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INSIDE

What Happens to Human Research in the New Pandemic Era?

Will 'normal' exist after COVID-19?

By Melinda Young

The big question in the clinical research world is how things will look when the COVID-19 pandemic has ended. Will everything go back to the way it was? If not, what changes will remain?

"I don't think we're going back to the old normal," said **Alison Lakin**, associate vice chancellor for regulatory compliance at the University of Colorado Denver, Anschutz Medical Campus. Lakin spoke about COVID-19 at a WIRB-Copernicus Group (WCG) web conference on April 8.

"We're living in this era of potential waves of disease that will impact us nationally, regionally," Lakin said. "There may be the need to have some continued social distancing, whether continuous or intermittent, and we'll need to manage the unpredictability of hotspots coming up."

> IN A POST-COVID-19 WORLD, SOME PATIENTS WILL NOT WANT TO GO BACK TO FACE-TO-FACE INTERACTION FOR EVERY TRIAL VISIT. RESEARCHERS NEED TO THINK ABOUT THAT IN THE FUTURE.

Research enterprises should think about how they will ramp up operations in a less stable world. "They should be aware of local context, and sponsors knowing what that context is will be really important," Lakin said. "Different sites will be opening in a different time than other sites." IRBs and research organizations need to understand the limitations of basic resources they previously had taken for granted, she added.

"We are not going to return to normal," noted **Jill Johnston**, president of study planning and site optimization

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at WCG. Johnston also spoke at the April 8 web conference. "It will be a new and improved normal. There is more acceptance of virtual trials and telemedicine."

The pandemic is transforming the way the human subjects world thinks of virtual clinical trials and patient visits. Practices are changing as well. "I'm not sure what the long-term impact will be, but there is a need for flexibility," Johnston said.

IRB Meetings Going Virtual

In a post-COVID-19 world, some patients will not want to go back to face-to-face interaction for every trial visit. IRBs and researchers will need to think about that in the future, Johnston added.

IRB meetings have moved to virtual space, and this change might remain after the crisis ends. For example, the University of Cincinnati IRB holds only remote board meetings now, explained **Michael Linke**, PhD, chair of the University of Cincinnati IRB, and adjunct professor of medicine at the University of Cincinnati College of Medicine. "After two or three meetings, it's working well, and we may use that process more moving forward," Linke said.

Now that people are forced to attend virtual meetings, they have experience in doing it and can see how well it works, he noted. "Maybe it's working better than people thought it would," Linke said. "It's hard to change people's behavior unless they need to."

The University of Cincinnati IRB uses web conferencing technology that allows board members to use webcams. "More people are using that now than they did before, and I think that makes the meetings better — when you can see people," Linke explained. "We have probably 12 people at the meetings."

IRBs also have learned a great deal more about disaster planning because of the pandemic, noted **James Riddle**, MCSE, CIP, CPIA, CRQM, vice president of institutional services and strategic consulting at Advarra in Columbia, MD.

"Everyone should have a disaster plan in place so that staff and IRB members know what to do in the event you can't have normal operations — when it could be from flooding, earthquake, fire, or pandemic," Riddle explained. "Have some emergency plan in place."

Pre-pandemic, Advarra's operations already were electronic. "We were able to make the switch to remote work very easily," he said. "All of our board meetings are held virtually."

IRB meetings for WCG included board members calling in and participating remotely before the pandemic. Now, the IRB is on a completely remote model, said **David Borasky**, MPH, CIP, vice president of IRB compliance for WCG. "The regulations were written in an era before the idea of doing things remotely was even thought of as being possible on a regular basis."

Regulators have welcomed remote meetings. Although some IRB leaders thought federal regulations favored videoconferencing over phone conferencing, that was never the case, Borasky explained. "You don't have to be in the same room or videoconferencing to have an IRB meeting."

The IRB operations shift toward electronic records, submissions, and reviews also might accelerate after COVID-19.

