IRB ADVISOR

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INSIDE

RELIAS MEDIA

Vaccine Challenge Trials Present Ethical Issues to IRBs, HRPPs

COVID-19 vaccine efforts accelerated

By Melinda Young

The most pressing research goal in decades is the race to produce a vaccine to cure COVID-19.

The United States — with more than 2 million COVID-19 cases and deaths exceeding 115,000[1] — has pushed to expedite vaccine research. In May, President Trump launched Operation Warp Speed, with the goal of producing a COVID-19 vaccine by January 2021.[2]

While that short timeline might prove impossible, bioethicists and researchers say it may be possible to shorten the typical 15-year-plus vaccine timeline through a challenge trial. In this model, participants receive the study vaccine, the are deliberately exposed to SARS-CoV-2. Safety and efficacy are important, but the risk-benefit balance for study participants is weighed more heavily in favor of the greater public good.

"The entire plan for the development of a vaccine candidate needs to be evaluated to ensure it provides sufficient evidence of both safety and efficacy that potentially hundreds of millions of otherwise healthy people will be willing to be vaccinated," says **Alex John London**, PhD, Clara L. West professor of ethics and philosophy and director of the Center for Ethics and Policy at Carnegie Mellon University.

> "THE STAKES ARE SO HIGH AND THE IMPACT ON THE WORLD IS SO HUGE THAT, MORALLY, WHAT IS INDEFENSIBLE BECOMES DEFENSIBLE."

"There are many organizations and companies with vaccine programs underway. More than 100 companies are trying to produce vaccines, and we've never had 100 companies working at the same time on a single disease," said

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Arthur Caplan, PhD, professor of bioethics at NYU Langone Medical Center. Caplan spoke about the challenges of developing vaccines and treatments for COVID-19 at a May 13 web conference sponsored by WIRB-Copernicus Group.

"The goal of having a vaccine available quickly is one I don't think is going to happen, even with massive effort and money poured in," Caplan explained. "The usual timeline for getting a vaccine developed is closer to 15 to 20 years, and the fastest is six years. It takes a long time."

Vaccine research sometimes lasts for decades and fails. "We've tried for 30 years to get an HIV vaccine, and they haven't proven safe and effective," noted **Walter A. Orenstein**, MD, FIDSA, FPIDS, fellow with the Infectious Diseases Society of America (IDSA), and professor and associate director of the Emory Vaccine Center. He spoke at an IDSA web conference on May 1.

"One of the advantages we have is there are many candidates, including eight vaccines in clinical trials and more than 90 vaccines in pre-clinical stages," said Orenstein, professor in the department of medicine, division of infectious diseases at Emory University School of Medicine, and director of the Emory-UGA Center for Excellence for Influenza Research and Surveillance.

'What Is Indefensible Becomes Defensible'

In a SARS-CoV-2 challenge trial, researchers would not wait for study participants to become infected. Instead, investigators would deliberately expose participants to the disease after attempting to immunize them, and study what happens.

"To put it mildly, that is ethically controversial," Caplan said. "Is it worth taking the risk of compromising subjects to deliberately give them a disease?"

Caplan argued that because COVID-19 is killing so many people and years of waiting for a vaccine might result in many more deaths across the world, the benefits outweigh the risks of a challenge study.

"The stakes are so high and the impact on the world is so huge that, morally, what is indefensible becomes defensible," Caplan stated.

There is no consensus among stakeholders, including ethicists, IRBs, and researchers, on the potential benefits of a challenge trial, says **Karen J. Maschke**, PhD, research scholar and editor of *Ethics & Human Research* with The Hastings Center in Garrison, NY.

"For example, the World Health Organization [WHO] says in its draft ethical framework for COVID-19 challenge trials — released on May 6, 2020 — that 'It must be reasonable to expect that the potential benefits of SARS-CoV-2 challenge trials outweigh risks,'" Maschke explains.

When evaluating potential risks and benefits, research organizations should consider how these affect research participants, society, and third-party contacts of participants, she says.

Other ethicists have noted it is difficult to determine the potential benefits of a challenge vaccine trial because no one knows the degree and duration of naturally acquired and vaccine-derived immunity for those who receive the vaccine, Maschke explains. Also, most vaccines that are tested prove to be ineffective. Instead, IRBs and researchers should focus on the risks to participants and potential

benefits to society of a SARS-CoV-2 vaccine, she adds.

