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INSIDE

RELIAS MEDIA

COVID-19's Effects Hit Healthcare, Research Institutions

Virus creates research challenges

By Melinda Young

Mere weeks into the United States' experience with the coronavirus pandemic, many academic and research institutions have closed all, or part, of their usual activities.

IRBs have learned that their disaster plans did not prepare them for the effects of a fast-moving virus, COVID-19, that has demonstrated its far-reaching ability to shut down normal business and social interactions. This novel coronavirus, spread to more than 194,000 cases worldwide and 5,723 cases in the United States as of March 17. *(Up-to-date figures are available at: https://bit.ly/33SUYfv.)*

By March 15, 2020, the disease was declared a pandemic. It paralyzed Italy's social and business enterprises, and threw the nation's healthcare system into chaos with more patients needing intensive care and respiratory equipment than the system could handle.

> THE FDA RECOMMENDS THAT SPONSORS EVALUATE ALTERNATIVE METHODS FOR ASSESSING PARTICIPANTS, INCLUDING PHONE CONTACTS AND VIRTUAL VISITS.

The pandemic prompted closures of American universities, sporting events, schools, churches, entertainment venues, cruise ships, Disney properties, and many other businesses and sites for an indeterminate period.

The pandemic also is causing unfortunate challenges for clinical research, said **Paul Biddinger**, MD, MGH, endowed chair in emergency preparedness, director of the Center for Disaster Medicine, and vice chairman for emergency preparedness

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in the department of emergency medicine at Massachusetts General Hospital in Boston. Biddinger spoke at a web conference on March 13 that was co-sponsored by WIRB-Copernicus Group (WCG) and Accumen.

"It's hard for us to support clinical encounters with patients if either the principal investigator or research assistant comes into contact with COVID-19, from a management or resources utilization standpoint," Biddinger noted. "We cannot use a single piece of personal protective equipment that could be used by a clinician in clinical care."

PPE Is Limited

Health systems and academic medical centers are experiencing a limited supply of personal protective equipment (PPE), and must only use it when necessary — or it will not be available when an influx of COVID-19 patients enter their system.

Research purposes are necessary — but not always during a national emergency. "We have to be careful how many people enter a room for a clinical encounter," Biddinger explained. "We need to consume fewer masks, gloves, etc., so this is having an impact on clinical research capabilities."

Despite an incredible need for knowledge and the intention to understand what is happening with the virus, research institutions should proceed with caution when it comes to human subjects research, he added.

"We need to continue to acquire knowledge, and we can't put the entire site on hold for a year to stop medical knowledge," Biddinger said. "But, we need to know when to start and stop research studies, looking at resources utilization and the importance of the project."

Clinical Trial Guidance

On March 18, the FDA issued guidance for IRBs, investigators, and industry for conducting clinical trials during the pandemic. The guidance acknowledges challenges, such as quarantines, site closures, travel limitations, and interruptions to the supply chain for the investigational product. The FDA recommends that sponsors evaluate alternative methods for assessing participants, including phone contacts and virtual visits. Also, they should offer additional safety monitoring for trial participants who may no longer have access to investigational products. *(The FDA guidance is available at: http://bit.ly/3a5odOq.)*

Research organizations can conduct some elements off site such as remote assessments, said **Mike Cioffi**, senior vice president of clinical solutions and strategic partnerships at WCG MedAdvante-ProPhase. Cioffi spoke March 18 at a WCG webinar on clinical trials in the era of COVID-19.

IRBs and research organizations need to consider the scientific validity of collecting data remotely, Cioffi noted. "I encourage people to look at the type of data you're collecting and see if it's going to be valid," he said.

Research organizations could leave decisions about whether to continue in-person monitoring of study participants to investigators, suggested **Greg Poland**, MD, professor of medicine and infectious diseases at Mayo Clinic, and director of Mayo Vaccine Research Group.

"They know those research subjects best and know how critical is

what they're doing," Poland said. "If I'm testing a new antihypertensive and it requires blood tests, I would probably delay that trial because healthcare providers and that lab have maximal capacity for what they need to be doing."

But if a researcher is conducting an oncology study, which may be more urgent, institutions and investigators need to decide jointly. Some are deciding to delay enrollment of new subjects, except for COVID-19 research, Poland added.

The COVID-19 pandemic highlights the importance of isolation ethics, such as avoiding doctor's visits for minor illnesses and using telemedicine whenever possible, said **Arthur L. Caplan**, PhD, professor of bioethics and founding director, Division of Medical Ethics at NYU Langone Medical Center in New York City. Caplan also spoke at the WCG webinar.