The University of Cincinnati IRB has worked from home during

the crisis, Linke noted. The IRB office uses an electronic program that allows staff to set up groups for texting and videoconferencing, making it easy to hold staff meetings. IRB coordinators also can set up a group with investigators, Linke explained. "Each IRB coordinator has a certain group of investigators from the same field, and the investigators call them when they have questions."

Electronic group meetings and messages can be more efficient than email because there is less possibility of someone missing a memo or conversation. This method could continue post-pandemic, even when IRB staff return to the office.

It is likely that IRBs will continue to see clinical trials that hold all or most visits remotely in the post-COVID-19 years.

"One thing we're going to see change longer-term is that the pandemic is pushing studies urgently to use remote technology like teleconferencing and videoconferencing instead of in-person studies," Borasky said. "What we may see when we return to 'normal' or get through the critical part of the pandemic, and new studies start to open again, is that those technologies can be useful. Investigators and participants both like them, and there may be greater adaptation of those virtual technologies going forward."

The pandemic might be the tipping point that pushes clinical research to remote and virtual technologies, Borasky added.

During the crisis, sponsors and researchers are exposed to the idea of performing virtual activities in clinical trials, and they might like to continue with virtual visits post-pandemic, Riddle noted. "There's a transition we've been seeing of virtual activities being integrated into clinical trials. Most likely, this crisis will accelerate that process," he added.

"The utilization of virtual trials will increase access to people who were not able to get visits before," Riddle explained. "Remote visits or in-home visits really expand the number of people who are potentially able to participate in clinical trials, when before, they couldn't take the time to get to the clinic."

The key in making these changes is documentation. "If the research team is going to switch from taking blood pressure in house to relying on blood pressure coming off the iPhone app and recording it, then they need to document those changes. But they do not need approval from the IRB during the crisis unless it increases risk to participants," Riddle said. "If it's a permanent change, then submit those changes to the IRB."

In addition to virtual visits, studies also have changed from in-clinic visits to home visits, Riddle said. For studies that need to continue with in-person visits, some sites are spacing out appointments so there is time to disinfect after each person comes to the facility, he added.

Sociobehavioral research also has changed. "Any studies involving in-person contact had to be changed to remote," Linke said. "A lot of them involved in-person interviews, and these were switched, easily, over to some type of [videoconferencing] interaction. The interesting thing will be to see how many people will stick with this once they see how easy it is." Other sociobehavioral studies were put on hold because they involved researchers entering schools, he explained.

The University of Cincinnati IRB issued guidelines for biomedical studies. "We sent out guidance on which studies should be discontinued, which would potentially continue, and a set of criteria for evaluating these," Linke said. "For instance, it's like not having people utilize resources, including personal protective equipment, that are needed for the outbreak, and how to limit interactions and screen people for exposure or possible infection before they come in for a visit." ■

FDA Guidance Offers Foundation for IRB, Researcher Flexibility

Does not change existing guidelines

The Food and Drug Administration's (FDA) guidance on conducting clinical trials during the pandemic provides reassurance that IRBs and research organizations can employ flexibility as they make changes to accommodate a world in which many patient visits are conducted remotely. *(The guidance is available at: https://bit.ly/348DWdn.)*

The guidance does not change or modify existing regulations, but synthesizes existing regulations and emphasizes the built-in flexibility, said **Lindsay McNair**, MD, MPH, MSB, chief medical officer of WIRB-Copernicus Group (WCG) of Princeton, NJ.

"Considering how quickly the FDA must have gotten this out, it was nicely done and covers a lot of different things that sponsors and researchers are thinking about," McNair said.

Take Advantage of Changes

The important message from the FDA guidance was for research organizations to take advantage of changes prior to IRB approval, said **Michael Linke**, PhD, chair of the University of Cincinnati IRB and adjunct professor of medicine at the University of Cincinnati College of Medicine.

For example, the guidance, issued in March 2020 and updated in April, offers a discussion on how sponsors, clinical investigators, and IRBs may determine that research participants' safety is best served by continuing a trial per the protocol or discontinuing the use of the investigational product or participation in the trial. They can make a decision based on particular circumstances.

Another potential change is how trials conduct study visits with participants. These can be changed to remote visits for safety.

