting the vaccine outside of the study, to the extent it's feasible, and also to their willingness to continue to participate in research," Wendler explains. "Because these factors are unknown to a certain extent, it requires predictions of how individuals will react in order to figure out what is the best approach."

> "THE PRIMARY ETHICAL CONSIDERATIONS ARE TO ENSURE THAT THE TRIALS CONTINUE TO HAVE SUFFICIENT SOCIAL VALUE AND DO NOT EXPOSE PARTICIPANTS TO EXCESSIVE RISKS."

Researchers need to develop plans for how new information about vaccine clinical trials is conveyed to participants. "The plan will need to be approved by the review committees overseeing the study," he adds.

"Rapid evaluation of vaccine therapy has allowed manufacturers to move toward EUAs. If they show a modicum of success, we'd like to end those trials so people can avail themselves of those therapies," said **Jonathan Seltzer**, MD, MBA, MA, FACC, chief scientific officer at WIRB-Copernicus Group (WCG) ACI Clinical. Seltzer spoke at a WCG webinar on Dec. 2, 2020.

A concern about the COVID-19 vaccines that receive EUAs is there would be a push to give the vaccine to the placebo wing so there no longer would be a controlled trial, says **Herschel S. Nachlis**, PhD, research assistant professor of government and policy fellow in the Rockefeller Center for Public Policy and Social Sciences at Dartmouth College.

"The problem with the EUA is that even if the short-term evidence is good, it would undermine the large-scale, Phase III trial," Nachlis says.

The Pfizer/BioNTech and Moderna vaccines received the first COVID-19 vaccine EUAs in the United States, with a 95% success rate. The evidence was so compelling that it appeared to alleviate many of the public concerns about a fast-tracked vaccine.

"The results on the mRNA vaccines were 95% efficacy against any disease and 100% efficacy against severe disease," said **Kathleen M. Neuzil**, MD, MPH, FIDSA, fellow with the Infectious Diseases Society of America (IDSA) and director of the Center for Vaccine Development and Global Health and Myron M. Levine professor in vaccinology at the University of Maryland School of Medicine. She spoke at IDSA's virtual COVID-19 vaccine briefing on Dec. 3, 2020.[2]

"If we can get enough vaccine out there, we could have an impact on this pandemic very, very quickly," Neuzil said. "We can save lives. We can keep people out of the hospital

and get people back to work, and children back to school."

Most of the vaccine side effects are short-term, and oversight will continue as the EUA vaccines are released. "The CDC and FDA already have robust systems in place to continue to monitor these vaccines," Neuzil added.

Vaccine Hesitancy

However, when the first vaccine doses were rolled out nationwide to healthcare professionals, on-the-ground reactions and uptake of the vaccines suggested the public was unconvinced the vaccines were safe. In December 2020, one in four Americans surveyed by the Kaiser Family Foundation COVID-19 Vaccine Monitor said they would not take the vaccine.[3]

IRBs can ask COVID-19 clinical trial sponsors to increase their transparency, which is essential to building trust in these new treatments and vaccines. For example, some sponsors are releasing details about how their clinical trials operate.

"I think it's been good they have released the protocols for these trials to a degree of transparency that isn't usually achieved," Nachlis says.

The Biden administration likely will start federal efforts to improve the vaccine rollout and increase public trust in the science behind the vaccines.

"I think one thing we'll see is something more closely approximating the standard of very deliberate, rigorous, politically insulated, and the almost obscure regulatory process that we're used to," Nachlis says. "We'll return to some sense of normalcy."

The public health crisis will continue, but it will not be fed by election-year pressures, he adds. ■

REFERENCES

1. Wendler D, Ochoa J, Millum J, et al. COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science* 2020;370:1277-1279.
2. Infectious Diseases Society of America. IDSA media briefing: COVID-19 vaccine progress report. Dec. 3, 2020. https://bit.ly/2LQPvkk
3. Hamel L, Kirzinger A, Munana C, et al. KFF COVID-19 Vaccine Monitor: December 2020. Kaiser Family Foundation. Dec. 15, 2020. http://bit.ly/35kSRCW

FWA Revisited: 'Checking the Box' and IO Responsibilities Under the Revised Common Rule

By Sue Coons, MA

Revisions to the Common Rule took effect in 2018, but questions remain about how these changes have affected the Federalwide Assurance (FWA) and institutional responsibilities under the FWA. Two advisors from regulatory compliance provider Advarra hosted a webinar in December, "Institutional Responsibilities under a Federalwide Assurance" to offer clarification to IRBs and institutional officials (IOs) on how to navigate these changes.[1]

Details of the FWA

Federal regulations under 45 CFR 46.103(a) describe the assurance requirement: "Each institution engaged in research that is covered by this policy, with the exception of research eligible for exemption under § 46.104, and that is conducted or supported by a federal department or agency, shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements of [the Common Rule]."[2] The FWA is the only written assurance accepted by the Department of Health and Human Services Office for Human Research Protections (OHRP), said **Lauren Hartsmith**, JD, CIP, director of regulatory affairs at Advarra. "It's the mechanism through which the institution assures compliance with the Common Rule."

