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INSIDE



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# Diversity in Clinical Trials Should Start with the Fundamentals

*Clinical trial processes should begin with diversity in mind*

*By Sue Coons, MA*

Diversity in clinical trials involves more than just including more minority participants, panelists said at a recent webinar, Increasing Diversity in Clinical Trials. It is a commitment from leadership that addresses the diversity topic within every aspect of the clinical trial process.

PRA Health Sciences, a contract research organization (CRO) in Raleigh, NC, sponsored the April 28 virtual event. PRA chief scientific officer and executive vice president **Kent Thoelke** spoke about how the COVID-19 pandemic has given everyone a stark reminder about the inequity in healthcare delivery among different patient populations. "This only highlighted the need for making sure that clinical trials actually matched the patient populations that we were trying to treat."

This topic is about good science as well, he said. "Beyond the moral imperative of ensuring equity among access to clinical trials, the concept of good science is critical."

> "BEYOND THE MORAL IMPERATIVE OF ENSURING EQUITY AMONG ACCESS TO CLINICAL TRIALS, THE CONCEPT OF GOOD SCIENCE IS CRITICAL."

Relative to drug development, mechanisms of action can and do vary in different populations, such as by gender, race, or background. Drugs have failed when they have been tested in the wrong population or have been approved for the minority population when the target population is different. "From a scientific perspective, there is a paramount need to ensure that the populations we're treating in clinical trials match the populations



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that will be using the drug, and that we understand if there's a difference in safety or efficacy by mechanism of action that may be related to different racial or ethnic backgrounds. That's all critical."

The entire paradigm the drug development industry created needs to be reimagined. "[When] we create representative populations in our clinical trials, we create better science," Thoelke said. "We create safer drugs. We create better understanding and profiles around the efficacy of the drugs for testing, so this conversation is an incredibly important one."

## The Importance of Trial Diversity

Diversity involves several critical issues, and is the thread one pulls to realize there are fundamental problems with science, said **Jonathan Jackson**, PhD, assistant professor of neurology at Harvard Medical School and director of the CARE Research Center at Massachusetts General Hospital.

"[T]here is this fundamental truth that the medicines that we develop should work for everyone, but they don't," he said. "In order to be sure about that, and to make sure that we are more confident about the vaccines, the biologics, and the devices that we develop, we need to get this right during the clinical trials — not when a drug is out in the wild and people are paying for that risk."

People who are not white, not wealthy, not male, and who do not live on the East or West coast of the United States in an urban or a suburban center are underrepresented in trials. "That means we don't know if the drugs we are developing work for us until we're paying for them and taking them ourselves," Jackson noted. "We can do better. We're scientists, so let's science this."

In the future, clinicians will use genomic information to make treatment decisions. Algorithms will use those data, said **Quita Beeler Highsmith**, MBA, vice president and chief diversity officer at Genentech in San Francisco.

"Right now, 91% of the genomic material available to sciences are of European ancestry. Over 33 pharma companies are using artificial intelligence for drug discovery and in partnerships and collaborations," she said.

As a Black woman who could be diagnosed with triple-negative breast cancer, Highsmith's treatment algorithm could be based on that of a white woman. How does she know if the drug will be safe and effective for her treatment? "It is critically important that we begin to expand who gets to participate so that we can ensure that our future generations have the same opportunities for safety and efficacy as others have had in the past."

The third panelist reiterated the diversity conversation is not just about race. "There are people in rural environments who are unrepresented," said **Clyde W. Yancy**, MD, MSc, vice dean of diversity and inclusion for medicine, professor of medical social sciences, and chief of the division of cardiology at the Northwestern University Feinberg School of Medicine. Populations of non-English-speaking people, people with poor health literacy, older people, children, and adolescents are underrepresented. "The cause that we are advocating is really not planning a race or ethnicity play. It's saying time out. We need to completely pivot and rethink a broad landscape

of how we approach trials. This isn't a political problem. Let's use science to answer this question."

