IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

INSIDE

Relias Media

From Relias

MARCH 2021 Vol. 21, No. 3; p. 25-36

Study Shows Research Programs and IRBs Responded Quickly to the Pandemic

By Melinda Young

Human research protection programs (HRPPs) and IRBs nationwide responded quickly and efficiently to changing processes and policies during the early months of the COVID-19 pandemic, according to the results of a recent study.[1]

Investigators surveyed HRPP staff, IRB members, and researchers across the United States. "We used census divisions and sent out a call for participants from two institutions in each region of the census tract," explains **Nicole Lederer**, MEd, associate compliance analyst for the University of Toledo HRPP. "We tried to get a sample from all through the U.S. We were hoping to gain insight on where improvements could have been made to make things flow a little more smoothly."

> "COVID RESEARCH WAS COMING IN, AND IT WAS VERY IMPORTANT TO MAKE IT A PRIORITY, TO REALLY MOVE IT ALONG QUICKLY."

Many universities and research institutions moved to remote work schedules in March 2020. Investigators wanted to see how this affected their work, says **Mahesh Pillai**, MD, PhD, CIP, associate compliance analyst at the University of Toledo.

Sixty percent of participating IRBs and HRPP staff said their institution's administration provided clear directives regarding procedures for conducting research with human subjects during the COVID-19 crisis. Another 26% reported they received some directives, and 14% reported none.

"These results posed additional questions," Lederer says. "A lot did pose clear guidance, but some did not. Where was the breakdown?"

Another survey question asked how well the IRB accommodated changes

Financial Disclosure: Dr. Ball, nurse planner, reports she is on the speakers bureau for AORN and Ethicon USA. The relevant financial relationships listed have been mitigated. None of the remaining planners or authors for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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:
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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.

1.5 ANCC contact hours will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

This activity is valid 36 months from the date of publication.

This activity is intended for clinical trial research physicians and nurses. It is in effect for 36 months from the date of publication.

AUTHOR: Melinda Young
AUTHOR: Sue Coons
EDITOR: Jill Drachenberg
EDITOR: Jonathan Springston
EDITORIAL GROUP MANAGER: Leslie Coplin
ACCREDITATIONS DIRECTOR: Amy M. Johnson, MSN, RN, CPN

implemented by their institution. Ninety-three percent of respondents said their IRB was accommodating, and 7% were neutral. The neutral response might have been from institutions that shut down research during the crisis, Lederer says.

The study also revealed 72% of participants believed their COVID-19-related research was reviewed and approved faster than usual, and 16% said it was the same. "Everyone was trying to figure out what was going on and how to help the situation," Pillai says.

"It was a public health crisis, and everyone was concerned about this," Lederer adds. "COVID research was coming in, and it was very important to make it a priority, to really move it along quickly." Researchers wanted to obtain data on what was happening related to the pandemic during this huge public health crisis, she notes.

About 39% of the survey respondents said they planned to add a section on disaster preparedness to their HRPP procedures. Research institutions might have created disaster plans for localized crises, such as major weather events or data breaches, but many had not anticipated a disaster that would shut down the entire nation, as well as many international supply chains.

"We haven't had a major pandemic in a while; the last one was in 1918," Pillai says. "We haven't had a pandemic of this magnitude that would shut down everything, and I don't think we saw it coming."

Turning to Agencies for Guidance

IRBs and HRPPs that were looking for guidance referred to federal websites, such as the U.S. Department of Health and Human Services (HHS), for information on creating policies and procedures during this new pandemic, Pillai explains. For example, HHS offers emergency preparedness information on COVID-19 and HIPAA.[2] The Food and Drug Administration and the Office for Human Research Protections (OHRP) also offer guidance on COVID-19, including crisis management information.[3]

"OHRP's guidance document on disaster preparedness was not designed for a national pandemic; it was localized," Lederer explains. "Planning for a national pandemic was not on the forefront of any HRPP offices' minds, and it wasn't made a priority."

The fast and efficient move to remote IRB work by most HRPPs likely was facilitated by the fact that most larger research institutions had implemented electronic IRB submission systems. "Since they have flexibility, they could do more of their work remotely," Pillai says.

It also helped that federal agencies issued guidance documents fairly quickly, and the national shutdown of in-person activities gave IRB administrators more time to create revised or new policies and procedures for the pandemic. "Institutions and higher administration were quickly able to formulate their own internet procedures, and those procedures were implemented really fast," he says.

Administrative tasks that were not a priority were put on hold. "Those tasks are all very important," Lederer explains. "But when it comes to accommodating changes associated with a pandemic, those are the kinds of things that probably were put on hold so the public health crisis could be addressed and research participants were protected."