Hartsmith thinks of the FWA as a written agreement in which an institution makes certain commitments it must honor. One of the mechanisms where an institution assures compliance within the FWA is a box in the applicability section that institutions can voluntarily select. If that box is selected, it indicates the institution is extending OHRP's compliance oversight authority to all research at that institution regardless of funding source, Hartsmith said.

"[Checking the box says] at this institution, we will follow the Common Rule for all research regardless of funding. If there are any issues with that research or if OHRP has questions about that research, OHRP

has the compliance oversight authority over that research, and we will honor that."

The box is not automatically checked. The selection can be changed later by going through the FWA process, updating the form, and resubmitting it to OHRP, Hartsmith said. She directed the participants to the OHRP website where they can click on the "Register IRBs and Obtain FWAs" tab and then go to the "IRB & FWAs Status" tab. From there, an institution can obtain a copy of its FWA to see if the box is checked.

If an institution is contemplating changing its voluntary checking of the box, get advice from legal counsel first, said **Lisa Rooney**, JD, managing director of Advarra's regulatory consulting services. "There are two states [New York and Virginia] that say that if you do not agree to abide by the Common Rule for all research regardless of funding source, then you will need to abide by the state laws that we have in place for human subjects research. That can have some negative effects on your human research protection program."

The checked box on the FWA is important to consider in multisite research, even in research activity that does not receive federal support. That research may be affected if one or more sites have an FWA and have checked the box. "If one or more of those sites has checked the box on the FWA, that site is committing to following the Common Rule for all research conducted at that institution," Hartsmith said. "The FWA ultimately becomes much broader than just having importance for research that's conducted or supported by the federal government."

Assurance Requirement Deletions

Under the Common Rule revisions, several requirements of the assurance process were deleted. These include an IRB roster, IRB grant review, a declaration of ethical principles, and a list of reviewing IRBs. Hartsmith emphasized that although these regulatory requirements were deleted, the FWA process remains unchanged, and these requirements are part of the FWA process.

"On an FWA, institutions still are going to need to designate a statement of ethical principles. They're going to need to designate at least one IRB, and they're going to need to submit an IRB roster and report changes in IRB membership to OHRP."

However, now that process is handled through the IRB registration system. "OHRP has said, however, that the public will learn about any changes to the assurance process before they're implemented, and that they'll have a chance to comment on the proposed changes."

Webinar participants questioned why provisions deleted from the regulations still are required on the FWA. Section 103 in the Common Rule sets the minimum information to be addressed in a written assurance process, but the government can go above and beyond that, Hartsmith explained. "The first step in terms of trying to modify the FWA process was to change the regulations, and then OHRP will need to go through a separate process to change the actual assurance form." Now that those elements are not written into the regulations specifically, she said, OHRP has the flexibility and the ability to modify the assurance process.

Research Eligible for Exemption

Another consideration under the revised Common Rule is the exception of research eligible for exemption, Hartsmith said. "Again, you need to be engaged in research, and it needs to be nonexempt research." If the box is unchecked on the FWA, the Common Rule

will apply for any activity that is supported or conducted by a Common Rule department or agency that is nonexempt, that meets the definitions of human subjects research, and in which an institution is engaged. If the box is checked on the FWA, the Common Rule applies for nonexempt activities that meet the definition of human subjects research, and in which the institution is engaged. The difference is whether the activity is supported by a Common Rule department or agency, Hartsmith said.

The revised Common Rule names eight research exemptions. One exemption is research in educational settings. "[The exemptions] cover a lot of what I would consider to be low-risk activities," Hartsmith said. "If an activity fits into one or more of these exemption categories, it's considered exempt research."

The concept of limited IRB review also is in the revised Common Rule and is noted in four of the eight exemptions. "Even though limited IRB review might be involved in an exemption, it's still considered exempt from other requirements of the Common Rule," she said.

In terms of when the Common Rule in its entirety applies, it has to be nonexempt activities. "If the activity meets one of these categories, then you don't have to worry about the Common Rule."

Research and Human Subjects

To meet the requirements of the Common Rule, an activity also needs to meet the definition of research and the regulatory definition of a human subject, Hartsmith said. "The activity is going to need to be a systematic investigation, including development, testing, and evaluation designed to develop or contribute to generalizable knowledge." The revised Common Rule includes four explicit carve-outs from the definition of research. Hartsmith suggested studying the full regulations to learn about those.