Under this construct, it is unethical for researchers to continue clinical research if it poses a public health risk or a personal risk to research participants and staff.

"If someone is in a Phase III study and they're getting efficacy for treating cancer, then there is a responsibility to talk with the sponsor and institution about continuing to provide care," Caplan said.

But for a study that does not involve a life-and-death issue for participants, or that does not involve finding a cure or vaccine for COVID-19, continuing the clinical trial during a pandemic has less convincing ethical underpinnings.

All Eyes on Developing Vaccine, Treatments

The U.S. Department of Health and Human Services (HHS) has expanded and formed partnerships with pharmaceutical development companies to expedite development of a vaccine for COVID-19. One partnership is with Janssen Research & Development, part of Johnson & Johnson.

THE COVID-19 PANDEMIC HIGHLIGHTS THE IMPORTANCE OF ISOLATION ETHICS, SUCH AS AVOIDING DOCTOR'S VISITS FOR MINOR ILLNESSES AND USING TELEMEDICINE WHENEVER POSSIBLE.

There also are some potential drugs for treating COVID-19 infection being studied in China and elsewhere, said **Scott Gottlieb**, MD, former FDA commissioner and current member of the boards of Pfizer and Illumina.

"There is an antibody-based prophylaxis, where you give monthly injections, for treatment of Ebola," Gottlieb explained at the March 13 web conference. "This could be used for frontline healthcare workers who are going to be exposed to coronavirus — like people in nursing homes."

If prophylaxis treatment is developed, and studies show it works with COVID-19, then it could be available by the end of summer. "It would provide a natural backdrop against transmission and reduce morbidity and mortality," Gottlieb said.

Vaccine efforts are much further away: "We have to be realistic and believe a vaccine is two years away," he said. While it would be possible to inoculate frontline healthcare workers first, this might not be the best strategy in the event the vaccine makes them more susceptible to the virus, he added.

HHS also offered development support for developing a high-throughput COVID-19 diagnostic test. The test could be used in a diagnostic system that processes up to 1,000 tests in 24 hours. It is receiving support from HHS Office of the Assistant Secretary for Preparedness and Response. The test can produce results in three hours. Its development is expected to be completed this spring, and it could be considered for the FDA's emergency use authorization. *(More information is available at: http://bit.ly/39Rwo0B.)*

Protect Employees

For IRBs and research offices that maintain some on-campus staffing and business, the CDC has published charts and toolkits on keeping the workplace safe, at: https://www.cdc.gov/coronavirus/2019-ncov/downloads/workplace-school-and-home-guidance.pdf. The CDC encourages people to:

• Practice good hygiene:

- Stop handshaking;
- Clean hands at the door and email handwashing reminders;
- Remind people to not touch their faces and to cover coughs and sneezes;
- Disinfect surfaces regularly;
- Increase ventilation through open windows or adjusting air conditioning.

• Use caution with meetings/travel:

- Use videoconferencing for meetings;
- Hold meetings in open, well-ventilated spaces;
- Adjust or postpone large meetings and gatherings;
- Assess business travel risks.

• Stay home if:

- Employees feel sick;
- They have a sick family member at home.

• Avoid crowding:

- Schedule appointments to stagger customer flow;
- Use online transactions when possible;
- Limit attendance at larger gatherings.

These measures, including the hundreds of closings of entertainment, tourist, travel, sporting events, festivals, conferences, and other events, are intended to flatten the pandemic's curve, Biddinger said.

"We'll continue to see rising numbers of cases, but perhaps all of our efforts are blunting the curve, keeping the peak as low as possible," he explained. "The higher that peak, the more people we will see who need hospitalization and intensive care." The higher the peak, the more likely the influx of very ill patients will overwhelm EDs and ICUs.

The rapid pace of the pandemic's spread, and of the state and public response, gives public health officials and emergency preparedness workers hope that the United States' experience with the pandemic will not be as overwhelming as Italy's experience in early March 2020, Gottlieb said.

"The question is, 'Will we look like Italy or South Korea?'" Gottlieb asked. "South Korea's epidemic looks like it has peaked [by mid-March] and has declining cases, vs. Italy with 15,000 cases and over 1,000 deaths [by mid-March]; the two nations are similarly sized."