Sociobehavioral and educational researchers adapted more easily to the new virtual reality of IRB and research work because they already conducted many online and virtual research activities. "For them to modify their procedures was not something that was uncommon to most of these researchers," Lederer notes. "Making that virtual transition was something they were already familiar with in terms of informed consent and confidentiality measures."

Although the biomedical research community was less familiar with virtual processes, they adapted. "Biomedical research institutions had to determine whether research was essential or provided direct benefits to participants, and they had to figure out which of these procedures can be conducted on the phone or Zoom call," Pillai explains. "Then, they made changes to their research to accommodate these new procedures."

As the pandemic continues — and some areas likely will see their COVID-19 cases and hospitalizations drop faster than other areas — research sites will need to adjust their policies and activities to what is happening in their individual states, Lederer says.

"We had the majority of respondents indicate they followed guidelines as implemented in their state to create guidance to protect human subjects during the pandemic," she says. "Institutions are following what their states are doing. If their state is shutting down, they're shutting down."

States and research institutions will need to keep a close eye on the COVID-19 numbers to inform future decisions, Pillai says.

"I think there will be regular evaluation of the procedures," he adds. ■

REFERENCES

1. Pillai MR, Lederer N. Impact of the COVID-19 pandemic on human subjects research. Presented at the PRIM&R Advancing Ethical Research Virtual Conference, Dec. 1-2, 8-9, and 15-16, 2020. Poster/Abstract:46.
2. U.S. Department of Health and Human Services. Emergency situations: Preparedness, planning, and response. Content last reviewed Jan. 20, 2021. http://bit.ly/3nAhDW6
3. Office for Human Research Protections. OHRP guidance on coronavirus: Research guidance on coronavirus. Content last reviewed April 8, 2020. http://bit.ly/3nAWgUn

Researchers and IRBs Reconsider Minimal Risk After Trial Results

Increased mortality rate in some hospitals led to new IRB monitoring and oversight

By Sue Coons, MA

A clinical trial that involved studying electronic health record alerts (e-alerts) for acute kidney injury seemed to be minimal risk to both the researchers and the IRBs that approved it. However, when two hospitals involved in the study reported an increased mortality rate, the researchers and the IRBs reconsidered what is truly minimal risk in these types of studies.

F. Perry Wilson, MD, MSCE, a nephrologist and associate professor of medicine at the Yale School of Medicine, and colleagues decided to study if e-alerts would help improve patient outcomes of mortality, dialysis, and progression of acute kidney injury (AKI). Wilson also is the director of Yale's Clinical and Translational Research Accelerator.

Wilson says the researchers thought they would see broad improvement in care processes, and likely a "smaller, but still beneficial effect on clinical outcomes in AKI."

"Our observational data were quite clear. Healthcare providers were not picking up on AKI when it happened, so it seemed a reasonable assumption that cluing them in would be helpful," he says.

Wilson and colleagues were concerned about e-alert fatigue. "In fact, it's our concern about alert fatigue that makes us argue that we must do these studies," Wilson says. "The vast majority of EHR [electronic health record] alerts are implemented without any rigorous scientific support — and they clutter up the system. We envision a future where all alerts must be vetted before they are implemented in order to reduce the burden of alert fatigue."

Waiver and Minimal Risk

In a discussion of the study results, Wilson wrote about the decision to

waive informed consent.[1] This waiver required these three principal items:

• The intervention did not infringe on the rights or welfare of the patient. Letting a provider know the patient has AKI should not interfere with the rights or welfare.

• The study could not feasibly be conducted with consent, since enrolled patients could not be told to keep this from their providers.

• The intervention must be no more than minimal risk. "A purely informational alert, we reasoned, must be minimal risk," Wilson wrote. "It is merely aggregating data that are already present. In fact, we even ensured the elements of our AKI order set were minimal risk (no fluid boluses here — just low-risk suggestions like urinalysis and following fluid input/output numbers)."[1]

There was some discussion with the IRB about whether this study may be minimal risk, Wilson says, particularly regarding who was receiving the alert. "Might an intern, who is less experienced, not react appropriately to the alert? Is that a risk?" he asks. "In the end, though, the measuring stick we used was whether we were providing any new information (we weren't — one could easily make the diagnosis of AKI without the alert) or directing specific interventions (similarly, we weren't). In the end, the IRB concluded that providing factual information that was broadly available is minimal risk."

Unsettling Results

The researchers studied six hospitals (four teaching and two non-teaching) in the Yale New Haven Health System in Connecticut and Rhode Island, ranging from small community hospitals to large tertiary care centers. Over 22 months, 6,030 adult inpatients with AKI were randomized. The researchers integrated a pop-up alert in the EHR that would tell the provider that the patient had AKI, give "salient" information, and a link to an order set that could help with the diagnosis. The main outcome was a composite of AKI progression, receipt of dialysis, or death within 14 days of randomization.