The risks of a SARS-CoV-2 vaccine trial are predictable, and they include risks to bystanders, as well as the study's volunteers, says **Jonathan Kimmelman**, PhD, James McGill professor and director of the biomedical ethics unit in the department of social studies of medicine at McGill University in Montreal.

"One additional variable to consider here is the uncertainty about complication and fatality," Kimmelman says. "COVID-19 is still a new condition, and we don't have a clear sense of mortality rates and risk factors for complications."

Since the available information will change with time, IRBs should be asking whether the research community knows enough now to assess the risk, he adds. *(See story on methods of reviewing a challenge vaccine trial in this issue.)*

"Or, does it make sense to wait until that knowledge, and the knowledge about rescue medication, becomes available?" Kimmelman asks.

Any challenge studies involving SARS-CoV-2 should have sufficient social value to justify the study design. "But I don't think the social value of a challenge study can be determined solely from looking at the protocol for that study alone," London says. "In particular, proponents argue that the main advantage of such a study would be the prospect that it will shorten the timeline for vaccine development. But I am not persuaded that it will do that."

With unknown benefits to participants and better-known risks of a challenge vaccine trial, transparency is paramount. "If research regulators permit one or more challenge trials to go forward, they should be transparent about what risk-benefit assessment they applied, and about how they determined which individuals should be eligible to participate," Maschke says.

In addition to questions about safety to research participants and those around them, there also is a question of whether a challenge study would produce enough information about a potential vaccine's safety and efficacy in the populations most at risk of serious illness and death from COVID-19. For instance, no one would propose purposely enrolling at-risk people to participate in a challenge trial for the vaccine because it would endanger their lives. But, if they are not part of the vaccine trial, how will any vaccine be shown to be effective for those populations?

> "WE CANNOT SKIMP ON THE ASSESSMENT OF SAFETY, INCLUDING THE SAFETY PROFILE OF THE VACCINE IN OLDER PEOPLE AND OTHER PEOPLE IN HIGH-RISK CATEGORIES."

"We cannot skimp on the assessment of safety, including the safety profile of the vaccine in older people and other people in high-risk categories," London says. "Because other approaches will generate this information in the course of testing vaccine efficacy, I am not convinced that challenge studies will save time once all things are considered."

WHO recommends a specialized, independent committee — at the national or international level — review challenge studies in conjunction with local ethics boards, Maschke notes.

"I support a heightened approach to ethical review, which should be independent of the funding bodies, the researchers, and the institutions where the trials will be conducted," she says. "Of note, the WHO framework says that research participants should be compensated for any study-related harms."

This compensation might include access to critical care services, free treatment, and compensation for research-related injury. "My view is that from an ethical standpoint, trial participants who become ill should be treated for free and receive some type of compensation for injuries related to their research participation," Maschke says. "However, to my knowledge, no one has said who should pay for injury-related harms or for medical treatments if diagnosed with COVID-19. In my view, the trial sponsors/funders should bear these costs, as well as the costs associated with the need for extra hospital beds, personal protective equipment, and medical support staff dedicated to the study."

This is so the clinical trial is not competing for access to these resources during an ongoing medical response to the pandemic, Maschke explains.

"In addition, a detailed containment, contact tracing, and medical care plan should be in place in the event that the research staff or other third parties become infected," she says. ■

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Actions for IRBs Reviewing Vaccine Challenge Trials

Create a concrete plan

As the world looks for a safe and effective vaccine against SARS-CoV-2, IRBs should review the bioethical implications of this type of study design, including assessing risks and benefits.

Several research ethicists offer these suggestions:

• Ensure the purpose of the trial is clear. "There needs to be a tight case that benefits to society are sufficient to redeem the considerable risks and uncertainties," says **Jonathan Kimmelman**, PhD, James McGill professor and director of the biomedical ethics unit at McGill University in Montreal. "One particular thing IRBs should think about is whether findings for the study are likely to actually inform vaccine development. IRBs should think of any trial as a diagnostic; they are done to inform a decision of whether to abandon a vaccine or develop it further, and whether to use a vaccine in practice."