South Korea took the right actions by enacting strict mitigation steps early on to have the public engage in social distancing. The nation also implemented broad-based diagnostic screening and identified people in clusters, getting them into quarantine, Gottlieb explained.

"They used tools to reduce the scope of the epidemic, while Italy was slow to implement mitigation steps and allowed the virus to spread in the country," Gottlieb said. "Now, Italy's healthcare system is overwhelmed, and the epidemic is on the brink of being out of control everywhere." ■

Real-Time IRB Process Reduces Turnaround by 71%

Modifications made during meeting

The IRB of the Medical College of Wisconsin in Milwaukee experienced a protocol review turnaround time of 70.6 days, despite using a robust pre-review system.

"We felt like we had done what we could prior to the regular submission process to improve turnaround time, so we were looking for something creative," says **Ryan Spellecy**, PhD, director of the human research protections program and professor of bioethics at the Medical College of Wisconsin. "That's when we came up with a real-time review process. Even if things were perfect and firing on all cylinders, we wanted to see what we could do to speed up the process."

An investigator and one other key research team member attend the IRB meeting to answer any of the IRB members' questions in real time. The IRB turnaround time has dropped to 20 days, a 71% reduction through 2018.[1] Before the real-time IRB process, the median time for study approval was in the 60- to 80-day range, over a three-year period, Spellecy says.

"The reduction is pretty significant," he adds. "In 2019, the average was 18 days."

Occasionally, IRB members will catch a problem that will lead to tabling a study, but it is far more common to find things that would need to be improved with minor modifications. Those modifications can be made during the IRB meeting, Spellecy explains.

"Those minor modifications are discovered during the IRB meeting," he says. "The study team comes into the room, and we say, 'Thanks for coming in. We had these questions about your application.'"

For example, an application might say the study will enroll 30 people, but the informed consent form says that 40 people will be enrolled. It might turn out the consent form is an older version. Someone from the research team will need to log into the application and make the change during the meeting, Spellecy says.

"They can go across the room to the computer workstation, review it, and make the changes," he says. "We get a text message that the changes are made, and we bring this back into the meeting and approve the study on the spot."

Previously, this type of minor error would have garnered an approval with modifications. The study team would have up to a week to make the change. Then, it would go back to the IRB for processing. That one small mistake would take a week or two to resolve, Spellecy says.

Process Familiarizes Researchers, IRB

Another benefit of the real-time IRB process is that investigators and board members get to meet each other in person. "Anecdotally, they say, 'It's nice to put names with faces,'" Spellecy explains. "Researchers become more comfortable reaching out to the IRB with questions. It humanizes the IRB to an extent."

The real-time IRB process works this way:

• **Study teams indicate interest.** When research teams submit their studies to the IRB, they indicate whether they would like to use the real-time process. Those that agree must meet criteria set by the IRB, and are placed in the queue, Spellecy says.

"We ask them to be facile enough with the online review system to be able to go across the room and make those changes quickly," he adds. "We request they submit several proposals without hiccups, so we can see they're an experienced study team."

It is not practical to use this process with every study, Spellecy notes. "It has a cost; extra staff members have to be there to shuffle the study team around," he explains. "Principal investigators have to take time out of their schedules to attend the IRB meeting."

Occasionally, the IRB allowed new researchers to apply for the real-time process with the request that they have a mentor sponsor them and walk them through the process.

"We allow folks, who can benefit from it, to use the real-time process as long as there is someone who can help them," Spellecy says.

• **Coach investigators on the process.** "We coach investigators who have not done this before," Spellecy says.

Sometimes, researchers will introduce themselves with a long explanation of the importance of their research. But this wastes time, so they are asked to keep their introduction short and simply answer questions.

Study teams insert changes using Click Commerce. For example, the IRB might ask for a modification of a specific section, and the researcher must be familiar enough with the online IRB management system to know what this means and how to make the change quickly, Spellecy says.

• **Researchers attend the IRB meeting.** The study team is required to attend the meeting to answer questions from IRB members. The IRB also requires sponsors to attend the meeting via teleconference.

If the IRB asks that researchers change wording in the informed consent document or something else in the review application, they often need the sponsor's permission before they can submit the change. For the real-time process to work, sponsors have to give an answer during the IRB meeting.

"Sponsors make their staff available with a phone call during the IRB meeting to answer questions and to give a quick approval of the change," Spellecy says.

The process increases the meeting time by three to 10 minutes on average, he notes.

