IRB ADVISOR

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INSIDE

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Study Results Show Public Support for Alternative Vaccine Design

Accelerated trial risk acceptable

By Melinda Young

The results of a recent study indicate potential research participants are open to alternative vaccine trial designs, including challenge trials in which participants are exposed to COVID-19.[1]

Researchers started the study in May 2020 as coronavirus vaccines development began. They wanted to see what people thought about accelerated clinical trial vaccine designs.

"Where we started was recognizing that early after vaccines, before trials were run, folks talked about ways to facilitate vaccine development," says **Joshua Kalla**, PhD, assistant professor of political science and assistant professor of statistics and data science at Yale University.

> "IT SEEMS LIKE THE AVERAGE PERSON SURVEYED IN THE UNITED STATES IS OK WITH PEOPLE BEING SICK AND HAVING TO PARTICIPATE IN THESE TRIALS IF THEY CAN GET OUT OF THE PANDEMIC FASTER."

For instance, one type of accelerated trial design would expose participants to the virus after they were given the study vaccine. The goal would be to see if the vaccine was effective at preventing them from contracting COVID-19.

"There were lots of people pushing for human challenge trials, and there was push-back on the scientific validity and ethics of these accelerated designs," Kalla says. "We were interested in what the public thinks about these types of accelerated designs and whether the public thinks they're ethical. Public opinion matters."

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One of the important functions of IRBs is to determine societal attitudes, which play an important role in determining what is ethical. "The World Health Organization came out with a document on accessibility of COVID-19 studies, and they stated challenge research programs should be informed by consultation and engagement with the public," he explains.

The researchers spoke with IRB members and decided to seek a broader population to learn about their thoughts on the ethics of vaccine trials. "What we did was run a large online survey across a number of different English-speaking countries," Kalla says. "We presented people with two fictional trial designs: One was closer to the standard vaccine trial, which ended up being what most pharmaceutical companies went with — the status quo approach — and the other was accelerated design."

The status quo approach was described as recruiting 9,000 healthy volunteers, administering the vaccine to 4,500 and the placebo to the other 4,500. The human challenge design was to recruit 80 healthy volunteers ages 18-30 years and give 40 people the vaccine and 40 people the placebo.[1]

"We did tell participants that 40 people in the placebo group would be exposed to the virus, and all participants were young people, so it was unlikely there would be serious complications and very unlikely that any would die from the virus," Kalla explains.

Researchers described it as a controlled setting in a medical research center where people would receive healthcare while participating in the clinical trial. "The key difference is the standard trial design tends to have a larger sample size and takes longer, but they're not impacting people with COVID-19," Kalla says. "With the other design, researchers are intentionally exposing people to COVID-19, and we ask people which of these two trials they prefer."

Most of the study's participants preferred the accelerated design and thought it was ethical. "We found, overall, people preferred the challenge trial to the standard trial design. This was true across countries and among older people, people of color, and people who lived in higher COVID-19 case areas," Kalla notes. "We asked how ethical they thought the challenge to be — 75% said it was ethical and 6% said it was not ethical."

While conducting the study, investigators did not know how much faster a challenge trial might be from the traditional design. They changed the examples to reflect different timelines. For instance, one case predicted the challenge trial would produce a vaccine by November 2020 and the traditional trial by May 2021, a six-month difference.

"Often in a standard design, more people tend to get sick with COVID-19 than in the human challenge trial design. [This is] because the standard design has a larger sample size," Kalla says. "There would be a larger pool of people who are going about their lives as usual."

The researchers' study case predicted half as many people would die from COVID-19 with use of the accelerated design — 1.2 million vs. 2.4 million — because the accelerated design would produce a vaccine six months sooner.

As it turned out, there was an early push for some pharmaceutical companies to conduct a challenge

trial, but none had done that, Kalla notes. The first human challenge trial was launched in the United Kingdom well into the pandemic.[2]

"We didn't know what to expect," Kalla says. "I think it's very interesting that people are OK with having volunteers sign up for a human challenge trial."

Study participants were told everyone who participated volunteered and understood the risks. "It seems like the average person surveyed in the United States and in much of the English-speaking world is OK with people being sick and having to participate in these trials if they can get out of the pandemic faster," Kalla notes.