Two IRBs associated with the six hospitals approved the study, along with support from Yale's interdisciplinary center for bioethics. An interim analysis took place at 50% recruitment of the alert (before the enrollment of the two non-teaching hospitals), and the trial continued to completion.

Upon reviewing the final results, the researchers saw the two non-teaching hospitals showed a higher mortality rate in the alert arm.[2] Wilson says his first thought was there was an error in the code. "Once we confirmed the results were as reported, we considered two possibilities. One was that this was statistical noise — a type 1 error. The other is that the alert engendered certain harmful behaviors. To ensure we were as thorough as possible, we chased down that option with a series of mediation analyses."

The researchers dug deeper into the data, and the individual hospitals began their own investigations as well. "At first, I thought we'd find some clear signal that explained the results. I was betting on inappropriate fluid administration," Wilson explains. "But we didn't see that. After the exhaustive search, I realized that had we seen the opposite result, we would not have expected any single thing to be responsible. In other words, if alerts were protective, we'd expect a variety of care processes — different ones in different patients — that improved outcomes. I think the same is true with alert harm."

Analysis showed "no sign that any mechanism of death was distributed unevenly between the groups," Wilson wrote. The researchers wondered if they were seeing an example of heterogeneity of treatment effect. He described this as a "phenomenon whereby the impact of an intervention differs among different groups due to a variety of factors upstream and downstream of the intervention — many of which may not be easily measured."[1]

Moving Forward

The new question: If these studies need to be conducted under a waiver of informed consent, what type of monitoring and requirement will make them minimal risk? "The IRB felt, and continues to feel, that these studies are important, and acknowledge that they can't feasibly be performed with informed consent due to contamination across the study arms," Wilson explains. The IRB believes that for most alert studies, the risk remains minimal but wants safeguards to ensure that is the case.

"For our ongoing studies, we have adapted the design to enroll only at the teaching hospitals initially and perform an interim safety analysis at 50% recruitment before we expand to non-teaching hospitals," he says. "Then, at the non-teaching hospitals, we will also perform an interim safety analysis. An external DSMB [data and safety monitoring board] will evaluate whether the study should continue at each of these time points."

This study led Wilson to think twice about studies that are

"obviously" minimal risk. "The truth is it can be hard to know in the absence of data," he concludes. "Things we now consider 'quality improvement' deserve closer evaluation. Many programs that seem obviously good (like programs to reduce readmission, or to reduce falls in the hospital) may have unintended consequences." ■

REFERENCES

1. Wilson FP. The challenge of minimal risk in e-alerts. *The BMJ Opinion*. Jan. 18, 2021. https://bit.ly/2NiYw6u
2. Wilson FP, Martin M, Yamamoto Y, et al. Electronic health record alerts for acute kidney injury: Multicenter, randomized clinical trial. *BMJ* 2021;372:m4786.

IRB Reduces Student Study Review Time from 65 Days to 8 Days

By Melinda Young

It is possible to shorten IRB review time dramatically, but it requires some resources and time.

The IRB of Northcentral University in La Jolla, CA, a large, online academic research institution, serves a nontraditional population of students, some of whom want to complete a research study as part of their academic plan.

The IRB's streamlining process reduced the submission-to-approval time to eight days, down from an average of 65 days before the new process, according to new, unpublished data, says **Heather Miller**, PhD, IRB director at Northcentral University. The new process offers several one-hour educational classes on improving the IRB submission. Student researchers and other researchers can take these classes if they like.

"We created a structure where the information coming in — if they go to our educational classes — looks good," Miller says. I wanted to reduce conflict and anxiety. Our students have full-time jobs and lives, and online institutions are catering to them." The newest course is about setting up consent letters through the institution's online app that collects survey data, she adds.

Virtual students may not have access to as much hands-on research support as students attending a research institution in person, but it is important from an IRB's perspective to not cut regulatory corners in their studies. Most of the institution's more than 800 submissions are from students, although faculty also submit studies to the IRB.

"I'm really concerned about students doing things properly, even if their studies are minimal risk," Miller says. "They need to understand how to protect human participants regardless of risk level of their study so they're prepared for the future."

Finding the Right Process

While some research programs may say a student researcher does not need a consent letter because the study is exempt, Miller sees asking them to write a consent letter as an opportunity to help students with their research training.

Before focusing on streamlining the IRB experience for student researchers, the IRB's average submission-to-approval time for students' studies was 65 days. After streamlining the process, the average time plummeted to eight days, she says.

Finding the right way to change the process was challenging. The IRB had to try several changes. "My first goal was to be open, accessible, and have a transparent process," Miller says.