THE IMPORTANT MESSAGE FROM THE FDA GUIDANCE WAS FOR RESEARCH ORGANIZATIONS TO TAKE ADVANTAGE OF CHANGES PRIOR TO IRB APPROVAL.

"There has always been an allowance that changes made to protocols that stop immediate harm to subjects can be done without IRB approval, but it's a situation that rarely came up," McNair said. "In circumstances like this, saying to research participants, 'We don't want you to come into the hospital right now; we want you to be monitored remotely' is a change that could prevent an immediate harm to subjects. Therefore, you don't need preapproval from the IRB, but should notify the IRB that you've made this change."

Early on, IRBs became more flexible. "We're not expecting or requiring research sites to get IRB approval of [COVID-19 change] notices they send to participants," said **James Riddle**, MCSE, CIP, CPIA, CRQM, vice president of institutional services and strategic consulting with Advarra in Columbia, MD. "Advarra will ask that if you are going to make a permanent change to your research to continue remote visits after the crisis is passed, that the change in research would be submitted to the IRB. You can imagine that during the course of this crisis that research sites might get more comfortable with using remote visits and telemedicine and want to continue those visits after the crisis is over. If they want to continue remote visits, they will need to submit a modification to the IRB."

Guidance Helps Research Sites Cope

The FDA's guidance was timely, helping research sites cope with the crisis even as their institutions were shutting down. For instance, research organizations suddenly were faced with closing clinical trials or quickly changing them as their sites were not open for study participant visits. Many were unsure of how to proceed and whether they needed to obtain IRB approval for changes.

Traditionally, researchers need IRB approval for protocol changes before implementing them. This can take days or weeks. But there has been an

exception for changes when there is an immediate or apparent hazard, said **David Borasky**, MPH, CIP, vice president of IRB compliance with WCG.

"Historically, we would see these exceptions when there was an unexpected reaction to study medicine. The investigator would stop dosing immediately, and then tell the IRB about it," Borasky said.

At the start of the pandemic, many researchers were uncertain of how to proceed. When U.S. colleges began to shut down because of COVID-19, WCG received multiple inquiries from research sites, sponsors, and others, and then the FDA guidance was published, he added.

"The timing was great," Borasky noted. "The biggest takeaway message is the FDA is reiterating the fact that there's a lot of flexibility in the regulations for research sites, research sponsors, and IRBs," Borasky said. "I see that as encouragement that all of us who are players in this should be utilizing that flexibility."

The guidance leaves out details about remote monitoring, but it emphasizes the need for documenting everything correctly. "If it means changing the endpoints of the study, then communicate with the reviewing division of FDA," McNair said. "Basically, the guidance emphasizes that any changes that occur due to COVID-19 or if individual participants in the study are diagnosed with infection, then make sure all is documented and submitted with the clinical study report at the end of the study, so it can be considered when assessing the impact on the study and data."

WCG and other IRBs are promoting flexibility in regulatory compliance, Borasky said. "We're saying to our study partners, 'We recognize that you have to quickly make changes to minimize potential exposure to the virus in the best interest of research participants and study teams,'" he explained. "Implement that immediately and then notify the IRB."

The guidance provides reassurance. "If the FDA is OK with eliminating a number of data points, without making the study invalid, then the IRB is OK with it — if the sponsor reaches out to the IRB to do that," Borasky said. ■

Second Phase of Pandemic Raises More Questions, Concerns for IRBs

Research organizations and IRBs continue to face challenges and make tough decisions based on the best available information about a pandemic that changes daily as it spreads across the world.

Early on, most colleges and universities closed campuses and started online classes. This change left researchers in limbo. By April, most hospitals had begun shifting resources to clinical care for nonelective procedures and more serious conditions, including COVID-19 patients. Biomedical researchers and their study sponsors have had to decide what to do about ongoing clinical trials.

The Food and Drug Administration (FDA) provided some guidance in March, but left the decision to each investigator, sponsor, and institution.