The study's findings suggest IRBs might want to think outside the box about accelerated design of clinical trials and not assume that these are ethically unacceptable to the public.

"IRBs may want to think beyond the single community member on its board and think about using tools like surveys to get a broader sense of what a community person thinks about a study," Kalla says. "There may be biases if we limit it to the point of view of a single IRB member because they are not representative of the mass public." ■

REFERENCES

1. Broockman D, Kalla J, Guerrero A, et al. Broad cross-national public support for accelerated COVID-19 vaccine trial designs. *Vaccine* 2021;39:309-316.
2. Gallagher J. COVID-19: World's first human challenge trials to start in UK. BBC News. Feb. 17, 2021. https://bbc.in/3wcOsxe

IRB Project Cuts Protocol Modification Time in Half

By Melinda Young

An IRB process improvement project reduced the protocol modification time by half.

Before the process improvement, all modifications — including the simple ones — were assigned to the IRB chairs, and it would be several days before they were completed, says **Katie Sellers**, CIP, IRB director of the human research protection program at East Tennessee State University (ETSU).

"Now, modifications are mostly approved the same day they come in," she says. "It really has helped our researchers because it allows fast changes for studies."

At a different IRB, Sellers saw how IRB coordinators could play a larger administrative role and that it helped with streamlining and eliminating redundancies.

"Once I arrived at ETSU, we talked about ways we could do something like that," Seller says. "We got input from chairs and members, and buy-in from leadership. [We] ultimately decided to change the program to empower IRB coordinators to perform more professional functions on behalf of the IRB." These included delegations of administrative review.

This is how the streamlining process worked:

• **Obtain buy-in.** The ETSU IRB structure includes two chairs and one vice chair for each IRB. Each IRB includes a full-time IRB coordinator as support. Previously, the IRB chairs performed all the reviews. Every new study or modification submission would be assigned to the chair for review, Sellers says.

The change required the IRB chairs to give up some of their responsibilities and put these new responsibilities on the IRB coordinators. Sellers first met with the IRB coordinators to gauge their feelings about taking on these added responsibilities.

"The coordinators were the first ones I talked about it with, and they seemed confident in taking on more responsibility," she says. "Both had been here for over five years. They also supported reducing some of the redundancies."

Previously, coordinators pre-reviewed submissions to ensure everything was included. The coordinators sent the submissions to the chair for review. Then, the chair would send it back to the coordinator to finish processing.

It took a little longer to obtain buy-in from the chairs. "I started the conversation and they were a little hesitant at first," Sellers says. "One of our chairs had been here for 13 years and had never done anything like this."

They discussed how the changes would work and how it would give the chairs more time to focus on bigger issues with protocols, Sellers notes.

"With all of the Common Rule changes that have happened over the last couple of years, there are more

new policies and requirements overall for IRB review," she explains. "After the chairs had time to think about it, they were more comfortable with the change because they realized how much their workload had increased over the last several years."

• **Make the change.** Logistics were the next step. The IRB had to revise its policies, giving more delegation to IRB coordinators. The electronic submission system also was adjusted, routing forms to IRB staff instead of to chairs.

"Then, we did some education before we launched it, publishing newsletters so it wasn't a big change for our researchers," Sellers says. "We wanted them to know to call the staff first and not the chairs."

The IRB coordinators could jump into the review of modifications, but it was six months before they were fully comfortable with making human subject research determinations.

"We had a formal education session with chairs and coordinators," Sellers says. "We had case studies that we worked on together to make sure we all did things consistently in the same manner."

Sellers asked the staff to re-review previous determination forms to see if they would make the same determination as the chair.

For the first months of the change, Sellers and the chairs would check the determination forms for consistency and to ensure everything was handled correctly. The process has become more efficient because changes are made almost immediately.

"We saw that it cut our overall modification time in half, from six days to three days," she says. "Having the chairs not be in charge of so many administrative changes means they can focus on the larger changes and initial reviews, enabling them to complete the reviews more quickly."

• **Reinforce the process improvement.** Sellers and the IRB coordinators submitted a poster about the project to the Public Responsibility in Medicine and Research (PRIM&R) 2020 annual conference. This helped augment the changes.