Genomics can better identify patients at risk, and information technologies can better communicate risks and benefits. "There are ways that we can use contemporary technologies and science to more quickly, more appropriately, and in a much more representative way answer questions," Yancy said. "The question we pose is 'Why is this conversation necessary?' It's not necessary. It's critical. We're at a time where everything — everything in health and society — is undergoing a fundamental pivot — a pivot, we hope, toward equity. As Dr. Jackson pointed out, equity for all cohorts. This is the time to pause and rethink exactly how we do things. We should not fear the disruptive moment; that's what we need in clinical trials. We need to come up with a way to get more information relevant to more patients more quickly, more efficiently, and with more intelligence. We can't be just more of the same. We have to do it differently and be smart about it."

## Barriers to Trial Diversity

Jackson named 10 reasons why it is difficult to achieve diversity in clinical trials:

- lack of awareness of research opportunities;
- deep mistrust of the healthcare system and research studies;
- confusion and concern over what research is;
- limited transportation options/ times;
- study inclusion/exclusion criteria;
- lack of plain language use in documents;
- fear of placebo and/or fear of intervention;
- health insurance coverage;
- limited diversity of study staff;
- insufficient return of value.

"We hear about famous studies that have some kind of diversity," Jackson said. "People will really tout it, but we don't have a clear understanding about why that is."

Although this is a scientific problem, researchers are not necessarily taking a scientific approach. "We're sort of hoping that the plural of anecdote is data, and it's just not true here as it's not true anywhere else," he added. These issues need to be rethought from a more systemic framework. "Systemic problems need systemic solutions."

Historically, the burden of solving the diversity problem has been placed on potential research participants. "Nowadays, there's a bit of a shift, and we're putting that burden on individual research teams," Jackson explained. "That's not going to work, either. We need to build an infrastructure that's full of carrots and sticks in order to get this right, but it's not going to happen if we leave teams underresourced, unequipped, with no data practices, ontology, or frameworks, and without any real incentive to get this right."

The 10 barriers are downstream phenomena, Yancy said. "We need to go back upstream and say at the outset, at the intent, 'When you establish the hypothesis or set the drug discovery plan, are you writing a protocol with an inclusive angle?'"

The root cause of the barriers is culture, he said. What is the culture of the sponsor? Does the sponsor want to get this done in the most expedient way? Is the sponsor looking for a population where the answer will most likely be positive and will give greatest return on investment?

"We have to immerse in this notion of inclusiveness," Yancy said. "If we talk about inclusivity with a predominant question, with a primary question, and deal with this upstream, these barriers that we will articulate in the moment would be much less difficult to overcome."

Highsmith said Genentech has asked all of its molecule teams to create inclusive research plans from the beginning. "To this point, you have to be thinking about this from the very start." Genentech's EMPACTA study of COVID-19 pneumonia dispels the myth that patients of color do not want to participate in clinical research, she added.

Of the more than 380 patients in the study, 85% were from minority racial and ethnic groups. Most patients were Hispanic, with significant representation of Native American and Black populations. The trial was conducted in the United States, South Africa, Kenya, Brazil, Mexico, and Peru.[1]

"The patients are out there, and they're willing to participate if you ask them. But we also have to think about the reward system a little bit differently," Highsmith said. "Most of the time, we're rewarding the company people and site on first patient in. When we did EMPACTA, we went to other sites."

Genentech has conducted studies in cities such as Oakland and Detroit. "Some of those sites we had never used before, and maybe it did take one, two, or three days longer to get the IRB up and running, but at the end of the day, we had a bigger pool of patients to choose from," Highsmith said. "Site election is really critical in thinking about where are people living. ZIP codes can routinely determine your health."

Highsmith added, "One of the

things that we've learned in our EMPACTA study is you've got to be in the community, the hospital that people are driving by in their neighborhood. That's the hospital they trust. They don't trust having to go across town to the big academic institutions."

Genentech is starting a new research site alliance initiative in which the company will work with communities of color to "broaden who has access," Highsmith said. "Then, we have to work on our processes, and we have to look at our inclusion/exclusion criteria. So many times, the inclusion/exclusion criteria are based on a white male from 20 years ago. We need to be thinking about it differently, thinking about body mass index, thinking about creatinine clearance. Thinking about things that might be normal for people of color that would exclude them from the clinical trial for no real scientific or valid reason."