The program grew from a partnership between the university's academic success center and the IRB. It includes collaboration with the academic success center's writing experts, facilitates IRB webinars, and provides IRB application coaching. Researchers who take the writing and IRB submission classes can show the instructor their actual study and receive some help with it.[1]

IRB members and staff teaching the classes can identify red flags before the studies are submitted to the IRB. "It's a really supportive environment," she says. "The instructors tell students to attend the office hour [open-door information meeting] for help, and then the IRB director or chair and I can mitigate problems that would have been passive issues if they were not identified early."

Shifting to a more transparent IRB process proved daunting. It took hours of staff time, helping researchers, explaining regulatory issues, and meeting with each student investigator at one-on-one appointments. "IRBs have to be well-

resourced, and it takes hours of time," Miller says. "It was not sustainable."

Miller held a virtual meeting with Northcentral IRB analyst Jenelle Dembsey. She discovered Dembsey aspired to become a writing instructor for professionals. This led to the idea that if the IRB could teach student researchers how to write informed consent documents, their IRB submissions would greatly improve.

"The IRB application is a genre of writing," Miller says. "We formed a partnership where I trained IRB members working with the university's academic writing center."

Students could access the IRB submission writing classes through the academic writing center's scheduling system to make an appointment. "What we did was capitalize on this existing structure and started group writing sessions for the genre of writing the IRB application," Miller says. "I trained half my team and allocated my resources, even on a tight budget, to the education arm, using these existing structures."

Miller trained one academic writing center staff member to think like an IRB member and to understand what IRBs look for in study submissions. The writing center staff member could help for six hours a week.

"I wanted to teach her one thing: how to write a consent letter," Miller says. "Everyone in the IRB world obsesses over consent. If you have a well-written consent letter, you have 90% of the battle done."

The 60-minute classes for student researchers began with six people per virtual class. The classes started with how to write the informed consent document, but soon expanded. Now, there are 26 classes per week, divided into these four categories:

- How to choose eligibility criteria for participants;
- How to recruit participants and create flyers that are accessible for people with disabilities;
- How to write a consent letter;
- How to fill out the IRB application and understand terms, such as dual conflict.

"A lot of times, researchers struggle with eligibility," Miller notes. "They say, 'I'll include school teachers or nurses,' but [they struggle] when you get down into the nuts and bolts and who they want to talk to and who is eligible for their study."

"EVERYONE IN THE IRB WORLD OBSESSES OVER CONSENT. IF YOU HAVE A WELL-WRITTEN CONSENT LETTER, YOU HAVE 90% OF THE BATTLE DONE."

After working with the writing instructor for six months, the IRB developed its own sessions for researchers, using IRB staff and board members to teach the classes. They are paid an hourly rate per class.

"All of our board members are trained about the regulations. Four board members help to facilitate the classes, and six or seven do the reviews," Miller explains. "Janelle and I worked on a job description for teaching the sessions. We were looking for board members who could facilitate a Zoom session, show their face, and provide written feedback to students."

Every IRB member is expected to have regulatory knowledge, for which Miller provides weekly training sessions. "It took two months before we let them facilitate classes on their own," she says.

The educational sessions are not mandatory for students. But if any researcher, including students, encounters a problematic study submission, they are directed to the classes for help in improving their submission.

"Professors love the program," Miller says. "It alleviates all the anxiety they have [about mentoring students in research]. It gives them a place to send their students, researchers, and junior faculty for support."

IRB reviewers also like the program because they are reviewing study submissions written more clearly and completely. "They're not bogged down in a lack of clarity of who is going to be in the study, and there are no informed consent letters with typos and [lousy] margins," Miller says. "They can focus on what we are looking for, and what's really important."

Now, when a research submission is poorly written, the researcher is told their paper is not yet ready for review. The electronic system suggests they attend an educational session. "We give them webinars and resources to review prior to the session," Miller says.

Also, student researchers who engage in the program and its courses report a higher satisfaction of the overall IRB submission process, and they express feeling empowered, she says. ■

REFERENCE

1. Miller H, Dembsey J, Northern S, et al. Using existing university resources to streamline the IRB experience for student researchers with SBER studies. Poster presented at PRIM&R Advancing Ethical Research Virtual Conference, Dec. 1-2, 8-9, and 15-16, 2020. Poster/Abstract: 53.

IRB Improves and Simplifies Board Meeting Minutes Process

By Melinda Young

An IRB revised its board meeting minutes process from a clunky system of writing everything into an electronic document to one in which the minutes are automatically populated through the IRB's electronic system, saving staff time and work.[1]

"When we started, the electronic system was too static, not flexible enough to generate minutes," says **Erik V. Soliz**, MS, CIP, IRB program manager of the human research protection program at the University of Texas Southwestern Medical Center.