The trial should not be conducted unless it is going to inform an important decision. "IRB members might be surprised to discover that a lot of trials are done without a clear path toward making a decision," Kimmelman says. "For example, drug companies might cut short a development program — not because the treatment they are testing flags, but because of a shift in commercial priorities."

These sort of abortive research decisions disrespect patients and volunteers, who do not consider themselves as useful only to help companies make strategic decisions, he adds.

• Create a concrete plan. "Before [a challenge] study could be launched, there should be a concrete plan, outlining the many steps in development for the vaccine candidate in question, and an apples-to-apples comparison with alternative strategies, including adaptive trials that will compress development timelines," says **Alex John London,** PhD, Clara L. West professor of ethics and philosophy and director of the Center for Ethics and Policy at Carnegie Mellon University.

"These plans should take into account the extra steps that are needed to mount a challenge study, including the creation of a challenge strain and the determination of the challenge dose, as well as side-by-side plans for assessing the safety of the vaccine candidate in the diverse populations to which it is likely to be administered," London says.

• Assess the study's ethical precautions and safety steps. "Owing to the novelty, technicality, and stakes [of a SARS-CoV-2 vaccine], my view is you need a central and specialized IRB to approve the first few infection challenge trials," Kimmelman says.

With a few exceptions, there is not a good record of using specialized review mechanisms, he notes. A recent journal article outlines these mechanisms.[1]

A challenge study should only go forward if there is an acceptable plan to manage risks. But developing a risk management plan is not a sufficient reason to take this approach, London says.

"To warrant taking this approach in the first place, there must be a credible plan to ensure both social value and to secure trust in the results of the larger plan of development of which that study is a part," London adds.

• Determine whether the sponsor can produce a successful vaccine. Kimmelman says research organizations and IRBs should ask these questions:

- Is the sponsor set up to follow up an infection challenge study with a field study?
- Are they set up to manufacture a vaccine if it shows promise in challenge and field studies?
- Are their commercial partners set up this way?
- Is the commercial partner committed to following up results?

"If the answers to these questions are tentative, IRBs should look askance at the proposal," Kimmelman says.

• Ensure transparency. "How committed is the sponsor to disseminate findings promptly so that others can learn about how COVID-19 behaves in healthy

humans?" Kimmelman asks. "Will they publish negative or inconclusive findings promptly so we can reduce some of the uncertainty surrounding COVID-19?"

IRBs should check for publication plans, press for data-sharing, and ask about the deposition of individual patient data in a learned intermediary database, Kimmelman adds. ■

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New FDA Guidance Explains COVID-19 Expanded Access Policy

The Food and Drug Administration (FDA) published an eight-page guidance for IRBs handling expanded access to investigational products during the pandemic.

The FDA's guidance, issued in June, explains how IRBs might review individual patient expanded access requests for investigational drugs and biological products during the COVID-19 public health emergency.

"We applaud the FDA for continuing to put out timely guidance as people are managing this," says **David Borasky**, MPH, CIP, vice president of IRB compliance for WIRB-Copernicus Group in Princeton, NJ. "It reinforces guidelines already in place for research of this nature. It's not unique to COVID; it's a long-standing, individual patient expanded access to unapproved drugs for any condition. The FDA is getting a lot of requests from people who are not familiar with the processes or the mechanisms for getting this approved."

The first half of the guidance speaks directly to IRBs and investigators, outlining what they need to do, he says.

"The FDA didn't put this out to manage the supply lines," he notes. "There were stories early on about problems with hydroxychloroquine, where people were snatching it up to stockpile for use. But there's a difference between approved drugs used off-label vs. something that is not approved at all and is being made available through one of these pathways."

For example, expanded access might apply to a drug that showed promise for fighting viral infections, but never made it through the study process. The product might still be available in some limited supply, and patients want to try it without waiting for a new clinical trial to begin for that product, he says.

"IRBs get involved to make sure informed consent is obtained, even though expanded access is not research," Borasky says. "The IRB's role primarily is to ensure there is adequate consent, and the person receiving the unapproved therapy understands that it is unapproved and is not proven to work for the condition they have."