The definition of human subject means a living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction, or obtains or generates individual private information or identifiable biospecimens, Hartsmith said. The full regulations give other descriptions and requirements.

An institution must be considered engaged in nonexempt research activity for the Common Rule requirements to apply and for the need to even have an FWA to apply, Hartsmith said. The concept of engagement is not defined in the regulations or in a statute, but instead is largely addressed through OHRP educational materials. Hartsmith recommended that anyone wanting to learn about engagement begin with OHRP's mini-tutorial video on its website. An engagement analysis is really only necessary if an activity is nonexempt human subjects research covered by an FWA, she said. "I have a quotation here from the 2008 engagement guidance where OHRP says the determination of engagement depends on the specific facts of a research study and may be complex."

Understanding the concept is tricky, she said. "If you're trying to analyze whether or not your institution is engaged in research in a specific activity as it's contemplated by OHRP, and you're having a hard time doing that analysis and thinking through the issues, it's hard because this is a really tricky area. I recommend being patient, keep a copy of the relevant regulations and the guidance documents handy, and know you're aren't alone."

Generally, an institution is considered to be engaged when, for the purposes of a specific research project, its employees or agents obtained data about the subjects of the research through intervention or interaction, identifiable private information about the subjects of the research, or if the employees or agents obtained the informed consent of human subjects for the research, Hartsmith said. "OHRP has outlined specific scenarios where even if one of these things might be true, an institution might not be deemed to be engaged in research, but you'll need to go through the OHRP guidance document for more information."

Another rule states if the only portion of a nonexempt human subjects research activity conducted at an institution would on its own be considered exempt or would be considered not human subjects research, then that institution is not engaged, she said. One exception is that in any scenario where there is federal support, at least one institution needs to be determined to be engaged in any nonexempt human subjects research activity.

IO Responsibilities

Rooney spoke about IO responsibilities under a FWA vs. the institutional responsibilities. The IO commits the institution to compliance with federal regulations, she said. "In fact, the FWA instruction provides that the person signing the FWA on behalf of an institution has to be an official that is legally authorized to represent and bind the institution to the terms on the FWA."

When an IO signs the FWA, the IO is signing and assuring the

IO understands the institution's responsibilities under the FWA. "The IO is also assuring that any human subjects who are going to participate in research that falls under the institution's FWA will be protected and also assures that the IRB on which the institution will rely, be it an internal or an external IRB, will comply with the terms of the institution's FWA when reviewing research."

Rooney placed the IO responsibilities into two buckets. The first bucket are those responsibilities that remain constant, regardless of whether an institution relies on an internal or external IRB for the review approval or oversight of nonexempt human subject research that is covered by the institution's FWA. The second bucket consists of IO responsibilities that can change depending on whether an institution relies on an internal or external IRB.

"What is important to note here is that if an institution is going to rely on an external IRB for review and approval of research, the IO's responsibilities are governed by the IRB authorization agreement that's covering the research that's to be reviewed," Rooney said.

Regardless of where the IO responsibilities fall within these two buckets, the IO is responsible either solely or collectively, with support from the external IRB, for assuring the institution complies with the Common Rule when the institution, employees, or agents engage in nonexempt human subjects research.

Rooney reviewed several IO responsibilities that remain the same regardless of whether the institution relies on an internal or external IRB:

• Understanding human research protection program (HRPP) responsibilities. The IO should complete many different training modules, at the minimum the OHRP module specific to IOs.

• Setting the tone of respect for complying with the regulations and for protecting human subjects. "If a culture of compliance doesn't come from the top from your IO, then an institution will most likely not have a robust human research protection program, and may not be able to provide potential human subjects with the protections that are needed," Rooney said.

"IF A CULTURE OF COMPLIANCE DOESN'T COME FROM THE TOP FROM YOUR IO, THEN AN INSTITUTION WILL MOST LIKELY NOT HAVE A ROBUST HUMAN RESEARCH PROTECTION PROGRAM."

• Designating OHRP-registered IRBs to review research covered by the FWA. "You are required to designate an IRB on your FWA, be it internal or external," she said. This is simple with an internal IRB, but more complicated with an external IRB. With the external IRB, IOs must ensure the IRB is registered with OHRP, that it is active, and that it is registered to review the type of research that IOs are seeking. Lastly, the IOs also have to enter into a comprehensive IRB authorization agreement.

• Ensuring reports are submitted to federal agencies. These reports could give information about unanticipated problems involving risks to subjects or other serious or continuing noncompliance. For the internal IRB, it could involve a suspension or termination of IRB approval.

• Providing OHRP guidance to the research community.

• Submitting, renewing, and updating the FWA according to regulations and current policy at OHRP.