The old way of creating board meeting minutes sometimes took as long as a month for IRB staff to generate. Since the IRB revised its process, the staff can generate board meeting minutes within a week.

"It's impacted the turnaround time for creation and completion of minutes substantially," Soliz says.

Before changing the process, these problems were common:

- Mistaken voting numbers or attendance;
- Incorrect determination entered;
- Incomplete/mistaken summaries of controverted issues;
- Lengthy and wordy regulatory narratives.

"We created minutes using Word documents and PDFs," Soliz explains. "The system couldn't create list determinations, so we had to create macros in our Word documents so the words were populated to help us create the minutes."

This process was manual. IRB staff spent too long creating the minutes, and the documents were long, he adds. The IRB includes four boards, with one IRB staff person supporting each board.

It seemed unnecessarily cumbersome to manually input that information. Soliz sought an electronic solution to the problem. "We have a dedicated information systems group at our institution," he says. "We met with them, and I explained what our minutes look like and what we wanted our system to do."

Determine Needs

The goal was to update the electronic system with help from the institution's academic information system (AIS) team to include information about the board's determinations. For example, the electronic system stored data on whether an investigational drug was studied for a use not approved by the Food and Drug Administration, although the drug already was approved for another purpose.

"Everything we needed to generate minutes was in the system already, so it was just letting AIS staff know what we needed," Soliz says. "Those determinations were not being captured by the system, so we had those added to the system. We also provided the AIS team with a template of our board minutes, what that looked like, and which areas they could pull from the system to see what my staff needed to create the minutes. We went back to previous minutes and found a lot of incomplete and mistaken summaries and controverted issues that were captured incorrectly. There were wordy narratives."

After meeting with the AIS team, they modified the system to create and simplify the board minutes. The changes to the electronic IRB submission system are something that other IRBs could do, even with different electronic products.

"It wouldn't make a difference which electronic system is being used by an IRB because it's a collaborative effort between the HRPP [human research protection program] staff and those responsible at the IRB and the information technology department," Soliz explains. "If a system houses all the information they need, there shouldn't be a need for reprogramming because everything is already in the system."

When the electronic system pulls in the regulatory references and language, it eliminates the need for workaround, autofill solutions. "We rarely use macros anymore because the system is pulling the information we need," Soliz says. "In addition to pulling the citation, entered by my staff as determinations after each agenda meeting, it pulls each step my staff needs to generate the minutes."

Staff training was simple because IRB employees were part of the revision process. They attended meeting with the AIS team.

The revised system includes IRB staff recording minutes decisions based on the IRB's regulatory determinations for all agenda items. The electronic minutes template features specific regulatory codified citations. Because of this, the determinations section is greatly streamlined and easier to read both visually and in word length.

For example, the pre-update minutes about a new study included lengthy paragraphs explaining what the study involved. Some excess words included: "In accordance with labeling and their use, will not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks."

This is eliminated in the new, updated minutes. There is a preamble about how the board made the appropriate determinations on the criteria for approval. Then, it goes directly into determinations, followed by a list of relevant determinations, such as:

• HIPAA partial waiver for identification/recruitment (45 CFR 164.512): Yes;

• Vulnerable populations included: Yes;

• Vulnerable population categories: Pregnant women;

• Populations: Pregnant women/fetus — no direct benefit to women/fetus, yields biomed knowledge;

• Drug: Yes.

"It's a lot more simplified, and my staff no longer needs to use macros in the document, because the system is doing it," Soliz says.

The minutes are saved to the network drive in the office, and Soliz reviews them for completeness and accuracy. His associate director also reviews them. When reviews are complete, Soliz sends the minutes to the IRB chair, who also reviews and approves them, and they are presented to the board.

The board has noticed how much faster and more efficient the minutes are, Soliz notes. "There might be one or two times I've seen the board request changes when something in the minutes is inaccurate, but it's not like it was before. The board noticed there was a big change and fewer errors in the minutes."

So far, there have been no mistakes caused by the electronic process. "We did a test run to see what was being pulled from the system, and I believe the first round AIS hit it right on target," Soliz says. "Everything we needed, they had the system do for us." ■

REFERENCE

1. Soliz E, Fedewa J. Simplifying IRB minutes generation and review. Poster presented at PRIM&R Advancing Ethical Research Virtual Conference, Dec. 1-2, 8-9, and 15-16, 2020. Poster/Abstract:52.

Prominent Pastor, Scientists, Researchers Seek to Ease Vaccine Fears in Minority Populations

By Sue Coons, MA

Minority populations are more likely to participate in clinical research activities when they are encouraged by trusted authority figures, such as family physicians or pastors. One such pastor and author, Bishop **T.D. Jakes** of The Potter's House in Dallas, decided to use his popular YouTube channel to broadcast information about the COVID-19 vaccine to dispel myths and to encourage his followers to take the shots.