"We only do one real-time review per meeting," Spellecy says. "That's logistics because we have to have an extra IRB staffer available to usher the study team around, bring them to the meeting, take them to the work station, and let the IRB coordinator know when the changes have been made."

• **The IRB provides specific and timely suggestions.** IRB members often will pick up on an issue that is different from what the IRB staff's pre-review assesses.

The IRB member might know how a hospital process works, and IRB staff would not know that nurses handle this situation in a specific way. For example, a study drug was to be administered in a blinded study. A pharmacist on the IRB noted that researchers planned to blind the study by using commercially available bags, placed over the IV bag, Spellecy says.

"The pharmacist said, 'This doesn't come in a bag. It has to be administered from an investigational pharmacy, in a bottle, so this wouldn't work,'" he explains. "We had a talk with the study team and came to a resolution at the meeting, in real time."

While this process does not work for every IRB, it is a great tool for some IRBs and studies, he says.

"It's not a magic bullet, and it won't solve all issues or decrease turnaround time for every study. But we're proud of it, and want to help others adopt it," Spellecy says. "It's important people know it's not a cure-all." ■

IRB's Re-Engineered Program Makes It More Responsive

Program handles conflicts of interest

The revised Common Rule requires IRBs and research institutions to become more efficient and attentive. It also makes clear that an IRB cannot do all things for all stakeholders.

"The biggest change with single IRB review has made us realize there are institutional components of research review that need to be separated out from the IRB review," says **Kimberly K. Summers**, PharmD, director of research protection programs and adjoint assistant professor at University of Texas Health San Antonio (UT Health SA). "You have to develop some type of infrastructure in place to make that happen."

UT Health SA created a human research protection program (HRPP) office to handle institutional components of research protection work. For example, the HRPP office reviews research staff to ensure that everyone working on research projects is appropriately trained, qualified, and credentialed to perform the research they are proposing, Summers says. The HRPP office also reviews conflicts of interest and ensures all non-IRB committee reviews are completed, such as safety committee reviews and HIPAA compliance.

Since opening the HRPP office, the IRB's turnaround time has remained consistent at 28 to 30 days, Summers says. But the time from receipt of protocol to enrollment of the first subject has decreased significantly because HRPP staff help investigators navigate all ancillary committee and regulatory approvals, she adds.

"We do our institutional review process concurrently with the IRB review," Summers says. "They will communicate any outcomes of the reviews when they have an effect on the IRB's review."

The HRPP office also handles local context reviews to ensure state laws and other local considerations are communicated to the external IRB.

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"The local IRB's job is to focus on regulatory criteria for any studies they review — anything for which they have IRB oversight," Summers says. "Before, they only provided oversight for our site, but now they provide oversight for external institutions that we may not have had a relationship with before."

The IRB and HRPP divide research protection duties this way: "If our institution provides oversight for other research sites, we are the IRB of record, and the IRB office handles it," she explains. "If our institution refers the study to an [external] IRB, then our HRPP office handles that."

The HRPP office is not involved in contract negotiations for IRB of record agreements, but they make sure all details are handled before activation is approved.

"The financial aspects, institutional issues with payments — we make sure all of those are in place and everything is done by the clinical trials office, which is outside of the HRPP," Summers says. "The HRPP makes sure there is clearance from the clinical trials office before they get an activation letter."

The activation letter is a green light to investigators. The activation letter means the study received IRB approval, clinical trials clearance, approval from all necessary committees and departments, such as the cancer center.

"They might still receive individual letters, but this activation letter is the one they're looking for to get started," Summers says. "The HRPP office is there to help investigators get through all the different offices and approvals they need to get the study up and going so they can enroll their first subject."

Before the institution opened the HRPP office, investigators would seek IRB approval. But they often still could not enroll subjects after the IRB gave them a green light because there were other approvals pending.

"Now, there's a whole office that helps them through that process," Summers says. "HRPP and IRB are independent offices that don't report to each other, but both offices report to me."

The HRPP office runs a concierge service, making its manager and four analysts available during office hours to speak with investigators and answer questions. "We sent out satisfaction surveys about the process, and we received a lot of positive feedback," Summers says.

Separating HRPP and IRB functions has enabled staff in both offices to specialize and be more efficient in what they do.

"When everything was handled in one office, sometimes it could be overwhelming," Summers says. "Now, with the separation of the offices, each office knows they can depend on the other for their expertise."

The IRB and HRPP have developed a close relationship, she adds.