The FDA's guidance includes three categories of expanded access investigational new drug applications (INDs), including:

- **Individual patient INDs.** This includes emergency use INDs (e-INDs), and can be submitted to the FDA by a licensed physician as a new IND or by a sponsor of an existing IND as a protocol amendment. Requests for emergency individual patient expanded access does not require prior IRB review, but IRBs must be notified within five days of treatment with the IND. For non-emergency expanded access requests, IRBs must review and approve before treatment.
- **Intermediate-size INDs** for somewhat larger patient populations.
- **Treatment INDs** for larger populations.[1]

The FDA recommends a single IRB member review an expanded access submission for an individual patient if the physician requests a waiver from the full board review.

The FDA also recommends the IRB assess the risks and benefits for the patient, including reviewing a thorough patient history and treatment plan.

IRBs should ensure the patient's informed consent for the expanded access product includes information about how the purpose is to diagnose or treat, rather than to investigate, Borasky says.

"This is the FDA's best attempt at balancing the work that an IRB traditionally does in the expanded access context," he explains. "The biggest role for the IRB is to ensure content is adequate and people understand they're not getting an approved drug."

IRBs also should review the request to ensure risks are minimized to what is reasonable when compared with expected benefits for the patient. A willing sponsor should provide the drug for that purpose, Borasky says. ■

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Small IRB Copes with COVID-19 Pandemic Under Limited Budget

Workload never ends for one-person shop

Many IRBs have seen clinical trial submissions decline since the COVID-19 pandemic began. Clinical trials also were put on hold. But work at Great Bay Community College — a one-person IRB office — has increased.

"It does, to a degree, feel like I'm doing twice the amount of work," says **Aimee E. Huard**, PhD, professor and chair of social sciences and IRB chair at the college in Portsmouth, NH. "We've had more applications during the pandemic. We're almost exclusively an SBER [social-behavioral-educational research] IRB."

Huard believes the influx of new submissions is because the pandemic closed in-person classes and activities, giving instructors more time for starting minimal-risk studies.

"The pandemic gives professors and instructors a chance to think about their scholarship, and to study and focus on their own interests. They're doing research," she says.

Most of the studies continued after the pandemic, but some were stopped. For instance, all studies that involved K-12 schools were paused, Huard says.

"Almost all of the studies were in the early stages, and we didn't have anything actively impacted by COVID-19," Huard says. "Some studies have had to assess how interviews and in-person data collection were impacted remotely."

Huard has not received additional funding during the pandemic. She has continued to operate the IRB as efficiently as possible, despite these challenges:

• Educating researchers. "Education is the biggest challenge we have," Huard says. "Many of my colleagues have had minimal interactions with an IRB. If they did work with an IRB, it was during their graduate research."

The IRB does not have a budget to cover educational resources, such as CITI human research protection training. Huard assembles free resources in a grassroots educational program. Researchers are tested on the regulations and information she provides.

"The education programs are what I can find or borrow from things like PRIM&R resources, the SBER Network, and standards from the National Institutes of Health," Huard says. "Typically, I use these resources as a place to talk about the things they did or did not know that surprised them," she adds.

After researchers pass a quiz, she sends them an email as certification of their passing educational requirements.

• Slow response times. Every IRB copes with slower-than-desired turnaround and response times. The Great Bay Community College IRB is no exception.

"As a one-woman show, the response times tend to be slower than I would like them to be," Huard says.

Each day, Huard receives more emails than she can handle. She sends quick replies saying she will get back to them in a few weeks or longer. "I'm starting to answer some of the emails, where I said I'd get back to them in May, and now it's May," Huard says.

"I'd like to help faculty across the system with their students and personal research projects and projects in conjunction with different institutions, such as local hospitals or four-year university systems," she adds. "The response time is slow when I have department duties and things like that."

Huard uses a few methods for improving the response time. One is an auto-response on emails. She also asks the IRB to update its response times once a month, based on her workload.

"I use our board members as advocates, and they help me triage the work when things appear in my inbox," she says. "Each board member represents one of the campuses that is part of the system."

• **Budget.** A small IRB's limited budget is a challenge when it comes to providing training, improving turnaround times, and handling all the varied study submissions.

"I cannot provide our voluntary board with baked goods and coffee, and I would love to be able to reward them for all of their hard work," Huard says. "I have thought about getting free coffee for them when the economy is better."

The revised Common Rule's changes to continuing review have helped, but there still are activities that IRBs need to do. That workload remains, Huard notes.

For example, the Great Bay Community College IRB sends surveys to researchers that previously would have been up for a continuing review.

"We make sure we have the most up-to-date information on their projects," she says.