On Jan. 25, Jakes offered his webinar, "Conversations with America: Unpacking the COVID-19 vaccine," on his YouTube channel, which has more than 1 million followers. To help with this topic, Jakes invited:

• **Jill Waggoner**, MD, Jakes' personal physician, and an integrative medicine expert and author with the Methodist Health System in Dallas. Waggoner acted as cohost.

• **Onyema Ogbuagu**, MBBCH, FSCP, FIDSA, an infectious disease specialist and associate professor at Yale School of Medicine. Ogbuagu is the principal investigator of the Pfizer/BioNTech COVID-19 vaccine trial at Yale.

• **Kizzmekia Corbett**, PhD, a viral immunologist with the National Institutes of Health's (NIH) Vaccine Research Center and the lead scientist for coronavirus research. Her team worked with Moderna on an mRNA vaccine.

• **Anthony Fauci**, MD, director of the National Institute of Allergy and Infectious Diseases at the NIH.

Vaccine Rushed?

The first point Jakes addressed is the question of whether the vaccines were rushed through the development process. He asked Corbett to explain the vaccine development process, what precautions were taken, and why Americans should trust the vaccine.

While the vaccine was developed in nine months as America watched, Corbett said, the work that went into the vaccine development has been happening for years, since the first severe acute respiratory syndrome (SARS) coronavirus emerged more than a decade ago.

"Although it's so-called warp speed, there have not been any particular parts of vaccine development that have been skipped along the process. We have a full portfolio of preclinical data surrounding these vaccines as well as Phase I, Phase II, and Phase III clinical trials for these vaccines' development," she explained.

Jakes then asked her if she felt any "angst" about the lack of long-term outcomes data from the vaccine. Is she fairly comfortable there will be no major complications from the vaccines over the long term?

"No, absolutely no angst at all," Corbett replied. It is largely forgotten the first Phase I clinical trial actually started on March 16, she said, and the trial participants have been followed since then with no long-term adverse outcomes. "It's very clear that long-term side effects are not something to be worried about. Dr. Fauci has said several times, over and over, that, historically, side effects happen within the first two months of vaccine development, and that's exactly what you're seeing here as well."

Increasing Trust in the Vaccine

Jakes then asked Ogbuagu how to improve the level of trust people of color have in the health system overall, and with this vaccine in particular. "It's disheartening that the group that is disproportionally impacted is not at least disproportionately interested in receiving the vaccine," Ogbuagu said.

Historical injustices, such as the Tuskegee Syphilis Study, continue to influence Black Americans' perception of clinical trials. They also are concerned about the accelerated pace of the clinical trials, and possible side effects. "There are a lot of circulating misconceptions and misinformation on social media overall," he said.

Ogbuagu suggested finding trusted messengers and respected authorities to disseminate information about the vaccine. He also suggested working on what is called "vaccine literacy," which is "finding ways to communicate in language that people understand within the appropriate cultural context to get that message out about the role that vaccines play in public health to control diseases and eradicate epidemics." Showing trusted messengers and role models receiving their vaccines publicly helps as well, he said. "I think that has also played a great role in having people be just a little more comfortable with receiving the vaccine, and I hope that that number will continue to pick up."

Jakes then asked Ogbuagu about whether people with pre-existing conditions or allergies should worry about taking the vaccine. It became apparent early on that individuals who experienced worse outcomes with COVID-19 had comorbidities such as obesity, diabetes, and lung conditions. "One of the reasons why we think Blacks, African-Americans especially, are having worse outcomes is because of the prevalence of these comorbidities among those populations," Ogbuagu said. There was a good representation of individuals with medical comorbidities in the trials, he said, and the study results showed robust efficacy, even among individuals with these underlying conditions.

Ogbuagu then addressed media reports about severe allergies or life-threatening anaphylaxis some people experienced after receiving the vaccine. This tends to occur in people who have a history of these types of events, he explained, and they should be cautious about receiving the COVID-19 vaccine. Healthcare providers at vaccination

sites are aware some individuals may experience an allergic reaction, and keep emergency medications on hand to mitigate the side effects.

Ogbuagu stressed this is not a common occurrence. Data he has received on the frequency of these severe and anaphylactoid reactions showed about six in 1 million doses. "It is really, really rare."

Diversity in Vaccine Trials

Waggoner asked Ogbuagu about the racial diversity of vaccine trial participants. Ogbuagu said an alarm went out about insufficient enrollment of racial ethnic minorities midway through the Pfizer and Moderna Phase III trials.

"Let me just be clear," he said. "Sharing my clinical trial experience, it can be challenging to involve racial ethnic minorities in clinical research. I think some of the issues that fuel vaccine hesitancy also fuels that reluctance to participate in clinical trials and clinical research."