"[Creating] this poster was really meaningful to reinforce how important making constant improvements to the IRB processes and procedures are," she says. "It drove home some additional buy-in post-improvement so we have more leverage to make better changes to our program in the future."

Other IRBs struggling with the same issue contacted Sellers after the conference, saying they wanted to make this change in their own programs.

"Being able to share the poster and show people that we made a successful change really hit it home that we should be committed to making these process improvements," Sellers says. ■

REFERENCE

1. Sellers K, Zerby L, Cannon T. Streamlining IRB review process through staff empowerment. Presented at the PRIM&R Advancing Ethical Research Virtual Conference, Dec. 1-2, 8-9, 15-16, 2020. Poster/Abstract: 50.

Q&A: Data Safety Monitoring Board Experts Explain Role in Clinical Research

By Melinda Young

Data safety monitoring boards (DSMBs) have played a big role in delivering vaccines and treatments to the public faster in the past 18 months. DSMBs reviewed results and safety data of the various studies involving treatments and vaccines for COVID-19. *IRB Advisor* asked two scientists about how DSMB work has helped improve research protections during the pandemic: **Weichung (Joe) Shih**, PhD, director of the Biometrics Shared Resource at Rutgers Cancer Institute and professor of biostatistics at Rutgers School of Public Health, and **Dirk Moore**, PhD, member of the biometrics faculty at Rutgers Cancer Institute, associate professor in the department of biostatistics and epidemiology at Rutgers School of Public Health, and chair of the DSMB that oversees clinical trials conducted at Rutgers Cancer Institute. The following interview has been lightly edited for length and clarity:

IRB Advisor: Dr. Shih, can you please describe your role in guarding the data integrity of the first double-blind, placebo-controlled clinical trial of remdesivir?

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

IRB Advisor: Data monitoring committees have been around since the 1960s, although few trials sponsored by pharmaceutical/medical device companies used DSMBs until after 2000. How important do you see the role of the DSMB in today's research environment — especially with the COVID-19 pandemic and rapid development of vaccines and treatment?

> "POLITICAL ENCROACHMENT ON THE REVIEW PROCESS HAS BEEN MITIGATED BY THE UNPRECEDENTED DECISION OF MANY PHARMACEUTICAL COMPANIES TO MAKE THE VACCINE STUDY PROTOCOLS PUBLICLY AVAILABLE."

Moore: From the outset, DSMBs have been designed to be independent reviewers of a drug, vaccine, or device. This has been interpreted in terms of members having no financial stake in the outcome, either through stock ownership or other connection to the corporation making the drug. Also, while DSMB members may be compensated for their time, that compensation may not be tied in any way to whether the drug is ultimately approved by the FDA.

[Regarding] COVID-19 vaccines, there has been the appearance of some high-ranking U.S. government officials and news media outlets injecting political considerations into the approval process for these vaccines. Political encroachment on the review process — or the appearance of encroachment — has been mitigated by the unprecedented decision of many pharmaceutical companies to make the vaccine study protocols publicly available. In that way, one can read the detailed review criteria that have been put in place in advance of the study start date. This information can reassure the public that DSMB approval decisions are dictated not by external political pressure but rather by meeting preapproved safety and efficacy goals.

IRB Advisor: What are some of the risks if questions or issues related to data integrity arise in a clinical trial? What are the most effective safeguards to mitigate risks and prevent a worst-case scenario, such as with the now-retracted hydroxychloroquine study in 2020?[1]

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 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 was supposed to have been collected and warehoused in a huge commercial database.[1] Usually, high-quality medical journals would require the authors certify that they have full access of the data for audit when they submit their paper for publication. In this case, 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: Is there anything else you could explain about your work and how it relates to human research protection and scientific integrity?

Shih: I am on the faculty 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 to help ensure all studies conducted at our institution follow the standard requirements of human subject protection rules and regulations.

IRB Advisor: With some AIDS research and now with COVID-19 research, we are seeing how important it is for a DSMB to monitor interim results. This can help either when unexpected adverse events arise, or if intervention works so well that it better serves public health to bring it to the affected population quickly. Would you please describe how diligently and carefully DSMBs review studies, particularly during a crisis, to ensure safety remains a priority even when there is an urgent need for a new treatment or vaccine to be distributed to the public?