## Incentives for Diversity

The panel also discussed the idea of giving incentives or even enforcing penalties as a way of increasing diversity. The qualifying language on last year's FDA statement about diversity is nonbinding, Yancy said. "The language is just that. There are no consequences. It's guidance as it intends to be."

A carrot-stick approach could be used, but advocacy and awareness could be a different approach, as well as incentives. "For example, if there is an entity, a corporate entity in particular, that really makes a good faith effort and recruits a diverse population, why not extend the patent protection?" Yancy asks. "We should make this less of a binary question about whether we support underrepresented groups, and instead make it a more intellectual question: How do we approach this differently? Then I think we have an opportunity to be uniquely different than we have ever been before."

According to Jackson, the question is: How do we do good science? "Good science is inclusive. Good science is representative from the very beginning," he said. When you get it "right," you get more participants from a bigger pool, and trials enroll faster.

"Some incentives are great, but we don't incentivize having the right statistical test," Jackson said. "We don't necessarily incentivize having a thoughtful Data Safety and Monitoring Plan. We just expect those things to be done, and when they're not done, there are consequences. There are punishments, but most importantly, you kind of lose the respect of your peers. You lose that market edge, and I think the quicker we clarify that there is a market opportunity here, the less that we need those incentives."

"[Diversity] is a business imperative for our organization," Highsmith added. "I do think that our industry — whether it's pharma, whether it's the FDA — is saying to us that we want to see commitment to enhance participation in clinical research. There are those of us who are stepping up to get it done."

That success needs to start at the top. "I think the only way real change happens is that it starts with leadership and that it ends with culture," Yancy said. "If we can get those two things accomplished, then everything else just becomes an exercise of execution. Change the composition of clinical leadership, change the culture of performing clinical trials, and we will reap a return that we've not seen before." ■

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# The Role of Structural Racism in Lack of Clinical Trial Diversity

*By Sue Coons, MA*

In a recent webinar, titled "Increasing Diversity in Clinical Trials," panelists were asked what role structural racism plays in the healthcare system in the lack of clinical trial diversity. They also were asked if employing a more diverse clinical staff is more likely to increase enrollment of a more diverse patient population.

When discussing these topics, the panel is not accusing individuals of being racist, noted **Clyde W. Yancy**, MD, MSc, vice dean of diversity and inclusion for medicine, professor of medical social sciences, and chief of the division of cardiology at Northwestern University Feinberg School of Medicine. "We are saying that the construct of systems is such that it advantages one group and disadvantages another group."

For example, when a clinical trial is set up, who is trained to be a trial coordinator? Who is trained to obtain informed consent forms? Who reviews the protocol? Trial participants might be more comfortable with clinical staff who resemble them.

"All of these things reflect a structure, a process," Yancy said. "The way an IRB functions, the way protocols are disseminated, the way studies are funded, the way investigators are rewarded, particularly with academic credit, all of this is within a fairly strict system. That system, by design, whether it was overt or not, excludes certain important constituencies. When we talk about structural racism, we're saying that there's something inherent in the design of our systems whereby the execution of that process unfortunately leaves some people out of the equation. We shouldn't fear the phrase 'structural racism.' We should recognize it as an invitation to re-evaluate our processes and [ask], 'Have we developed processes that are more inclusive?'"

Structural racism is a powerful construct that may influence participation in clinical research studies, said panelist **Jonathan Jackson**, PhD, assistant professor of neurology at Harvard Medical School and director of the CARE Research Center at Massachusetts General Hospital. "It may impact behavior and it may impact trust. It also may impact other aspects of clinical trial design that are much more familiar to trialists and scientists." For example, not only could a measurement be miscalibrated for certain populations, but a measurement tool, such as one for pain management, may be inappropriate in certain contexts.

"THAT SYSTEM, BY DESIGN, WHETHER IT WAS OVERT OR NOT, EXCLUDES CERTAIN IMPORTANT CONSTITUENCIES."