"We're becoming more and more comfortable with the process and are improving efficiencies over time," Summers says. "It's been a world of change over the last five years." ■

Study Reveals Preferences for Simpler Research Language

CLEAR initiative is solution

Boilerplate language for informed consent documents is simple, but not always easy for study participants to understand. The goal for IRBs is to help researchers simplify the words and scientific jargon they use to describe studies to participants, but it is unclear how this can be accomplished.

One solution is the Consent Language Explicit And Reasonable (CLEAR) Initiative. Investigators of the CLEAR Initiative surveyed 120 people, in lay and scientific communities, to see which words and phrases they preferred to see in consent documents.[1]

"We have boilerplate language, referring to issues of privacy and in the case of injury or harm during research," says **Ilene Wilets**, PhD, CIP, IRB chair, program for the protection of human subjects at Icahn School of Medicine at Mount Sinai in New York City. Boilerplate language often contains a lot of jargon that many potential research volunteers would find difficult to understand, she notes.

An IRB might attempt wordsmithing, but how can they know what will work and what falls flat? The answer is to ask people which words and phrases they prefer to read in a consent document. "We call this project the CLEAR Initiative," Wilets says. "I like the word 'reasonable' in the CLEAR acronym because we want to protect people, but the pendulum has swung so far. We have so much in there that our text is lengthy and dense, and it confuses them," she says. "We're trying to simplify it, so we asked community members, through a survey, which words they like better."

Survey Revealed Preferred Terms

For instance, what should research participants call the person who conducts research: researcher, investigator, or study doctor? The answer, according to the CLEAR study, is that laypeople prefer using the word "doctor," as in "study doctor" or "research doctor."[1]

What would research participants prefer to be called: subject, volunteer, or participant? "We looked at the language consent forms typically use," Wilets says. "We're trying to understand which words are most meaningful to study candidates."

Researchers conducted the survey at the medical center. "A lot of people approached our kiosk, and they wanted to voice their opinion," she says.

Then, they analyzed the results, comparing the people who worked in healthcare research with the people who had no connection to the healthcare industry. If investigators had more time, they might have started the CLEAR Initiative with focus groups to gather more exhaustive information, she notes. "We ran out of time to do that."

The survey results found that about two-thirds of participants were employed in medicine, research, or healthcare. Their perspective was different from the one-third who were not employed in medicine or healthcare, Wilets says. For instance,

people who worked in healthcare or research knew what HIPAA was, and many laypeople did not.

"We're still analyzing the results, but the first thing that jumped out was when we asked survey respondents about what to call a researcher," Wilets says. "In our consent form, all different terms are used. It's not that any of these is incorrect, but we were wondering if one term was better than the others," she explains. "It might be incorrect if you said 'study doctor' because the person conducting research might not have an MD, and maybe is not medically trained."

But the survey results showed that members of the community felt comfortable with calling researchers "study doctors," while people in the research and healthcare community preferred the names "investigator" or "researcher."

If the CLEAR Initiative had conducted focus groups, they might have discovered why laypeople preferred that term. "Maybe people are conflating research with clinical care," Wilets says. "We would like more data to find out why they preferred 'study doctor.'"

The findings can help IRBs improve consent documents. For instance, among the survey's respondents of healthcare, research professionals, and laypeople, the most popular term for describing people who volunteer in research is "study participant." Those surveyed also preferred the term "experimental drug" to describe a new medication used in a clinical trial.

"The findings have helped us tweak our consent form," Wilets says. "We talked about the findings with our board members, and we had an IRB retreat recently — a full-day conference with members of the research community and IRB members. We talked about simplifying informed consent forms and looking at literacy levels."

"We know illiteracy is high, and we just wanted to simplify it as much as possible so people from all walks of life can understand consent language," she continues. "It's too much to ask investigators to keep track of different versions, based on different populations."

The goal is to present information in a way that people can understand. "CLEAR is not a template at this point," Wilets explains. "This is more about exploring the phenomenon of word preferences in our community, and we're still learning what those preferences are."

The study does not definitively select the best words and phrases to use for informed consent documents, but it suggests some simple changes that IRBs can make and will lead to more thinking about this issue.

"It is more of a springboard for thought in our office, and we want to spin it into something more definitive," Wilets says. ■

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Interactive Online Checklists Help Investigators With Informed Consent

Consent checklist replaces informed consent template

A recent study revealed that an informed consent checklist of basic consent elements guides investigators on how to present key information required by the Common Rule.[1]

As the deadline for the revised Common Rule approached, an IRB office reviewed its informed consent templates and worked to update key information, says **Lisa Rigtrup**, CIP, operations manager of the IRB at The University of Utah in Salt Lake City.