Moore: DSMBs meet regularly to review the safety and, in some cases, efficacy of drugs and vaccines. For example, the Rutgers Cancer Institute, being a National Cancer Institute-designated Comprehensive Cancer Center, has a DSMB comprised of physicians and other researchers with relevant experience. It meets twice a month to review, in sequence and on a set schedule, all investigational drug trials conducted at the institute. Any adverse events that have occurred are reviewed to ensure patient safety, and any protocol deviations are reviewed and passed on to the principal investigator for remediation. Any trials that are found to not adequately balance patient risk and safety are referred to the scientific review board for review and possible closure.

IRB Advisor: With the COVID-19 pandemic, researchers, public health officials, IRBs, and regulatory agencies are under a great deal of pressure to find solutions 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 these sorts of 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 cannot be a systematic review or meta-analysis ready yet. Hence, we should evaluate individual clinical studies with vigilance as they are presented.

IRB Advisor: Will DSMBs continue monitoring the coronavirus vaccines after FDA approval? If so, how will results be made transparent to maintain public trust? If not, which group will oversee post-approval monitoring?

Moore: Even after approval, vaccines are reviewed by collecting reports of adverse outcomes. In the U.S., the Vaccine Adverse Event Reporting System (VAERS) is an early warning system for potential problems. Anyone (patients or physicians) can report suspected vaccine reactions to VAERS. The VAERS database is open to independent investigators for analysis of early- or late-term adverse reactions. This transparency can help maintain public trust. We can expect

that the coronavirus vaccines will be similarly monitored.

IRB Advisor: In 1999, a young man named Jesse Gelsinger died during a gene therapy clinical trial. As a result, the FDA and other government agencies put in place more regulatory oversight to enhance protection of research participants. How do DSMBs and their independent role help prevent that kind of tragedy from recurring?

Moore: The process of ensuring patient safety in clinical trials requires a multipronged approach involving the IRB, the DSMB, and nurses and doctors treating the patient, as well as other regulatory officials. Safety measures must be established and clearly formulated into a data safety monitoring plan. The plan must include procedures for ensuring safety monitoring procedures are followed by all participants in the process, and it also must lay out requirements and procedures for rectifying any plan deviations. In this way, outcomes such as the one that befell Jesse Gelsinger may be prevented.

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

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 public clinical study.

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 that the process of 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, and more. From time to time, we learn lessons when rushing research with impatience, such as the [hydroxychloroquine study]. But retracting as soon as we realize the mistake (or deceit) was made is a responsible and necessary step for winning back public trust in science. ■

REFERENCE

1. 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 Approaches Research Participant Complaints Individually

Making participants feel validated is an important component

By Sue Coons, MA

Like many of its counterparts, the IRB at New York State Psychiatric Institute (NYSPI) evaluates any complaint from a research participant on an individual, case-by-case basis. *IRB Advisor* spoke with **Corinne Rogers**, MS, CIP, NYSPI IRB director, to find out more about her research-related dispute procedures.

"Thankfully, we don't get a whole lot of [disputes] since we are a smaller research institute," Rogers says. Usually, the complaints start with her because she is the director, and she begins the initial investigation. Sometimes, she learns an investigator has spoken with a participant who is planning to launch a complaint. Other times, the person who complains approaches Rogers directly.

First, Rogers gathers as much information about the complaint as possible. "If they email me, I will respond to them and see if they want to have a telephone conversation. If they call me, then I take a detailed account of exactly what the complaint is. I gather all the information that I need, including which protocol they participated in. If they don't know the protocol number, then they can give me the name of the investigator and what type of protocol it was."

Once she has the details, Rogers contacts the investigator to obtain similar information from him or her based on the subject complaint. Then, she and the investigator try to move toward a resolution, but the process depends on the type of complaint. For example, a common complaint is about not receiving a payment for participating.

"That's kind of easy for us to resolve if I can get in touch with the investigator and let them know that this is not acceptable," she says. "The

consent form says that [participants] were supposed to have received compensation in a certain time frame and in a certain way. If that didn't happen, I can generally get the investigators to get on top of that very quickly."