Jackson referenced Paris B. Adkins-Jackson, PhD, MPH, a research fellow at the CARE Research Center who has written about this topic. In a recent paper, Adkins-Jackson and colleagues discussed how to measure racism in academic health centers (AHCs).[1]

First, it is important to "identify and assess" racism operating at three levels: the individual level, the intraorganizational level, and the extraorganizational level, they wrote.

On the individual level, literature has shown implicit bias can be expressed during clinical encounters. This bias can be expressed through "limited time given by clinicians to patients of color, inequity in how that time is spent, inequity in conversational pace and tone, dismissive clinician body language, inequity in information-sharing, inequity in resource use, and inequity in decision-sharing." The authors proposed measuring these variables, along with patient assessment of level of trust and communication, and comparing them across racial groups.

On the intraorganizational level, structural racism can be experienced through a lack of consequences for clinician bias, the lack of efficient reporting mechanisms, and the lack of culturally responsive training for health professionals. The authors recommend using the Implicit Association Test to capture intraorganization institutional racism.

On the extraorganizational level, AHCs work with federal and government institutions to determine the policies and allocation of resources that can disproportionally affect people of color. The authors suggested using an index of factors that look at these resources to reveal how they may have contributed to structural racism.

Scores from the measurements of these three levels can be combined to yield a composite score to inform

"antiracist strategic planning and decision-making" over time, they wrote. "We suggest incorporating qualitative components at each level (e.g., randomized patient interviews at the individual level; observations and evaluations of AHC operations from preclinical health students and community health workers at the intraorganizational level; and local, state, and federal policy analysis at the extraorganizational level). In combination, this mixed-data formative assessment could ensure that a range of voices is solicited, recorded, and drawn upon to eliminate health inequity."[1]

Systemic racism reinforces already existing social inequities, Jackson said. "I think the most egregious problem of all is that it's going to flatten all of these things into the name of some sort of essentialized biological disparity." Problems will not be attributed to an incorrect measurement or tool, or even to a process that has been incorrectly implemented. "We're going to say that the problem is you. Because you've got more melanin in your skin, you don't feel pain. Because you have more melanin in your skin, you have a different relationship between this biomarker and this disease. It is simply not the case. The impact and the role of systemic discrimination, systemic racism more specifically, can't be overstated. It touches every aspect of our research workflow." ■

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# The Issue of Using Race in Clinical Trials

*By Sue Coons, MA*

One hot topic during a recent webinar on diversity in clinical trials centered around whether researchers should use race in a clinical trial. As one viewer asked: "How can we more clearly discuss the scientific value of racially diverse clinical trials without perpetuating the myth of biological race?"

"First of all, if you are thinking about using race in your studies, don't," said panelist **Jonathan Jackson**, PhD, assistant professor of neurology at Harvard Medical School and director of the CARE Research Center at Massachusetts General Hospital. "If you're going to be using a race as a construct, it may be potentially useful for dimension reduction, but it is not sufficient. That's not a reason to include it."

"If you're thinking about including race as variable, you have to consider that there are massive political consequences," he continued. "It is never neutral and it is never scientific to include this variable in our studies. We do it anyway because it's convenient, not because it is scientifically valid or vigorous." Race changes with almost every United States Census, he added, and it does not generalize beyond the United States.

"It's a really bad proxy of what we think of as different kinds of discrimination and racism. It obscures and masks true variability, which means if we are using it in our models, we're worsening our models by leading on this variable," Jackson said.

Race has less do with skin color and cultural practices than whether people have been a target of systemic racism. "We should be measuring that instead of what people call themselves," he explained. "It tends to be used in the wrong way, so you have very well-meaning scientists who want to try to understand how race is impacting these kinds of variables." It also inadvertently centers and normalizes whiteness, the use of the English language, wealth, and excessive education, he said. He also criticized using whites as a reference group in a global study when they actually are a global minority.

Panelist **Clyde W. Yancy**, MD, MSc, recently co-authored a paper about recalibrating the use of race in medical research.[1] "The only space where we allow the use of race is if your intention is to further elucidate evidence of healthcare disparities," he said. "We make explicit reference to the fact that race is not a surrogate for biology, and it's not even a surrogate for the social construct. Race is a surrogate for racism. That's a pause moment."