A lot of effort went into the clinical trials to host or optimize the enrollment of ethnic racial minorities, Ogbuagu noted. This included finding sites to reach a diverse population, community outreach programs, and adjustments to enrollment processes to help engage communities of color. In the Moderna trial, 35% of the clinical trial population (about 20% Hispanic, 10% Black, and 4.5% Asian) were racial ethnic minorities. The Pfizer trial included about 40% (about 26% Hispanic, 10% Black and 4% Asian), he explained.

Fauci noted the effort for diversity in the Moderna clinical trial. "Literally every Saturday at 10:00, we would meet with the leaders of the trial to encourage them to go the extra mile to get minorities involved."

Investigators should ensure the vaccine is safe and effective in all the demographic groups, particularly those with a higher incidence of severe outcomes — which is racial minorities, he said. "We've got to get them represented, because you want to be able to look at your community of individuals in the minority demographic group and say, 'We've actually tested the vaccine in you, and it is safe and it's effective in you.'"

Fauci wished the representation of Black participants was at 13%, but distrust in the community is "understandable." "You've got to address each and every one of the concerns that they have," he said. If asked, he explains the efficacy of the vaccine is reviewed by independent groups comprised of scientists, statisticians, and immunologists who do not answer to the government or the companies that produced the vaccine. "[We tell them], the whole process was both transparent and independent, and we have to keep making that very, very clear because we have to respect the skepticism in the African-American population about federal government medical programs. You can't walk away from that. It's a shameful history that we have to deal with."

Vaccine Access

Jakes also asked Fauci about vaccine distribution issues. "Can you give us any precursor information about distribution and what you have planned to make the vaccine available more readily for people, especially homeless people, oppressed communities, and neighborhoods where they don't even have grocery stores?"

The numbers of vaccinations have not met expectation, Fauci conceded. "I believe that the reason for that is that this was a brand-new process of an unprecedented challenge of trying to vaccinate so many people. There are going be bumps in the road and hiccups." The vaccine needs to be distributed in multiple ways, he said. Otherwise, it will exclude the people who most need it.

Jakes wondered if medical professionals could work with faith-based entities within local communities so vaccines could be administered in places such as churches or community centers. "Many of our communities are in food deserts and certain places like that where they can't get the vaccine," he noted.

One answer might be to find individuals who could administer an intramuscular injection, such as medical or nursing students, and set up clinics in community centers, churches, and even mobile units, Fauci said.

Fertility and Gene Distortion

Another concern long-term effects on fertility, Jakes said. Should pregnant women worry about taking the vaccine?

There have not been any considerations about long-term fertility issues, Corbett said. "Messenger RNA does not affect or alter one's DNA, nor does it alter your fertility."

The current recommendation is that women of childbearing age still receive the vaccines, she said. Although women were not supposed to conceive during the clinical trials, some did, and trial results have shown no complications from that small subset of women.

Fauci addressed the question of whether the mRNA vaccines interfere with or "distort" the genes of the person receiving the vaccine. "The

answer to that is, absolutely not," he said. "It's understandable why when people hear RNA, they hear DNA, genes. They want to know if it's going to interfere in some way or get into your genes and change your genetic makeup. Not a chance."

Side Effects

Jakes then brought up the issue of side effects. "What potential side effects or adverse reactions of this vaccine do we need to worry about, or are they all minuscule?"

It appears the real-world experience is mirroring what happened in the clinical trials, Ogbuagu said. "We can say that there have been no surprises. That's great, because the concern always is that the numbers that are exposed to a drug in clinical trials is kind of a finite number, although in Phase III we are talking about tens of thousands. When you roll it out to millions, there is always the concern that rare side effects may pop up."

Side effects fall into two buckets: local and systemic, he said. "The term we tend to use for some of the early side effects is 'reactive dynasty,' which means it's just people reacting to the vaccine." Other than local injection site reactions, systemic side effects also occur. The vast majority are mild to moderate, occur in the first few days after vaccine receipt, and resolve quickly. Based on the at least two-month experience for these two elite vaccine candidates, the side effects definitely are tolerable, he said. "It's something to warn people against so they know to expect that. We think the majority of these adverse events will happen very early from vaccine rather than long term. It's heartening to see the safety profile so far."

The muscle aches, fever, and similar effects are, paradoxically, a good sign, Fauci added. "It means your immune system is responding to the vaccine." The muscle aches, headache, and fatigue are due to inflammatory proteins cutting loose. "It lasts no more than 24 to 36 hours, but even though it's a little bit uncomfortable, it really is telling you that your immune system is working properly to respond to the vaccine."