The FDA chiefly said that researchers need to document the changes they make for each participant enrolled in research, said **James Riddle**, MCSE, CIP, CPIA, CRQM, vice president of institutional services and strategic consulting with Advarra in Columbia, MD.

But how do they make the best decision? Other than COVID-19 research, which clearly is the top priority during the pandemic, what type and phases of studies take priority over others? Riddle and other experts offered these suggestions:

• **Think of clinical trials in terms of their lifespan.** "Its lifespan could be as short as a week or two — or for 10 years in cardiovascular outcomes trials," said **Janet Wittes**, PhD, founder and president of WIRB-Copernicus Group (WCG) Statistics Collaborative. Wittes spoke at a WCG COVID-19 web conference on April 1.

Studies in the design and screening stages can be halted until the pandemic is over or winding down in the trial site's region.

"If your trial is in the design phase or in the screening phase, the decision is clear," Wittes said. "This is not the time to start recruiting; sit back, look at the protocol, make sure it's clean, and take time to fix it up." Investigators can complete their database so the trial can start quickly, she added.

Trials that are in their last stage, where study visits are complete or nearly complete, also can stop any remaining participant visits — so long as this is feasible, scientifically and for safety, Wittes said. Researchers should limit queries only to those

central to interpretation of the study. "Think harder about how to collect that query," she explained. "Centers will be very busy with COVID-19 patients. For queries that are not essential to the central interpretation of the study, just sit back and don't collect them."

Efficacy data, especially for primary and secondary outcomes, are what are important.

• For middle stages of studies, make hard decisions. Studies that have collected fewer than 20% of endpoints or have collected 20-80% of endpoints are the ones for which decisions are the most challenging, Wittes noted.

"Think specifically about that particular trial and what the nature of the trial is," she explained. "Is it a trial with imaging studies? Then the decision is quite different."

Other questions to consider include:

- What is the study's design? Is it randomized, adaptive, etc.?
- Would the study design impinge on how COVID-19 affects operations?
- Where does the study take place?
- Are there study sites where the pandemic currently is raging, or are the proposed study sites in locations where the pandemic has peaked?
- What axis should the investigator consider? For instance, are patients healthy, or are they seriously ill?
- Is the study drug well studied, or a new drug?
- Is the study's purpose to assess symptoms, or is it curative?

If study participants do not require medical treatment, investigators may pause such trials during the pandemic, Wittes said. If a trial is taking place in a hospital, perhaps because participants already are patients there, investigators would be less likely to stop or pause, she added.

Some well-studied drugs have been prescribed to thousands of people; investigators may be testing these therapeutics for other indications. In these cases, investigators likely do not need to collect as much information on safety, she noted.

> TRIALS THAT ARE IN THEIR LAST STAGE, WHERE STUDY VISITS ARE COMPLETE OR NEARLY COMPLETE, ALSO CAN STOP ANY REMAINING PARTICIPANT VISITS — SO LONG AS THIS IS FEASIBLE, SCIENTIFICALLY AND FOR SAFETY.

"[Investigators] can reduce data collection," Wittes said. "If it's a new chemical entity, you may have to think very hard about consequence of continuing the trial."

• Know the best way to modify trials. Research organizations should consider the study sites, environment, sponsor information, and data collection challenges before deciding to modify a clinical trial because of COVID-19, said **Jonathan Seltzer**, MD, MBA, MA, FACC, chief scientific officer with WCG, and president of WCG ACI Clinical. Seltzer also spoke at the April 1 web conference.

"Is it a risky environment for patients because of risk of infection?" Seltzer asked. "Will the site have [clinical staff] available, because a lot of researchers are not allowed to come into [offices] because of no more outpatient visits?"

Here are some additional questions to consider before modifying a trial:

- How can the site minimize risk to participants?
- Are there benefits for participants remaining in the trial?
- What are the risks of staying in the trial?
- Can fewer data be collected?
- Can the number of visits be reduced?
- Is it possible for study staff to make home visits to participants?
- Are phone or videoconferencing visits possible?
- What types of digital technologies are available that could help reduce in-clinic visits?