"To infer that there is something uniquely different as a function of race and imply that is biologic is a miss," he continued. "That is ill-advised. But if you're trying to elucidate ongoing disparities, then it's appropriate."

Yancy and colleagues did not recommend abandoning race from medical research efforts. "Dislodgement of race from research may hide still-evident and often egregious episodes of health disparities," they wrote. "If for no other reason than the further exposition of health inequities and systemic racism, the use of

race should for now persist in medical research. But the imperfectness of race as a tool is problematic."[1]

They suggested developing another variable to replace the use of race. "Such replacements need to proceed with rigorous validation practices, ensuring the generalizability of the results, and solidifying that whatever changes are made will help reduce, rather than exacerbate, existing inequalities," the authors wrote.

In a volatile social landscape, it may not be possible to determine exactly how race-specific research efforts may lead to a "better, more fair world." "At a minimum, however, medical research should not aggravate already-embedded gaps between the privileged and the disadvantaged," the authors concluded. "Just as the lens of science was used to establish a flawed premise of biological race-based differences, so should science now focus on illuminating that which is represented by race and become a trailblazer toward better health equity." ■

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# Clinical Trials with One Subject Raise Ethical Questions

*By Melinda Young*

It is unlikely IRBs will see many studies with one enrolled participant (the N=1 study design), but they should be prepared for this type of protocol.

The single-subject study design can be applied to chronic conditions like cystic fibrosis or to ultra-rare diseases.

"Like many emerging techniques, this will find a niche, but it will be fairly small," says **Jonathan Kimmelman**, PhD, professor and interim director of the biomedical ethics unit at McGill University in Montreal.

These types of trials are expensive. They involve niche conditions that typically are treated by rare diseases specialists, Kimmelman adds.

In one type of N=1 trial, the study participant starts as his or her own control in a randomized trial. The participant is randomized to either the treatment or control for a set number of weeks. Then, there is a period in which the treatment/control is washed out before the participant crosses over to the opposite arm, and this is repeated.

"N=1 designs have been used in clinical practice for a long time, and it's a great way to do care for individual patients and for certain kinds of clinical decisions," Kimmelman says. "When you do a N=1 study, you assume the drug will rapidly leave the system and its affects won't carry over to the next block."

Another N=1 study approach involves a protocol in which a patient is monitored before and after receiving a bespoke therapy, like a personalized antisense oligonucleotide (ASO).

"It's just like a regular clinical trial with no crossover and only one patient," Kimmelman says. "Patients get the treatment, you look at how they respond, and you make inferences about how other patients with similar, but not identical, genetic diseases might respond to a similar treatment."

This type could apply to drugs that are used in common mutations to determine whether they will work in uncommon mutations, he says.

One ethical concern in reviewing this type of study is the participant will experience much longer exposure to research, more cycles of placebo, longer periods on an unproven drug, and more frequent clinic visits. All of these add to the participant's burden.

"What goes on with N=1 studies is the number of patients experiencing this burden is going down, but those patients are experiencing much more burden," Kimmelman adds. "You're spreading risk differently with these N=1 studies."

IRBs should ask these questions of the N=1 study:

- How much extra burden is on this vs. the standard of care?
- Has the consent process been explained adequately?

One recent example of a study using the N=1 design is a trial in which investigators developed a personalized ASO for a 6-year-old girl with neuronal ceroid lipofuscinosis 7, a form of Batten disease. Researchers discussed how

the N=1 study of the treatment for a particular girl could be a possible template for the rapid development of patient-customized treatments.[1]

Thirty million Americans are affected by rare diseases. More than 7,000 distinct conditions exist, which creates research and drug development challenges.[1]

Another ethical challenge is how these studies are funded. "These are often patient-funded clinical trials," Kimmelman says. "I and others have written about the issues of patient-funded clinical trials."

For instance, these trials are expensive, and patients sometimes raise money through crowdfunding campaigns. "It misaligns the incentives for research with goals of high-quality science, they are not fully peer-reviewed, and are not having a proper evaluation of merit," Kimmelman says. "They are highly susceptible to fraud and misinformation."