• Confirming that assurances are in place for all the participating sites that are conducting nonexempt human subjects research activities for the study, and that IRB reviews and certifications are submitted to the appropriate authority.

• Not approving a research project that has been disapproved by the IRB.

• Serving as a knowledgeable point of contact for OHRP. Rooney shared a story in which an IO at an institution had no idea who the OHRP representative was during a site visit or why the agency may be visiting.

• Responsibility for signing any memoranda of understanding or agreements regarding the institution's HRPP.

Creating Authorization Agreements

The IRB authorization agreement is an important component of using an external IRB. "With the revised Common Rule, there is a provision under 45 CFR-46-103(a), which says that whenever an FWA-covered research protocol is going to be reviewed and approved by an IRB that is external to the institution that's conducting the research, the institutions and the external IRB

must enter into an IRB authorization agreement," Rooney explained.

These agreements can be relatively short and simple, such as applying to only one protocol, or they can run several pages and apply to all human subjects research covered by the institution's FWA. "At a minimum, the IRB authorization agreement has to include the skills of the institutions relying on the IRB for the research, as well as to allocate the roles and responsibilities between each entity, what those roles will be undertaken, and which people undertake those roles. Between the institution and the IRB, the institutions are ensuring compliance with Common Rule requirements when reviewing, approving, and conducting the research."

Make sure any roles and responsibilities are clearly allocated in the IRB authorization agreement, and that both parties understand who is responsible for each task before undertaking the review, approval, and oversight of research, Rooney said. "Failure to do so can result in noncompliance."

During a site visit, Rooney recalled when an IO and an IRB each claimed the other owned records particular to one protocol. "As a result of this misunderstanding, no one maintained these records and IRB documents, and that discovery was made in front of a regulatory agency. It's important to iron out these roles and responsibilities."

Changing IO Responsibilities

Rooney discussed IO responsibilities that can change when using an external IRB:

• **Training.** When relying on an external IRB, the IO will train IRB staff on how the institution's internal IRB will communicate with the external IRB and the investigators. "Beyond that, you as an IO may want to just ensure that the external IRB members are being trained," she said.

• **IRB resource, space, and staff requirements.** If the IO is using an internal IRB, he or she should provide sufficient resources, staff, and space. If the IO relies on an external IRB, then the IO should perform due diligence to make sure the external IRB provides them.

• **The receipt of written procedures, recordkeeping, and required reports.** "The IO could ask for a review of policies and procedures, IRB meeting minutes, and audit findings to conduct its own oversight and ensure that some oversight is occurring. The IO also could notify the IRB of any issues that the institution may discover while working with the external IRB," Rooney said.

• **IRB information.** The IO may ask the external IRB for a copy of the IRB roster. If the IRB does not want to give out the roster, it could provide certification indicating that it satisfies regulatory requirements.

• **Investigator oversight.** "Investigator oversight tends to be somewhat of a collective responsibility between the IO and the IRB when relying on an external IRB. The IRB authorization agreement should define how investigators will be overseen," Rooney said.

An IO satisfies responsibilities when relying on an external IRB by conducting due diligence before executing an IRB authorization agreement with an external IRB, Rooney concluded. Second, an IO needs to enter into a comprehensive authorization agreement that clearly allocates the responsibilities between the IO and the external IRB. Those responsibilities, she said, should collectively cover all Common Rule requirements related to the research. ■

REFERENCES

1. Advarra. Institutional responsibilities under a Federalwide Assurance (FWA). December 2020. https://bit.ly/3ijj7mE
2. Electronic Code of Federal Regulations. 45 CFR 46.103(a): Protection of human subjects. July 19, 2018. https://bit.ly/3bHvpnm

IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **Surveys and governors reported problems with COVID-19 vaccine hesitancy and vaccine refusal among:**

   a. people younger than age 30 years.
   b. Republicans.
   c. healthcare workers.
   d. Asian-Americans.

2. **What is an important research ethics question to ask in COVID-19 vaccine trials, according to David Wendler, PhD?**

   a. Is a placebo arm needed to collect valuable information that could not otherwise be obtained?
   b. Should COVID-19 vaccine trials be closed once viable vaccine candidates are found?
   c. Is it vaccine trial sponsors' responsibility to follow the health of all people who receive a vaccine that remains under investigation, but is offered publicly?
   d. Should children receive the vaccine without benefit of clinical trials data on children?

3. **Which is a responsibility of an institutional official?**

   a. Setting a tone of respect for complying with the regulations and for protecting human subjects
   b. Reporting research results to ClinicalTrials.gov.
   c. Visiting research sites to ensure compliance.
   d. Hiring IRB office staff.

4. **Which is one of the eight research exemptions in the Common Rule?**

   a. Research involving deception
   b. Research in educational settings
   c. Research involving prisoners
   d. Research involving minors

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

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