The IRB uses its college's technology for remote meetings. Also, the IRB accepts electronic PDF document submissions, but does not employ a fully electronic submission process, she says.

• **New rules, practices, and regulations.** Another challenge, particularly for SBER research, involves projects that direct students and/or faculty to fill out surveys and conduct interviews.

"We can't do the interview piece because our state is still on shutdown, for the most part," Huard says. "Researchers can't do anything with an [in-person] interview until we have more guidance from various governmental entities."

The challenge is to ensure the survey studies and other research submitted by faculty meet both existing regulations and new rules during the COVID-19 crisis.

"I have some researchers who are working remotely from different regions because their programs are online-based," Huard says. "If they live in Massachusetts, but are doing research in New Hampshire, it's a reasonable drive — but it's in two different states with different regulations."

In the early days of the pandemic, one researcher started to ask for IRB input on a study that met all human research protection regulations. But, as the researcher and Huard were communicating, state and federal regulations changed for the pandemic, she recalls.

"Things have settled down a little in that way, but there was a two-week period when everyone was trying to figure out what was happening," Huard says. "I had a flurry of emails in my inbox." ■

IRB Highlights Standardized and Effective Metrics Model

Collect performance data to share

As IRBs and research programs increasingly seek IRBs of record and form reliance agreements, they will need to know whom to trust.

IRBs also need their own performance data to share with sponsors, researchers, and others. The challenge is developing metrics that work and can be used by other IRBs for benchmarking purposes. At least one IRB has found a possible solution.

"This has been an evolution of trying to look at metrics of my own IRB as we venture into single IRB territory," says **Ann Johnson**, PhD, MPH, CIP, IRB and human research protection program (HRPP) director at the University of Utah.

"It's become clear that all speak an IRB language, but our metrics have not," Johnson says. "Unless we have the same metrics language that they're using, it will be challenging

to compare apples to apples between IRBs."

Johnson published a poster about a new model for recording IRB metrics at the 2019 Advancing Ethical Research Conference of Public Responsibility in Medicine and Research in November 2019. *(The poster can be found at: https://bit.ly/35Cmw9H.)*

"This poster came from the idea that even though IRB review processes can vary across institutions, we all perform the same IRB steps," Johnson explains. "We may have different names for them; we may throw in an extra step here and there that someone else doesn't, but we all follow the same pattern."

The standards metrics model measures the time from IRB submission to IRB approval by breaking it down into smaller parts for each activity.

"This is a metric that people care about," Johnson notes. "What I basically did was take that one big space of time and broke it into two parts: the pre-review time, which a lot of IRBs do, and the review time," she says.

The pre-review time is further broken down into these three parts:

- time during pre-review spent with the IRB office;
- time during pre-review spent with the investigator;
- time during pre-review spent with others.

The review time includes these three parts:

- time during review spent with the IRB office and members;
- time during review spent with the investigator;
- time during review spent with others.

"As an IRB, we like to point out to people that investigators can complain it took this long to get IRB approval, but the time spent wasn't all by the IRB," Johnson says. "I might have sent the study back for revisions, and [researchers] sat on it for three weeks."

This metrics tool helps IRBs gain a more accurate picture of how their own time is spent vs. time investigators spend on answering the IRB's questions and concerns.

"There's a certain amount of defensiveness that IRBs have because we get blamed for how long we took. That make us upset — especially if we do a good job," Johnson says. "We want to show where the time was spent. That's how my model works."

For example, IRB staff may go back and forth with the study team two to four times on revisions. To accurately reflect the amount of time the study was in the IRB staff's hands, the metrics should show how much time it was in the IRB office vs. in the researcher's office, she explains.

"We're counting how much time it's in each of our hands. We add that all up, and it becomes one big time bucket," Johnson says.

For years, Johnson struggled with this part of metrics and how to compare what the University of Utah IRB did compared with other IRBs.

"When comparing my IRB process with other IRBs, the others might say, 'We wouldn't send it back to the principal investigator then,'" Johnson says. "But if you put the time in the buckets, it doesn't matter how many back-and-forths there are; it keeps a tally over time. We're all comparing apples to apples."

IRBs can assess how their time buckets average out to pinpoint where they are spending the most time. If the time spent on a particular process seems excessive, they can use the data to develop a quality improvement plan.