These trials also might be unfair and inequitable. "It's unfair in that people with a lot of social capital and with cuter children and broader networks are more successful in raising that support," he says. "It has many features of fundraising that are setting one up for misalignment of merit and access."

Skilled researchers are a scarce resource and valuable commodity. There is an ethical question of whether this type of research is the best use of experts, he adds.

The trials might not be registered through ClinicalTrials.gov, although any research study should be registered.

"Because people have this mental picture that this [research] is purely desperate, treating children with rare illnesses, it frustrates the ability for people to think through the ways this is research and what you need to do differently in delivering these treatments because it is research," Kimmelman says. ■

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# IRBs Experience Some Obstacles in Tweaking Reliance Programs

*Achieving optimal efficiency takes time*

*By Melinda Young*

Whether institutions are the IRB of record or the relying IRB, setting up a seamless process involves many time-consuming processes — and it can take years.

"We've been serving as a single IRB, and we did our first big study in 2010," says **Hallie Kassan**, MS, CIP, director of the human research protection program at Northwell Health in Manhasset, NY. "It's very complicated, and there are many systems out there. [For instance], we use the SMART IRB agreement, but we don't use the SMART IRB Reliance platform when we're the IRB of record." Instead, the Northwell Health IRB uses its own protocol management system.

The reliance process is efficient, but it takes time to develop. "The goal of the single IRB process was to make research start up more efficiently and to get clinical trials up and running," says **Janelle A. Maddox-Regis**, MS, associate director of the IRB Reliance Program at Johns Hopkins University School of Medicine. "I think we're seeing the efficiency now. At first, it was challenging because there wasn't any broad guidance for sites to follow on how to start up a single IRB at your institution."

IRB directors had to learn much of this on their own, with the help of conferences, peers, and collaboration with other institutions. "We created documents and templates to make things more efficient," Maddox-Regis says. "Other IRBs have asked for these tools, and we have them on our website."

As IRB staff learn about the forms, the process becomes more efficient, Maddox-Regis notes. *(See story on maintaining consistency with reliance agreements in this issue.)*

One of the obstacles to an efficient IRB reliance effort is handling the technological details. "One obstacle is that people put in a request to have an account set up, and they have a hard time getting in touch with someone in IT to have the password to their account, so it can be delayed for days," Kassan explains. "Also, we have these accounts set up and researchers have a Northwell email, which they need to get their password reset. They're not checking

their Northwell email because they're not Northwell employees."

The passwords are reset after 90 days. Kassan receives calls from people who cannot access their information, and solving these technological issues is resource-intensive.

"It pulls in a lot of people who are trying to fix the problem, and I feel badly because the whole idea is to make things easier for study teams," Kassan says.

Kassan and Maddox-Regis describe other challenges and solutions in making a reliance program work:

• **Use the SMART IRB agreement.** This agreement helps create a consistent reliance process. *(For more information, visit: https://smartirb.org.)*

"One way to document the reliance is through an online platform," Kassan says.

IRBs do not select sites for studies, but the IRB of record can ensure sites are using SMART IRB and have signed a letter of indemnification. "If they signed both documents, we would assume the process would be more expedited," Maddox-Regis says.

In rare cases where a site did not sign onto the SMART IRB agreement, they received an exception to receive local IRB review. "Sites need to get an exception from the National Institutes of Health to obtain local review, or we have a standard reliance agreement we use where the site is not signatory to the SMART IRB agreement," Maddox-Regis says. "We didn't have many cases where we had to use it."

• **Use time efficiently.** Part of the process is for the IRB to approve the study before obtaining local information from the site.

"My job is to work with lead sites to execute all of the reliance agreements either before or concurrently of IRB review," Maddox-Regis says. "Reliance agreements, historically, have taken longer periods."

The goal is to execute all the necessary reliance agreements before the study is approved. This means the study and site have the context review as soon as possible after the IRB approves the study.

> "THE BIGGEST CHALLENGE IS FIGURING OUT HOW TO STREAMLINE PROCESSES TO ACCOMMODATE ALL THE NEEDS OF SITES AND RESEARCHERS."

"We work with the lead sites at Hopkins and we work closely with them to make sure that by the time the study is approved, they have appropriate instructions to ensure context review at the site," she says.