Another of the more common complaints is participants are upset because they were excluded from participation. "They don't think they should have been, and they want to know why. That one can be a little tricky sometimes depending on the nature of the protocol. We do psychiatric research, and some people may get hung up on feeling that they should have been allowed to be in a study and weren't." In these cases, Rogers works with the investigator to try and find the best way to approach the issue. "If we are not really getting anywhere in that department, then I might ask my IRB chair, who is a psychiatrist, to step in and assist with trying to resolve the situation to where the participant feels they've been validated. That's generally the process for how we can go most of the complaints."

The resolution process may change if an investigator receives multiple complaints. This would require a more thorough inquiry into the investigator's processes, Rogers says. "If it turns out that it's a pattern, then I would bring my compliance monitor to [oversee] their whole process to see what's going on and why there's a breakdown in the system."

Complaints on social media can add a public element to the complaint process. Rogers says NYSPI has not experienced this. A public comment probably would be handled differently, she says, with the potential of the institute's legal and public relations departments becoming involved with the resolution.

Take Detailed Notes

When handling complaints from clinical trial participants, Rogers says taking detailed notes is crucial. "In my experience, documentation is really important," she says. "We've had a couple of instances where we've had the same person come back and complain about the same thing for a couple of years. It was obvious that this person has some behavioral issues, but that doesn't mean that we shouldn't be responsive to their complaints and their concerns. That's why documentation is so important because you want to be able to have everything in front of you each time you have to revisit the situation."

It also makes sense to put standard operating procedures in place in case the person who normally handles complaints is unavailable at the time. "These things need to be handled very carefully. In my experience, it's important to make sure that there is a channel for the complainant to get to the person that they are trying to reach quickly," Rogers says. "If you are the person who is dealing with the complaint, you must look at the consent form that the participant signed to see what they were entitled to. A lot of times, reviewing the consent form solves a lot of these problems because the information will be right there."

For example, the consent form might say participants can expect payment in two to four weeks. "When someone calls to complain that it's three weeks now and they haven't received the payment, it's very easy to say, 'The consent form gives it up to four weeks. Let's give it another week. If you still haven't received it, please get back to me and I'll follow up on it.'"

The consent form also helps with exclusion and inclusion complaints. The consent form might not provide full details about the inclusion and exclusion criteria, in part to keep participants from misrepresenting themselves to get into a study. However, the consent form could say a participant may not be pregnant or currently in treatment to be included in the study.

Exclusion complaints are easier to handle if the criteria are clearly spelled out in the consent form, Rogers says. If an exclusion complaint is more

nuanced or begins to escalate, then the complaint process could include the assistance of a licensed medical professional outside the IRB. "At this point, that [complainant] may need a little bit more of a clinical interaction," she says. "We do have a lot of participants in our studies who have some significant mental illnesses."

Check for Resolution

When the complaint process is completed, Rogers follows up with the participant to ensure the complaint has been resolved. "I make sure that I either get confirmation from the investigator that the issue has been resolved in terms of payment being received by the complainant, or I will have a conversation with the complainant myself to make sure that their complaint has been resolved."

If a person is upset because he or she was excluded from a trial, then that issue may not be fully resolved. "The best we can do is take efforts to make sure that the participant understands why they couldn't be included and perhaps offer some other opportunities for studies where they may be able to be participate," she says.

Occasionally, a complainant has emailed the institutional official directly. "They have every right to do that," Rogers says. "Our IRB always gets involved in that, however. I don't have any recollection of an instance where we weren't able to resolve any of those things, and I clearly only remember that happening once. [The complaints] always basically come through my office."

Overall, it is important for IRBs to take complaints from clinical trial participants seriously, Rogers says. "People participate in research. It's a big thing," she says. "Although you might think that the complaint is trivial, it's not. People should be able to reach out to the IRB if they feel like they were treated in any way fairly or unfairly, or if they don't get what they think they are entitled to. Every effort should be made to resolve the situation for the participant to feel like they were validated so that they don't regret participating, and [that they] will continue to volunteer to participate in research studies. If they don't, we suffer as a whole." ■

Study Author Gives Recommendations to Improve Research Dispute Process

By Sue Coons, MA

An associate professor at Columbia Law School in New York City wrote about the handling of research grievances from research studies for the *Yale Journal of Health Policy, Law, and Ethics*. For her study, **Kristen Underhill**, JD, DPhil, MSc, spoke with personnel from 30 hospitals and universities to see how they resolve the complaints. The processes for resolving research participants' concerns are a "curiously unregulated space," she wrote.[1] While the United States court system might recognize claims about physical injuries during a trial or a negligent study design, it usually is left to the IRB to resolve disputes between trial participants and research staff.