Understanding the risks of having participants pull out of a study and developing COVID-19 is crucial to decision-making, Seltzer says.

"You don't want to send people home to die of heart failure vs. taking a 10-20% risk of symptomatic COVID-19," he says. "Do a risk-benefit analysis, and if you decide the trial goes on, think about how you can minimize that risk."

For instance, investigators might be able to conduct fewer visits, and have two data points.

• Make practical decisions, but maintain study integrity. During the pandemic era, researchers and IRBs might need to consider various trade-offs. For example, would it be better to keep participant monitoring the same as pre-pandemic, or is there a way to obtain the same or similar data using a remote device?

"Say you're looking at cardiac [outcomes]. Can you get [participants] an ECG at home? Or, do you need to get them into the hospital, or maybe wearing an Apple watch is

good enough for what you're looking at?" Seltzer asked. "If you have X-rays on the schedule, think about whether you really need them."

Sites might be able to use a local lab for lab data, or forgo standard vitals if the data are not necessary, he added.

"These are all very specific to the trial," Seltzer said. "Balance safety for the patient with preserving trial integrity. At the end of the day, if you can't use data, then we wasted everyone's time."

Researchers also might decide to take their foot off the gas pedal of gathering so much data, Seltzer observed. "This is something that has to be reported to the IRB, discussing modifications."

• **Develop a statistical analysis plan (SAP).** One way to balance the risks and benefits of trial modifications is through review and modification of an SAP, Wittes said.

Research organizations might consider the following:

- Carefully read SAP;
- Examine how operational changes due to COVID-19 affect the SAP;
- Ask statisticians who wrote the SAP speak with operational people;
- Amend the SAP as needed to conform to the operational changes;
- Explain why suggested changes are necessary;
- Provide thoughtfully designed sensitivity analyses.

Major changes to the SAP would include changes in how data are collected, how much data are collected, who collects data, and the primary endpoint.

"These have direct implications for a statistical analysis," Wittes explained. "One thing we think hard about is making sure the people who are making these operational changes, clinical changes, and statistical analysis plans are talking."

Here is an example of a change: Before COVID-19, researchers scheduled patients visit at weeks 22, 23, and 24. The operations people say participants could come in for just one of those three visits during the pandemic, Wittes explained. The statistical professionals say they will define weeks 22, 23, and 24 as the same point as just week 24.

"That's an example of the intersection of operational and statistical changes," she said. "It's important to explain in that analysis plan why those changes are being made [for] when that [information] goes to regulators."

Changes that are not explained to regulators are difficult to defend. "We have studies with a pre-COVID part, a during part, and an after part," Wittes said. "There must be a standard analysis plan to address that. Think very hard about plans' missing data." ■

Shortcuts in Clinical Trials May Cause More Harm Than Good

All clinical trials raise certain ethical issues. "But trials conducted during epidemics are especially difficult, both ethically and practically," says **Charles Weijer**, MD, PhD, professor of philosophy and medicine at Western University in London, Ontario, Canada.

Dozens of potential treatments for COVID-19 are under investigation: existing antiretrovirals, anti-malaria drugs, monoclonal antibodies, and Chinese traditional medicines among them. Additionally, companies are rapidly developing new drugs.

"It is critical that any new treatment for COVID-19 be rigorously evaluated in one or more randomized, controlled trials," Weijer stresses.

Uncontrolled trials that yield no conclusions "are themselves inherently unethical," according to **Gerald T. Keusch**, MD, professor of medicine and international health at Boston University School of Medicine. Keusch co-chaired a committee for the National Academy of Medicine on the clinical research response during the West Africa Ebola epidemic in 2014-2015.[1]

Poorly designed studies subject patients to the risks of adverse events without learning if the intervention works. That is ethically problematic.

"There is an ethical obligation to employ rigorous trial design that can provide answers about efficacy and safety," Keusch says.

Trials Conducted with 'Very Minimal Evidence'

Investigators are testing drugs in Phase III randomized, controlled trials with hundreds of patients on the basis of "very minimal evidence" indicating these are likely to work, Weijer notes. There are several key ethical issues to consider:

• It is unclear whether investigators are adequately

protecting the welfare interests of patients in COVID-19 clinical trials.