• **Solve technology interface issues.** "One issue is figuring out access to our electronic submissions system, an issue across the board," Kassan says. "How should teams outside of Northwell have access to it? How do we get them access?"

Some institutions decide they want relying IRBs to access the reliance IRB's management system. This might not go smoothly. "We have a process set up to get [other IRBs] access to our system, with a Northwell login," Kassan explains. "But that's one of the struggles."

Another struggle is differing processes between teams. Some teams that rely on the Northwell IRB want the IRB of record to manage all submissions and paperwork for all relying sites, and others want their own IRB to perform some of this work. "The biggest challenge is figuring out how to streamline processes to accommodate all the needs of sites and researchers," Kassan says. "Different researchers want different things, and we're trying to develop processes that are acceptable to everyone."

"Our rule here is that all investigators, like the principal investigator of an external site, need to set up an account to have access to our electronic system," Kassan says. "I thought it was important for the principal investigator of a site to go in and get their own documents if they have to and not to rely on someone at Northwell."

• **Look at local context.** Managing local context issues also can be difficult. One way to handle this is for local sites to complete a form that includes study-specific information, Kassan says. Sites can be blocked from participating if they do not complete a local context process.

"If a site is unmotivated to complete the paperwork, not doing what they need to do to participate, then they can't be approved to be in the study," Kassan says. "If they're relying on us for three studies, they're filling out the form three times. I'd like them to move to a bank of information where they don't have to do it every time because this is another obstacle."

• **Create modification form.** "One thing we recently did was create a modification form," Kassan says.

If the main site makes modifications to the protocol and the consent template, on behalf of the whole study, they submit a form to the IRB

of record. The approval is automatically sent to all the sites.

The main site doesn't have to remember to give materials to other sites," Kassan says. "We've been using the modification form for several months, and the study team is very happy about it because it takes a little burden off our local team."

Before the automatic notification system, word of the modification might be delayed if a study team was out of the office. "Because of the modification notification [process], when the main site is notified, the other sites are notified at the same time," Kassan says.

• **Find efficiencies.** "There are many institutions we work with many times," Maddox-Regis says. "Because we have collaborative relationships with them, and they rely on us for other studies, the reliance process has been much more efficient."

The IRB has reviewed many COVID-19-related studies. To make these reviews faster and more efficient, the IRB developed an emergency IRB that reviews only COVID-19 cases. "Our institution's COVID-related IRB, the emergency IRB, is comprised of board members from our other IRBs," Maddox-Regis explains. "In the peak of the pandemic, they were meeting every day because there were so many COVID-related projects."

To facilitate a more efficient review process with multiple relying IRBs, the institution requires all relying IRBs to be signatories to the agreement. "More than 850 institutions have signed onto the SMART IRB agreement, a master reliance agreement that we use in all reliance studies," Maddox-Regis says. "There's also an addendum to the SMART agreement, called indemnification, which requires sites to execute that."

These are the basis of reliance. "We have over 200 domestic institutions that have met those basic requirements through SMART, and it does expedite the process because they don't have to sign any new agreements or go through the legal teams to wait for any potential revisions or modifications," she explains.

Turnaround time for IRB reviews of projects with relying IRBs is the same as it was for single IRB reviews.

"IRB review, which is the lengthiest part of the process, is already done for [relying IRBs], and we can turn around site approval in a couple of weeks," Maddox-Regis adds.

The reliance process is much faster than multiple IRBs reviewing the same project, especially with some that meet less frequently.

For example, institution A submitted a multisite study in the pre-reliance world. That IRB experienced issues and tabled the application because they wanted to ask the investigator more questions. If the investigator responded after the IRB's cutoff for the next agenda, the IRB would have to wait another month to gather responses to issues.

Now, sites just need to complete two documents and send their local language, local context, and any other information relevant to the study.

"That passage is much quicker because we've already done the IRB review, and they gave us all the information we need to approve the research at their site, and the time savings is an asset," she adds. ■

# Consistency Is a Chief Goal for Relying IRBs

*Local context form can help*

*By Melinda Young*

Juggling the work of an IRB of record and becoming a relying IRB can be challenging. But one underlying goal can keep an IRB on track with both roles: consistency.