Individuals taking medication for underlying conditions also should not worry about the safety of the vaccine, Fauci said. "If you have an immunosuppressed state, the only time you have to worry in regard to safety is with a live attenuated vaccine. The mRNA vaccines and any of the others are not live attenuated," he said. "You may not get an optimal immune response if your immune system is being suppressed medically because of an underlying condition, but that's no reason [to skip the vaccine], because even a response that isn't optimal is better than no response at all."

To reach herd immunity in the United States, the country would need to vaccine 70%-85% of Americans. Communities that stay below this level still will risk contracting the virus. "If I were to predict — and I think this is the message to get out to Black and brown people — is that certain groups may achieve herd immunity and certain groups may not," Fauci explained. "That will serve to continue to fuel this cycle. Herd immunity really has to be tied to vaccine acceptance, and I think those have to go together."

Adapting the Message

The question returns to getting the message out and the best way to do that. Corbett said the most important thing is to listen to people first. "I try not to say anything to anyone unless I'm asked because I find that people's inquiries around the vaccine are fairly specific to their own personal story, to their own personal community story, etc. The more that you listen, the more you can gauge what really needs to be said to a particular person around their vaccine hesitancy."

If someone asks her about catching the virus from the vaccine, she explains it this way: "This vaccine only takes an mRNA shot of one particular protein from coronavirus. This protein does not replicate like a virus. It has no other components of the coronavirus. It is simply one specific protein, and it's the protein that we've been studying at the NIAID for several years and trying to understand it in a large amount of detail. You cannot get sick from this one particular protein. It is not going to give you the virus. You can't pass this protein on to anyone else. It basically just alerts your immune system of what the protein looks like. Your immune system essentially takes a snapshot of it, so that when it appears again to your body by way of the virus, your body says, 'Oh, I've seen this protein before, let me go fight against it.'"

Fauci said they are monitoring virus mutations, and initial data do not indicate a threat to vaccine efficacy. "It's much more likely that a mutation would block the effect of a monoclonal antibody that's against one particular component of the spike protein. When you get vaccinated, you get multiple polyclonal antibodies against all different parts. It's less likely that it would interfere with the effect of a vaccine than it would with the effect of an individual monoclonal antibody. Having said that, it looks good for now, but we want to make sure we keep following it very, very carefully." ■

IRB ADVISOR

PHYSICIAN EDITOR
Arthur R. Derse, MD, JD
Director and Professor
Center for Bioethics
and Medical Humanities
Institute for Health and Society
Medical College of Wisconsin
Milwaukee

NURSE PLANNER
Kay Ball, PhD, RN, CNOR, CMLSO, FAAN
Consultant/Educator
Adjunct Professor, Nursing
Otterbein University
Westerville, OH

EDITORIAL ADVISORY BOARD
Monica R. Chmielewski, JD
Partner
Foley & Lardner, LLP
Chicago

John Isidor, JD
CEO, Human Subject Protection
Consulting, LLC
Cincinnati

Robert M. Nelson, MD, PhD
Deputy Director
Senior Pediatric Ethicist
FDA
Washington, DC

James Riddle, MCSE, CIP, CPIA, CRQM
Vice President, Institutional Services and
Strategic Consulting
Advarra
Columbia, MD

Susan Rose, PhD
Retired
Los Angeles

Mark S. Schreiner, MD
Emeritus Associate Professor of
Anesthesia and Critical Care
University of Pennsylvania
The Children's Hospital of Philadelphia

Jeremy Sugarman MD, MPH, MA
Harvey M. Meyerhoff
Professor of Bioethics and Medicine
Johns Hopkins Berman Institute of
Bioethics
Department of Medicine
Johns Hopkins University
Baltimore

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 test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the test, 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 emailed to you.

CME/CE QUESTIONS

1. **Researchers who surveyed human research protection programs and IRB staff found what percentage of respondents believed their COVID-19-related research was reviewed and approved quicker than usual?**

   a. 46%
   b. 51%
   c. 66%
   d. 72%

2. **A process to improve student researchers' IRB submissions relied on:**

   a. designating two hours a week to one-on-one time with IRB staff.
   b. assigning each new researcher an experienced mentor to walk him or her through the process.
   c. providing researchers with IRB submission and writing classes.
   d. routine audits of student researchers' submissions, followed by suggested corrections.

3. **What did researchers posit might have caused the higher mortality rate in the minimal risk e-alert study?**

   a. Statistical error
   b. Error in code
   c. Heterogeneity of treatment effect
   d. Inappropriate fluid administration

4. **According to Bishop T.D. Jakes, what would increase the numbers of Black Americans receiving the COVID-19 vaccine?**

   a. Providing transportation to vaccination clinics
   b. Using community centers or local churches as vaccination centers
   c. Providing online help to sign up for vaccine appointments
   d. Opening vaccination clinics in local grocery stores and pharmacies