"This can have a lot of impact on how we make decisions about improving processes," she says.

For example, the IRB found its pre-review process took a long time, and investigated the cause. "At first, this concerned us," Johnson says. "Then, we looked at the review bucket and saw things were speeding through that bucket."

It was clear the IRB office was spending a lot of time in the pre-review process to make sure everything was correct. Then, when the study went to the full board for review, most minor details were resolved and the board could make a faster decision, she adds.

"People like that we get everything cleaned up in the beginning, and it sails through the board review," Johnson says. "The board members were getting less frustrated because fewer things needed to be tabled. That was something we discovered by comparing the two sides of the buckets."

Another way IRBs can use the metrics is by looking at investigators' time buckets. They can compare the amount of time they take between different types of studies.

"For expedited studies, we find investigators generally get their things turned around quickly," Johnson says. "For convened board reviews, we find it takes them a lot longer. We don't know the reason for this."

It makes sense if investigators take longer with convened board review studies because of their complexity. But, it also could be because the IRB is not doing a good enough job of asking for revisions and is confusing researchers, she notes.

"If that's the reason, then it's something we can fix," Johnson says. "We're just taking a look into how that's happening."

With data, IRBs can help investigators reduce the amount of time they spend making changes after IRB review or pre-review, she adds.

"That's what we're looking at right now," Johnson says. "We're ensuring our revisions are well-written, and we have reminder systems beyond what we already have." ■

Enhance Health Literacy Among Study Participants

IRBs can help improve health literacy among potential research participants using several tactics, including asking studies to use plain language in informed consent (IC) forms.

"We have a responsibility to make information more clear," says **Sylvia Baedorf Kassis**, program manager in the Multi-Regional Clinical Trials Center (MRCT) at Brigham and Women's Hospital and Harvard in Boston.

IRBs can review informed consent and subject recruitment materials to ensure the study information is clear and adheres to regulatory requirements.

For instance, IRBs can give investigators feedback on the language they use, and suggest they read online resources on health literacy when their materials need improvement, Baedorf Kassis says.

The key is not for IRBs to develop and rely on specific templates, she notes.

"Templates can help, but it's really a philosophy change," she adds. "We encourage investigators to understand the needs of their population so the materials being developed are as close to perfect for that community as possible."

IRBs might ask researchers how they incorporated patient or potential participant feedback into developing their research question, consent form, and recruitment materials, Baedorf Kassis says.

"If you incorporate feedback and use the language of the people you are working with, you are more likely fostering understanding of your concept," she adds. "It's a two-way street and an opportunity to learn from and communicate in better ways for people who need the information."

The MRCT offers a health literacy case study library with examples of how organizations are integrating health literacy into clinical research settings. *(The library is accessible at: https://bit.ly/2UOQyTw.)*

Researchers can use these techniques for enhancing health literacy among potential study participants:

• **Incorporate plain language.** "One of the things that is low-hanging fruit is plain language strategies," Baedorf Kassis says. "Include fewer technical terms, which is hard to do for science and medicine, but try to explain things in less technical terms."

IRBs also can use review consent forms, keeping plain language tips in mind. MRCT offers these examples:

- Ensure language is organized logically, and its content flows.

- Determine key concepts and present messages based on what the audience knows.

- Use everyday words, such as "use" instead of "utilize."

- Simplify terms and definitions, using visuals and word/picture pairings to help explain the concept.

- Use active voice, which leaves less room for error and provides clear instructions.

"A lot of people focus on grade-level material, and it's not a perfect proxy," Baedorf Kassis says. "It's a good check to see where you're at, but you have to do a little bit more than doing a reading level, saying, 'It's at eighth-grade level, so we're good to go.'"

• **Use clear design.** IRBs can ask investigators to fix text and presentation through clear design techniques.

For example, they can use design techniques that help present content clearly by breaking down information into short chunks, highlighting important information, eliminating redundant information, and breaking up blocks of text with white space. *(Find out more at: https://bit.ly/2xJW01v.)*

"It's not rocket science; it's a better division of information," Baedorf Kassis says. "You can divide information with boxes, as needed, providing a more visually appealing section so people can follow information more readily. You can use bullets instead of long sentences."

Bulleted points help people follow long stretches of information. Graphics also can help make complicated data easier to understand.