"Because we're a biomedical campus and behavioral science campus, we had to create different templates to accommodate different study designs," she explains. "One thing we found was it made our templates unwieldly."

The templates were an inefficient way to help investigators with informed consent and all the ways these forms needed to be written according to the study's type. "That's when we came up with the idea of providing guidance and checklists to our research community," Rigtrup says.

The solution was an informed consent checklist, similar to an internal checklist used by the IRB office to conduct pre-reviews of applications, she adds. "We reached out to our biggest departments and

said, 'We're thinking about doing this checklist; can you give us some feedback?'" she says.

Engaging stakeholders and making the change transparent helped the IRB achieve buy-in when the checklists were rolled out. "It took away some of the shock and made sure some of the biggest departments and stakeholders around campus were prepared," Rigtrup says. "Initial outreach softened the blow quite a bit."

The online informed consent (IC) checklist provides users with basic IC elements, such as: "Is there a statement that the study involves research and an explanation of the purposes of the research?" It includes drop-down information under the categories of discussion, sample language, and regulatory references. *(The University of Utah IRB's checklist can be found at: http://bit.ly/2xwYeRt.)*

Originally, the IRB used separate templates for various research authorizations, such as a HIPAA authorization. With the checklist, each area has its own tab.

"We've gotten really good feedback from our research community," Rigtrup says. "It has required very little tweaking."

The initial outreach in rolling out the checklist contributed to its positive feedback, she adds. Plus, researchers praise the checklist formatting. They use the checklist's phrasing and topic priorities when they write IC forms.

"The impression I get is that the checklist is sensitive to their patient population, and they're able to use informed consent wording that makes sense to people," Rigtrup notes. "The checklist has helped them move wording in a way that the informed consent conversation makes more sense. Anything they can do to enhance the process is good."

The checklist's success led to the end of almost all informed consent templates: "Our templates are gone; they're not using them anymore," Rigtrup says.

The only exception is the oncology department, which created a template for its Phase III clinical drug trials. A template works in this case because the oncology trials are homogenous, so a template would need few adjustments.

STUDY COORDINATORS REPORT THAT THEY APPRECIATE THE CHECKLIST BECAUSE IT HELPS THEM DO THEIR JOBS BETTER, AND THEY REQUIRE FEWER SIMPLE REVISIONS.

"The oncology department said, 'If the IRB does not want to handle this anymore, would it be acceptable to create our own template to use?'" Rigtrup says. "We said, 'Absolutely, and if you want to run it by us, that's fine.'"

The checklist's chief benefit is that it helps investigators improve their review submissions, she says. "If they check off everything on the checklist, chances are their revisions are very low," Rigtrup says. "Using it has reduced some of the basic errors."

This saves time for IRB staff and members, giving them the opportunity to focus on bigger issues, she adds.

"We also are finding it has cut some of the apron strings with investigators," she says. "You have researchers who would really depend on the IRB to catch a lot of things, and now we say, 'Here are the tools, and you need to know this information in detail.' We're putting some of this information back on them."

Study coordinators report that they appreciate the checklist because it helps them do their jobs better, and they require fewer simple revisions, Rigtrup says. "When researchers are collaborating with other universities, sharing their resources among multisite studies, they don't have to change too much in their IC document because there is template language they have to adapt to each site," she adds. "It seems to make things easier for multisite studies."

IRB staff check human research protection program guidance regularly and compare new guidance to what is in the checklist, making sure everything is up to date.

When the checklist first rolled out, IRB members needed a little education about its language, content, and how these fit with regulatory requirements.

"Just because the language is not what they're used to seeing doesn't mean it's not acceptable," Rigtrup says. "We show people the part of the checklist a regulation goes with so they can see that it meets the requirements."

The Common Rule's flexibility has helped people accept the change, she notes.

From the IRB's perspective, it is a case where trying something new has paid off: "It adds to our flexibility and ability to do things in an adaptable way, which is the future for IRBs," Rigtrup says. ■

New Working Group to Produce Guidance for Pediatric Gene Therapy

Mission to advance research policy

The NYU Grossman School of Medicine's working group on Pediatric Gene Therapy and Medical Ethics (PGTME) formed in the fall of 2019 to address and propose recommendations to issues involving gene-based therapies in pediatric populations, including research activities.