In her interviews, Underhill found that, like the IRB at New York State Psychiatric Institute, many IRBs said their complaint resolution processes include "procedural flexibility." This flexibility allows the complaint process to be tailored to each dispute. For example, a complaint that can be handled through facilitated negotiation can free up time and resources for more complicated disputes. Relevant stakeholders also can be added to the process as needed on a case-by-case basis. Underhill's respondents also said the processes allows individuals to feel heard and respected. This would be more difficult using a standardized process, they said.

Overall, the respondents said complaint frequency was low, indicating to Underhill a possible problem with access to dispute resolution. Participants might not know they can complain, or how to begin the grievance process. They could fear retaliation or lack of access to the study drug if they complain. This could cause a higher dropout rate for the study, with unhappy participants choosing not to participate in the future. They also might share their perceived negative experiences with others in the community.

Underhill also addressed neutrality. Some respondents were uncomfortable playing the role of a neutral third party, she said. Ties to investigators and institutions complicated the

loyalties. The respondents also said they often lacked resources or training to handle disputes, especially for complex ones that involve "mental illness, threats of violence, and volatile interpersonal dynamics." The respondents said they wished they had access to other dispute resolutions from other institutions for comparison. Accreditation organizations could ask for examples of a written process for dispute resolution but do not set requirements for development or implementation.

Since the frequency of disputes often is low, the respondents wished their processes were more consistent, since they changed based on the type of complaint. The low number of complaints also made it more difficult to gauge the success of the resolution. "Institutions with larger research portfolios with a larger absolute number of complaints are less likely to have this problem, but informants from such institutions still noted difficulties with documenting complaints in a way that allows them to monitor for consistency and systemic problems," Underhill wrote.

Underhill made several recommendations for how the dispute resolution process can be improved. One is to include the input of participant representatives in the development of the dispute resolution process, a step most respondents did not use. "Having a say in process development is important, in part, as a matter of procedural justice, but also as a matter of improving system accessibility, the durability of resolutions, and perceived legitimacy of the process (and the research institution more generally)," she wrote.

Secondly, the low uptake of the dispute solution process reflects a lack of information, particularly lack of awareness of the forum and the process for dispute resolution, Underhill noted. She suggested better education of subjects during study enrollment and follow-up. "Subjects' awareness and understanding of protocols and 'subjects' rights' — and thus, their expectations of how they should be treated — will inform whether they recognize wrongs as actionable," she wrote.

To address the neutrality issues, Underhill said IRBs have several advantages to managing research-related disputes. They can suspend protocols, require revisions or remedies internal to research protocols, or cancel the protocols entirely. They can bring outside assistance into the dispute process, such as department chairs, legal counsel, human resources, and compliance departments. Multisite studies can refer the complaint to either the local IRB or the IRB of record.

Underhill also recommended these changes to the dispute process:

- increasing publicity and accessibility through informed consent procedures and integration of participant community leaders;
- compensating participants for physical injuries;
- building IRB expertise and resources for conflict resolution;
- using records to identify recurring complaints and improve consistency;
- providing for advisory third-party review and reconsideration of decisions, even if that review is not binding.

Adjustments to processes for research-related harms are ethically warranted, she concluded. "The Belmont Report and other ethical guidelines have spoken widely on the need to minimize subject harm but have said little about how institutions can (and should) offer redress when they fail to do so," Underhill wrote. "Participants in human subjects research take on many burdens in the interests of scientific progress; when they experience unintended harms, they should not bear the additional burden of unfair processes." ■

REFERENCE

1. Underhill K. Righting research wrongs: An empirical study of how U.S. institutions resolve grievances involving human subjects. *Yale J Health Policy Law Ethics* 2019;18:2.

When Complaints Are Not Resolved

By Sue Coons, MA

IRBs can resolve most research-related complaints, but a policy implemented last year by the National Institutes of Health's (NIH) Office of Human Subjects Research Protections (OHSRP) offers assistance when the conflict reaches a stalemate.