"You can integrate a study flow diagram into the process," Baedorf Kassis says. "You don't have to be a graphic designer. We can all do some basic things in PowerPoint."

• **Use the teach-back method.** The informed consent process

includes conversations with participants.

"Even in these times [of the pandemic], when things are done remotely or via online methods, there is still some conversation happening with research professionals to go over the information," Baedorf Kassis says. "Part of health literacy is a two-way conversation."

Conversation or interactive techniques are important. The teach-back method can help researchers assess how much participants understand what they just read and heard.

The teach-back method includes these four parts:

- Sharing information: Use simple terms and describe information in a way that is well-received by the target audience.

- Confirming understanding: Ask participants to repeat what they have just learned.

- Rephrasing or clarifying and reconfirming understanding: If the participant does not repeat the key information, demonstrating understanding, then repeat the information differently and ask for teach-back.

- Moving on and repeating: Once the participant demonstrates understanding, move on to the next topic. *(Find more information at: https://bit.ly/2xIrCoc.)*

"IRBs can reinforce for investigators the conversational teach-back techniques, where they ask probing questions about what was just shared," Baedorf Kassis says. "Have them ask, 'What are the main things that will happen to you if you get screened for the study?'"

• **Try usability testing.** Usability testing is evaluating a service or product through testing. It is a way to find out if potential participants understand research communication. *(Find out more at: https://bit.ly/35F6nQE.)*

"Usability testing can be done at all levels. IRBs can do it with their own templates, and investigators can do it with the content they develop," Baedorf Kassis says. "It gives you the information you need in order to make the next step in the research decision-making process. Is this document usable to the type of person who will be recruited into your study?"

There is a considerable amount of information available online about these techniques. More resources will be available soon, she notes.

"I'm working with a small group to develop more specific IRB resources and help IRBs to do health literacy training internally," Baedorf Kassis says. "There is a little guide that I have been working on." ■

Biometrics Expert Discusses Data Integrity for COVID-19 Clinical Trials

Issues can include bias, result repeatability

The first remdesivir double-blind, placebo-controlled clinical trial for treating COVID-19 was published recently in *Lancet*.[1] A member of the trial's data safety monitoring board (DSMB) is **Weichung Shih**, PhD, director of the biometrics shared resource at Rutgers Cancer Institute and professor of biostatistics at Rutgers School of Public Health. Shih discussed the role of biostatisticians in protecting data integrity for clinical trials and the challenges during the COVID-19 pandemic.

Shih and colleagues quickly analyzed and transmitted data from 10 participating hospital sites to the database. They found remdesivir was not the magic bullet solution for severely ill COVID-19 patients, as was the hope. But the drug did shorten the recovery time for patients with moderately severe illness.

The following interview with *IRB Advisor* was conducted via email and edited for length and clarity:

IRB Advisor: What was your role in guarding data integrity of the first double-blind, placebo-controlled clinical trial of remdesivir?

Shih: I served as an expert of biostatistics in the DSMB for that trial. There were five members in the DSMB: two medical experts, one epidemiologist, and two statistical experts, all independent from the trial sponsor and investigators. The DSMB was charged and guided by the DSMB Charter to ensure the interests of patients and the objectivity of the trial sponsor. Investigators are protected, as they were masked with respect to the treatment assignments on patients throughout the study, while the DSMB may access the unblinded data all the time.

IRB Advisor: What are some risks when there are questions or issues related to data integrity in a clinical trial? What are the most effective safeguards to mitigate

risks and prevent a worst-case scenario, such as the now-retracted hydroxychloroquine study findings?[2]

Shih: Potential issues with a clinical study include bias, lack of generalizability, and/or repeatability of the results. In general, from the design viewpoint, a randomized, double-blind clinical trial with a properly selected control treatment and sufficient number of subjects/participants from different study centers is the gold standard for investigating a new experimental therapy. From the conduct viewpoint, composing an independent DSMB is a common and useful practice to mitigate potential risks and to prevent a worst-case scenario for a clinical trial.

As I understand, the *Lancet*-retracted publication of hydroxychloroquine study was not a prospective clinical trial, let alone a well-designed and carefully conducted trial, but a secondary analysis of observational COVID data that were supposed to have been collected and warehoused in a huge commercial database. Usually, high-quality medical journals would require the authors certify they have full access of the data for audit when they submit their paper for publication. In the case you mentioned, it seems the authors later admitted they could not vouch for the veracity of the data sources after the paper had been published.