"Our mission is to advance research policy, education, and medical ethics," says **Lesha D. Shah**, MD, assistant professor of psychiatry, and medical director, Child, Adolescent and Family Services, at Icahn School of Medicine at Mount Sinai in New York City.

The working group's members include physicians, medical ethics experts, patient advocates, researchers, pediatric disease authorities, and public health and ethics professors. "We've assembled a group of quite diverse expertise, and there is no other group like it," Shah says. "We're working with every stakeholder community." *(For information, visit: http://bit.ly/2xvuJQ0.)*

The working group received funding for three years. It will hold a conference in the fall, where the group might produce some work products, but there is no deadline for when guidance and recommendations will be published, she notes.

"We want to understand pediatric gene therapy challenges and evolving ethical challenges," Shah says. "The plan is to have some kind of consensus guidelines in the long-term."

The group's five priority areas are:

• **Equity in trial recruitment.** The group will assess and address recruitment, enrollment, and participation in gene therapy trials, and look at gene therapies, Shah says.

• **Lived experience of patients, parents, and families.** "The scope could be quite broad, but we wanted a qualitative, ethnographic approach to understand their experience," she explains.

• **Informed consent.** This priority addresses pediatric assent and surrogate decision-making, as well as informed consent.

• **Risk and benefits.** "This includes how we design clinical trials and how we educate patients and parents to make informed decisions," Shah says. "It's how we justify individual risk vs. societal benefit."

• **Vector immunity.** Vector immunity issues are important to study design and participants' risks. "It is not well documented in any of the literature, but it is understood that with the administration of gene therapy, you have the potential for a vector immunity-related phenomenon," Shah says. "Gene therapy is administered by means of a viral vector. Repeat administration is precluded because of the potential immune response."

The working group holds open-ended listening sessions with patients, parents, and advocates. The goal is to learn more about their experiences, and to bring the right people to the table before the group identifies a strategic plan, Shah says.

"Pediatric patients are special and a vulnerable population, so considerations for including them in research are important," Shah says. "Sometimes, current guidance on pediatric enrollment does not account for nuances that pediatric gene therapy would bring to life. Also, gene therapy is a brand-new technology with a lot of implications." ■

IRBs Can Prepare for Cannabis Research

The cannabis industry is a booming economic force across the nation as states increasingly legalize the sale of medical and/or recreational marijuana. It remains on the national Schedule I list of drugs that are not acceptable for legal sale.

But what do healthcare providers really understand about the drug's safety, risks, and benefits? Not enough, human research protection professionals say.

"Cannabis research is important, but its legal status impedes that research," said **Amanda Higley**, PhD, CIP, IRB chair for Advarra in Seattle. Higley spoke about cannabis research at a recent teleconference.

"This is a pivotal time in the world," she said. "We're addressing research gaps and quality."

While there is a need for clinical trials to assess safety and treatment use of cannabis, such research is

hindered by the federal government listing it as an illegal drug, Higley said. The FDA recognizes the pressing need to conduct research about circumstances for which cannabis might be used as a medication, she added.

Without ample cannabis clinical trials, healthcare practitioners and the public rely on anecdotal, weak evidence, or studies with indirect ways of obtaining evidence. For example, a recently published review of cases involving marijuana and violence combined information from news media accounts, journal articles, and anecdotal clinical experience. The study makes the case that people with pre-existing medical conditions use marijuana to alleviate their symptoms although it can worsen their conditions over time. It also discusses the link between aggression and the use and potency of tetrahydrocannabinol (THC). *(The study is available at: https://bit.ly/2xSZLl3.)*

"I got cases from the internet and different news organizations. The scientific discussion and rationale mostly came from journal articles, and putting it together came from my clinical experience," said **Norman S. Miller**, MD, JD, chief executive officer of Health Advocates in East Lansing, MI. "Good research should be done to show what marijuana is and what it is not."

The FDA has not approved cannabis to be marketed for treatment of any disease or condition. But it has approved Epidiolex (cannabidiol) and three synthetic cannabis-related products (Marinol, Syndros, and Cesamet). These are available only through prescriptions. *(For more information, visit: http://bit.ly/2wXNGut.)*

Although marijuana is a Schedule I drug that has no currently accepted medical use in treatment in the United States, researchers and sponsors can submit an investigational new drug application to the FDA for a clinical trial. They also must register with the Drug Enforcement Administration.