Policy 104, *Managing Research-Related Complaints from Subjects*, applies to NIH investigators, non-NIH investigators when the NIH IRB is the reviewing IRB, the NIH IRB, the OHSRP, and Institute/Center (IC) leadership. The policy was implemented on Sept. 21, 2020.[1]

The policy advises the principal investigator (PI) to notify the OHSRP Office of Compliance and Training in the case of unresolved complaints, regardless of whether the NIH IRB is the reviewing IRB. OHSRP will work with the appropriate parties and offices to assist with the complaint. Matters outside the scope of the Human Research Protection Program (HRPP) will be referred to the appropriate NIH office or IC. Matters within the scope of the HRPP also could be handled by NIH offices other than OHSRP.

The IRB may take any or all of the follow actions, according to the policy. It can modify the research protocol and/or consent(s), suspend or terminate IRB approval for some or all of the PI's studies, require additional education for the investigator(s), and inform other IC or NIH officials to consider additional actions.

Looking to the Future

Could federal regulations, state statutes, or professional accreditation standards require the use of a neutral third-party mediator or arbitrator in the future? Relocating the dispute resolution system outside the IRB could have more cost than benefit, said **Kristen Underhill**, JD, DPhil, MSc.[2] The non-neutrality of IRBs can be problematic, but this is offset by the structural advantages of IRBs involved in dispute resolution for research-related injuries and by the IRB mandate to protect subjects.

"Imposing the requirement of a third-party neutral from outside the institution would also scale up the costs of disputes and could impose inefficient levels of process for minor complaints. Requiring subjects to bear these costs would impair access to the forum, as most subjects would be unable or unwilling to pay," Underhill wrote. "Institutions could bear the costs, but this may impair neutrality of the forum for third-party decision-makers that were repeatedly retained. Requiring research sponsors to bear the costs would increase the expense of research more generally, posing tradeoffs between paying for more research or more administrative costs."

Nor does Underhill believe changes to the Common Rule should be made to address the resolution systems. This could increase inefficiencies in the current system and discourage innovation. "Mandating and monitoring IRB compliance with new regulatory requirements for complaint resolution, especially when the frequency of complaints may be low, is likely to increase inefficiencies in the current system," she noted. "It may also discourage innovation, such as institutions that began using local trusted authorities in culturally or linguistically distinct participant populations to assist in handling disputes."

Underhill spoke to personnel from 30 hospitals and universities to see how they resolve grievances from research studies. The respondents indicated an openness to guidance about the issue. This, along with the informal nature of many of the respondents' processes, could facilitate the incorporation of new ideas without a regulatory requirement, she wrote. ■

REFERENCES

1. Office of Human Subjects Research Protections. *Policy 104: Managing Research-Related Complaints from Subjects.* Sept. 21, 2020. https://bit.ly/3iMjgAZ
2. Underhill K. Righting research wrongs: An empirical study of how U.S. institutions resolve grievances involving human subjects. *Yale J Health Policy Law Ethics* 2019;18:2.

CME/CE OBJECTIVES

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

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

IRB ADVISOR

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CME/CE QUESTIONS

1. **Researchers recently assessed public interest in COVID-19 challenge trials and found:**

   a. people believed the risk was too great to research participants.
   b. people thought the risk for healthy participants ages 18-30 years was acceptable.
   c. people thought only adults under age 25 years should be enrolled.
   d. people said they would never enroll in a challenge trial.

2. **According to Weichung (Joe) Shih, PhD, what is the gold standard for investigating a new experimental therapy?**

   a. A challenge clinical trial design
   b. A clinical trial with at least 50,000 participants
   c. A randomized, double-blind clinical trial with a control treatment and sufficient number of participants
   d. A series of case studies, replicated by different researchers

3. **What step does Corinne Rogers, MS, CIP, say is crucial to the New York State Psychiatric Institute IRB's research dispute resolution process?**

   a. Asking the complainant to speak to the researcher first.
   b. Making sure each complaint goes through the standardized process.
   c. Taking detailed notes of the complaint.
   d. Discussing the complaint with the IRB members.

4. **How can IRBs manage research-related disputes?**

   a. Require revisions to research protocols.
   b. Offer compensation to participants who complain.
   c. Ask investigators to explain consent forms to participants again.
   d. Ask the complainant to withdraw from the study.