IRB Advisor: Researchers, public health officials, IRBs, and regulatory agencies are under a great deal of pressure to find solutions to the COVID-19 pandemic as quickly as possible. What are some of the risks, as well as regulatory and best practice safeguards, of collecting data and assessing its integrity under outside pressures?

Shih: Medical evidence has hierarchies like a pyramid. At the bottom of the lowest level of evidence is authoritative opinion — based on, perhaps, some anecdotal case report without critical appraisal or consensus. Next is retrospective, observational studies, which should be interpreted with all sorts of possible confounding factors in consideration. A higher level of evidence is individual prospective cohort studies, or clinical trials that we just mentioned. On the top of the highest level of evidence is systematic reviews or meta-analyses of relevant randomized, controlled trials. Naturally, the lower the level of evidence, the easier and faster to obtain the data, and vice versa. The lower level of evidence also is associated with higher risk of introducing bias, lack of generalizability, and repeatability. During the COVID-19 pandemic, when many research studies are being conducted, there could not be a systematic review or meta-analysis ready yet. Hence, we should evaluate individual clinical studies with vigilance as they are presented.

IRB Advisor: How can researchers, IRBs, and DSMBs help maintain public trust in the research enterprise, even when mistakes (or deceit) occur?

Shih: The researchers, IRBs, journal editors, news media, and health officials or decision-makers need to frame their judgment with an eye on the quality of data in terms of the level of evidence every time they are in touch with a clinical study for the public.

The public is most interested in the result of a study. That's why the result is always the headline of the news. But we know the process of the getting the result is critical for the result. We should explain to the public that a single research paper rarely establishes any finding with great certainty. Nothing is firmly established until many studies have confirmed it, by different researchers, using different methods, under different settings, investigating different aspects of it. From time to time, we learn lessons when rushing research with impatience, such as the recent incidence you referred to. But retracting as soon as realizing mistake (or deceit) was made is a responsible and critical step for winning back public trust in science.

IRB Advisor: Is there anything else you could explain about your work and how it relates to human research protection and scientific integrity?

Shih: I am a faculty member of the Rutgers Biomedical Health Sciences. I teach a course on design and analysis of medical experiments at the Rutgers School of Public Health. I have authored a textbook on this subject based on many years of research and experience practiced at the Biometrics Division of the Rutgers Cancer Institute of New Jersey with my colleagues. I have served on the Scientific Review Board of Rutgers Cancer Institute of New Jersey to help ensure all studies conducted at our institution follow the standard requirements of human subject protection rules and regulations. ■

REFERENCES

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2. Mehra MR, Ruschitzka F, Patel AN. Retraction — Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. *Lancet* 2020;395:1820.

IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **How would a SARS-CoV-2 challenge vaccine clinical trial work?**

   a. One arm of the clinical trial would receive the SARS-CoV-2 study vaccine, and the other arm would receive remdesivir as a prophylactic treatment.
   b. Researchers compare three or more vaccines to determine which works best and can be manufactured quickly.
   c. Participants receive the study vaccine, then are deliberately exposed to SARS-CoV-2.
   d. A large cohort of study participants receives one of two vaccine candidates, or a combination of the two candidates to see which produce the best results

2. **The Food and Drug Administration's recommendation about expanded access drug use during the pandemic suggests that IRBs:**

   a. ask an IRB member to review an expanded access submission for an individual patient if the physician requests a waiver from the full board review.
   b. convene the full board to review the physician's expanded access request.
   c. ensure informed consent for the expanded access product explains the drug is under investigation in a clinical trial.
   d. ensure patients are not harmed by the experimental treatment.

3. **The most common IRB data metric to collect describes how long the review process takes, including:**

   a. the time it takes researchers to complete the protocol review application.
   b. pre-review time spent with the IRB office and review time spent with the investigator.
   c. time from the electronic submission form to upload to the IRB's portal.
   d. time spent spell-checking the submission document.

4. **IRBs can use plain language techniques and simplify informed consent documents by:**

   a. using words with no more than three syllables.
   b. using everyday words, such as "use" instead of "utilize."
   c. providing a passive, calmer voice in the language of the document.
   d. running the research language through grammar check.