• Failure to conduct prior research in animal models and Phase II trials with smaller groups of patients generally is thought to violate equipoise. This requires that at the start of a trial there be a state of honest disagreement as to the preferred treatment.

"But if there is no evidence in animals or humans that a drug has an effect against COVID-19, how can we say equipoise exists?" Weijer asks.

• Proceeding directly to Phase III trials may not be a responsible use of resources. "The worry is that we may be exposing patients with COVID-19 to ineffective or possibly harmful treatments that could have been weeded out with smaller preliminary trials," Weijer observes.

• The sheer number of treatments under evaluation is affecting ongoing and planned clinical trials for other diseases. An increasing number of clinical trials globally are putting recruitment on hold. This slows the pace of other medical research.

"Should some of these trials be postponed or canceled, this would undermine the social value that was key in the ethical justification for enrolling human volunteers," Weijer warns.

• The use of unproven interventions for COVID-19 outside of ongoing clinical trials is ethically worrisome.

"It seems as though every modern epidemic starts with unwarranted enthusiasm about untested treatment, only to be corrected by time, experience, and evidence," Weijer notes.

Thus, clear public health messaging is critical. "Plainly irresponsible messages about some unproven treatments, including malaria drugs, have already cost lives," Weijer laments.

Off-label uses of drugs for COVID-19 treatment, "based on hype and weak data, is one of my biggest ethical concerns right now," says **Holly Fernandez Lynch**, JD, MBe, assistant professor of medical ethics and health policy at University of Pennsylvania Perelman School of Medicine. Such practices may backfire, says Fernandez Lynch, because they likely will inhibit rigorous investigation.

"IT SEEMS AS THOUGH EVERY MODERN EPIDEMIC STARTS WITH UNWARRANTED ENTHUSIASM ABOUT UNTESTED TREATMENT, ONLY TO BE CORRECTED BY TIME, EXPERIENCE, AND EVIDENCE."

That is the case not only for off-label use of approved drugs, but also for drugs that are not yet approved for any use. "We're taking a big gamble that these off-label uses are going to be safe and effective, and that they're going to be better than some of the other options under investigation," Fernandez Lynch cautions.

Another concern is that patients will favor certain investigational options over others, based solely on the amount of media attention they receive. "Patients will likely have a preference for what they can actually get their hands on," Fernandez Lynch predicts.

This favors off-label prescribing over unapproved drugs, but not for strong scientific reasons. This speaks to a need to make clinical investigations more accessible.

"That can be a challenge in emergency circumstances," Fernandez Lynch admits. "But it is even more critical because of them."

Well-Designed Trials Take Time

Poorly designed trials could lead patients and providers to form treatment preferences that are not supported by actual evidence of efficacy.

"This can lead to the widespread use of ineffective or harmful interventions, and delay recruitment into studies that would tell us what actually works," says **Alex John London**, PhD, director of the Center for Ethics and Policy at Carnegie Mellon University in Pittsburgh.

In reality, the vast majority of medical interventions fail in clinical testing; about half of those fail in Phase II testing. These are cases in which researchers have had time to pick the best candidates for an indication and to conduct carefully planned studies before introducing the intervention into humans.

"Just because a treatment is urgently needed doesn't mean that it is going to be easier to discover," London notes.

Well-designed clinical trials play an important role in epidemic response, according to a National Academy of Medicine report.[1] "When there are no established

effective treatments for a disease, new interventions should be tested as early as possible in well-designed, randomized clinical trials," says London, one of the committee members who wrote the report.

The goal is to quickly generate reliable medical evidence so physicians know whether an intervention is likely to help or harm a patient. This also helps policymakers know that scarce resources are not squandered on interventions that are ineffective or even harmful.

Clinicians have the discretion to prescribe drugs already approved to treat one condition on an off-label basis.

"But in an outbreak of this size, that practice risks creating the perception that a drug works for a new indication when that has yet to be established," London cautions.