One way to keep processes consistent and efficient is to use the SMART IRB reliance agreement. IRBs also can set up templates and documents that relying institutions can use and complete.

It is important to work with multiple institutions, says **Janelle A. Maddox-Regis**, MS, associate director of the IRB reliance program at Johns Hopkins University School of Medicine.

## Create Master Consent

The IRB of record can create a master consent form. Each relying IRB can provide its own standard consent with site-specific information added to the master consent as an addendum. "Part of their local review is completing a local context form that tells us all about their site, state laws, and local policies," Maddox-Regis explains. "There's a standard template they complete that says, 'Give us your research subject injury language, your HIPAA language, and any signature line requirements.'"

Relying IRBs also can use any processes and policies of the IRB of record, including training requirements and conflicts of interest policies, says **Hallie Kassan**, MS, CIP, director of the human research protection program at Northwell Health in Manhasset, NY.

"We've been the IRB of record for a lot of sites that don't have any of their own policies and procedures," Kassan says. "Those sites piggyback on Northwell's policies and procedures, and agree to follow the policies and procedures we have in place." As the IRB of record, Northwell also will give relying sites a training session on the electronic submission system, she adds.

Sharing policies and procedures is a way to remain consistent. It is the study team's responsibility to bring information, such as local policies and procedures, to the attention of the IRB of record, Kassan says.

## Informed Consent Consistency

Consistency is more challenging with informed consent documents. Each research institution uses its own consent template that reflects its institutional policies, as well as state and local laws, Maddox-Regis says. For example, a Maryland state law addresses enrollment of non-English speakers or people lacking decision-making capacity.

"We knew when working on a study that has 30 different sites that we have to think strategically about how we meet the requirement on collecting local information from the site," Maddox-Regis explains. "We have to make sure that information is in that version of the consent form."

This could require a two-part consent form in which one copy is the master consent form that describes study procedures, risks and benefits, and all required elements of consent. This part cannot be changed by sites, and it is approved by the study/reviewing IRB.

"As part of the site onboarding process — which happens after the master consent — the study [team] creates an addendum consent form, and we call that part two consent," she says. "This allows us to collect information from the site, which is required from their consent form."

For instance, HIPAA authorization language could vary from site to site. "We as a reviewing IRB are required to obtain any relevant local context information relevant to research studies," Maddox-Regis explains. "Sites, as part of the site approval process, have to tell us everything they know about their site that is relevant to the study."

If a study team enrolls pregnant women, they have to explain which study language needs to be included in the part two consent.

Part one consent is a timestamped and IRB-approved PDF. Part two includes signature lines that are site-specific.

"When we're approving the site, we take the master consent form that's approved by the reviewing IRB, and the part two consent, and turn them into PDFs or combine them and stamp it so that version is provided to the relying IRB and study team," Maddox-Regis explains. "The reason why is so the site has one version of an approved consent, and they're not able to obtain consent from participants with only partial consent, such as having only part two." ■

IRB ADVISOR



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# CME/CE QUESTIONS

1. **According to panelists in a recent webinar, how can clinical trials become more diverse?**

   a. Require more minority trial participants
   b. Penalize trials that are not considered diverse
   c. Discuss diversity techniques during trial conception
   d. Consider partnerships between academic medical centers and smaller hospitals

2. **According to experts, race is used in clinical trials because:**

   a. it is a neutral variable.
   b. it can show ongoing disparities.
   c. it can show biological factors.
   d. it is a scientific variable.

3. **What is the goal of the single IRB review process, according to Janelle A. Maddox-Regis, MS?**

   a. Cost savings
   b. Easier for researchers
   c. Consistency
   d. Fewer mistakes

4. **What is the N=1 study design, according to Jonathan Kimmelman, PhD?**

   a. It is a study with one enrolled participant, often used to study rare diseases.
   b. It is a study design in which each participant is visited by a study team member at his or her home.
   c. It is a study design in which an IRB perform one review for all studies that pertain to that particular rare disease.
   d. The goal of these studies is to achieve 100% efficacy for the study treatment.