The FDA supports researchers who intend to study cannabis by providing information on the clinical research process and support through meetings and information from the FDA Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance group, according to testimony given Jan. 15, by **Douglas Throckmorton**, MD, deputy director for regulatory programs — CDER, before the U.S. House Committee on Energy and Commerce, Subcommittee on Health. *(The testimony is available at: http://bit.ly/2TSF4hA.)*

Of the four drugs containing marijuana derivatives that were approved by FDA for treatment, there is reasonable evidence for efficacy in treating neuromuscular disorders, sleep disorders, and Tourette syndrome. There is not good evidence for efficacy in treating depression, anxiety, psychosis, and glaucoma, Higley said. "The studies to date have a number of limitations," she said.

For instance, there are design elements that are important for IRBs to consider when reviewing these protocols. "A cannabis protocol should include as much information as possible about the chemical agent," Higley explained.

Studies involving marijuana should include plant characteristics, including species, variety, strain, how it is harvested, how much of the plant is used, extraction methodology, and concentrations of relevant chemicals. "We believe if sponsors of principal investigators fail to provide this information, then it is within the purview of the IRB to require it," Higley said.

IRBs also should ensure investigators list all potential risks in informed consent documents for studies of marijuana or any of its derivatives, including cannabidiol (CBD) products.

"There also are many unanswered questions about the science, safety, and quality of products containing CBD," Throckmorton told Congress. "The agency is working on answering these questions through ongoing efforts, including feedback from a recent FDA hearing and information and data-gathering through a public docket."

Throckmorton listed these potential risks associated with using CBD products:

- **Liver damage.** "We are concerned about potential liver injury associated with CBD use that could go undetected if not monitored by a healthcare provider," Throckmorton testified.
- **Drug interactions.** Drug interactions were seen in CBD studies. For example, Epidiolex studies show a risk of CBD affecting a patient's other medicines.
- **Male reproductive toxicity.** Laboratory animal studies show male reproductive toxicity, including a decrease in testicular size, inhibition of sperm growth and development, and decreased circulating testosterone, Throckmorton said.

When IRBs review studies involving THC-containing products, they should be aware of the risk that a research participant might drive under the influence.

IRBs also might ask questions about any placebo-controlled design, Higley noted. "Cannabis studies can show a high response rate in a placebo group," she said. "The pros and cons of providing a placebo group should be evaluated." ■

IRB ADVISOR

CME/CE QUESTIONS

1. **Why does Arthur L. Caplan, PhD, say researchers should practice isolation ethics when determining whether to suspend or continue their clinical trials during the pandemic's social distancing stage?**

   a. Isolation — meaning a plastic screen between participants and research staff — is the only way to prevent infection.
   b. All in-person visits should be suspended until the national emergency is lifted.
   c. Oncology studies should be allowed to continue, but all others should be suspended.
   d. Decisions about suspending studies should be made with the idea that only the most urgent, critical, and pertinent studies should continue.

2. **The University of Texas Health San Antonio created a human research protection program (HRPP) office to handle institutional components of research protection work. How do the IRB and HRPP office divide their duties?**

   a. The IRB office handles IRB meeting duties and protocol submissions, while the HRPP office ensures compliance with conflicts of interest policy, safety committee reviews, HIPAA, and training.
   b. The IRB office handles external IRB reviews, and the HRPP office handles oversight when the institutional IRB is the IRB of record.
   c. The HRPP office handles animal research protection, and the IRB handles human research protection.
   d. The HRPP office establishes review boards for HIPAA, scientific merit, and human research regulatory compliance, while the IRB handles only investigator-initiated research protocol reviews.

3. **The University of Utah IRB has developed an informed consent checklist that includes the basic elements described in the revised Common Rule, including which of the following?**

   a. For research involving infectious disease treatments, subjects must be provided with adequate personal protective equipment.
   b. Research involving children requires informed consent by parents/guardians and minor assent.
   c. For research involving more than minimal risk, participants should be informed about compensation and whether medical treatments are available.
   d. Principal investigators must not receive anything more than $50 in cash or material goods from sponsors of their studies.

4. **The NYU Grossman School of Medicine's working group on Pediatric Gene Therapy and Medical Ethics is creating recommendations for studies involving gene-based therapies in pediatric populations, encompassing:**

   a. equity in trial recruitment and vector immunity.
   b. regulatory compliance.
   c. lived experience and animal studies.
   d. informed consent and conflicts of interest.