It also can make it more difficult for patients to access those drugs for the indications where they have been proven to be effective. Additionally, if trial administrators cannot recruit enough participants, the information they produce can be misleading. Likewise, if trials are not coordinated with similar endpoints and measures, it is going to be difficult to compare their results.

"This makes research less efficient, and that raises questions of justice," London says.[2] Protocols that establish a single approach for testing multiple interventions across different clinical centers is a way of conducting trials quickly. "This ensures that the many different stakeholders who rely on that information can make better decisions," London says. ■

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Unique Ethical Concerns for Study Participants in Neuroscience Research

Innovative neuroscience research is vital, but individuals with mental illness pose some unique ethical concerns in terms of their participation.

The results of a recent study provided some reassurance on the decision-making processes of individuals.[1] Researchers surveyed 25 individuals with a mood disorder and 55 individuals without a mood disorder about four psychiatric research projects: an experimental medication (pill form), noninvasive magnetic brain stimulation, experimental medication, (IV infusion), and implantation of a device in the brain.

Respondents rated the research projects as somewhat to highly risky, regardless of their health status. The more risk they perceived, the less willing they were to participate, regardless of whether they had a mood disorder.

Neuroscience researchers have to consider several issues, according to **James J. Giordano**, PhD, MPhil, chief of the neuroethics studies program at the Georgetown University Edmund D. Pellegrino Center for Clinical Bioethics.

• Whether the pathology itself in some way interferes with the individual's capability to be fully informed. "The absence of neuropsychiatric capacity renders these patients incompetent. By definition, the incompetent patient does not understand what information is being provided and, therefore, they can't consent," Giordano says. A person with medical power of attorney to make decisions for that patient may be able to provide consent for the individual under those circumstances.

• Whether patients are entering the trial with "therapeutic misconception." Many research participants have an underlying assumption that they are going to receive treatment. This may be particularly prevalent in neuropsychiatry patients.

"What tends to happen is that patients participate in a clinical trial with implicit hope that the trial will give them some benefit," Giordano explains.

This is a difficult problem to address fully. "Even where it's actively and explicitly addressed, misconceptions about incurred benefit of treatment rendered in a clinical trial seem to loom on as a potential emotional bias," Giordano observes.

There are two points that are especially important to convey: What assignment to treatment and control groups entails, and that participants will not know which group they are

in. "Even so, many still believe that participation in the trial will gain them some therapeutically beneficial outcome," Giordano adds.

• **That any patient with any form of cognitive compromise, where they cannot fully comprehend what is involved in the protocol, is part of a vulnerable population.** "There are particular concerns and caveats that researchers must attend to when dealing with vulnerable populations, particularly as it relates to possibilities for implicit coercion and relative burden and harms that may be inflicted," Giordano says.

Inclusion of such vulnerable patients often is important, as they might be the population targeted for potential therapeutic effect. "Necessary precautions need to be taken so that these individuals are fully informed, to the extent of their capacity, about all phases and methods of the study and their ability to withdraw without penalization," Giordano says.

Most individuals working in this area are keenly aware of necessary safeguards that are incumbent to the research. Still, things can go wrong. "There may be some misapprehension on whether subjects are fully comprehending," Giordano notes. "Therefore, it is best to be overly cautious and diligent in ensuring active informed consent."

Big Data Present Issues

Big data also pose ethical issues unique to neuropsychiatric research. On the positive side, it "increases the scope, types, and extent of information capable of being gathered and synthesized in psychiatric research," Giordano offers.

For researchers, the ability to use massive amounts of diverse data certainly is appealing. "However, it's important to realize the information that we are gaining in current studies may be useful, and utilized, for studies in the future," Giordano says.

The way the data are used could change depending on how they are correlated with other future findings. "In some cases, such data may be de-anonymized, both at present and in the future," Giordano suggests. "This has implications medically, socially, and perhaps legally for research subjects."

For example, information collected today may be correlated to emerging data to infer pre-existing neuropsychiatric disorders. "That could incur problematic issues for individuals' insurability, access to care, employability, and social regard and treatment," Giordano explains.

For researchers, this means patients and subjects need to be fully informed on how their data could be used. "A comprehensive informed consent process needs to address each area that may be a potential issue or problematic," Giordano says. ■

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Researchers Identify Ethical Concerns with Pragmatic Trials

Pragmatic trials raise some new ethical issues that need greater attention, according to the authors of a recent study.[1]

"Existing ethics guidance is not well-suited to pragmatic trials," says **Stuart Nicholls**, PhD, the study's lead author and a senior clinical research associate at Ottawa Hospital Research Institute in Ontario, Canada.

Pragmatic trials aim to evaluate interventions under real-world conditions. "The current empirical ethics literature does not reflect the full range of stakeholder perspectives," Nicholls says. Previous studies focused on a narrow range of topics, such as when written consent approaches may be modified.[2-6] "We aimed to explore more broadly what ethical challenges may arise in the design and conduct of pragmatic trials," Nicholls explains.

Nicholls and colleagues interviewed 45 stakeholders, including ethicists, clinical investigators, methodologists, and patients. Participants reported ethical concerns about how "minimal" risk is determined, when it is appropriate to alter traditional informed consent practices, and how to distinguish between quality improvement and research.

They also expressed concern about determining what protections are owed to the broader populations the trial affects and the diversity of participants. During interviews, Nicholls and colleagues heard feedback regarding justice and equity. "This is particularly important,

given the potentially heterogeneous populations within pragmatic trials," Nicholls notes.

There is a general feeling that more pragmatic trials are needed, says **Spencer Phillips Hey**, PhD, another of the study's authors and a faculty member at the Harvard Medical School Center for Bioethics. Mainly, the creators of clinical trials enroll people who are most likely to benefit from what is studied. "A drug that looks really promising in an idealized trial might not actually work so well in clinical practice," Hey observes.

Pragmatic trials give a better idea of how an intervention's going to work in the real world. Including groups that are excluded often from research is another potential benefit. "Getting more people, particularly historically under-represented groups of people, involved in research is an encouraging feature of some pragmatic trials," Hey offers.

One unresolved ethical issue is how researchers are going to protect the interests of these broader participant groups. "We have not really come to a clear consensus on how to handle this move toward pragmatism while still appropriately protecting the rights of the participants," Hey laments.

Traditional informed consent is not always going to be possible in these studies. This means investigators have to find other ways to protect participants. "We still have to think about how to best show respect and safeguard their interests, even if we are not getting consents," Hey suggests. Exactly when it is ethically permissible to waive consent in the first place is debatable, too. "This is probably the biggest area of controversy," Hey notes.

One condition in the Office for Human Research Protections regulations for waiver of informed consent notes securing traditional consent is "impracticable." Some people might interpret this to mean if there is not enough money to obtain informed consent from everyone, that means consent is impracticable, and a waiver is needed. "But cost alone is not a sufficient justification," Hey cautions.

For some pragmatic trials, traditional informed consent remains ethically necessary. "There seems to be a push from some investigators [who say] that just because a trial is pragmatic, it's taken as justification to not get consent. That is very much putting the cart before the horse," Hey explains. Whether consent is needed depends on multiple ethical considerations, such as whether the individual's welfare is adversely affected. If it turns out informed consent is needed after all, researchers have to either find a way to do it, or perhaps conduct a smaller study than they planned. In other cases, the study design has to be re-evaluated. "You may have to tweak the questions a bit, and then it's ethically acceptable to get a waiver," Hey suggests. There are various types of pragmatic trials, each with its own ethical considerations depending on the study design. "Pragmatic trials mean different things to different people," Hey observes.

One study might use electronic health record data to prospectively follow patient outcomes. Another randomizes huge numbers of patients at dozens of hospitals with no opportunity for the patients to opt out. "Both of those things can be pragmatic trials. But the ethical consequences that flow from those study design choices can be different," Hey explains.

As it stands, investigators often struggle to find guidance on the particular ethical questions their study raises. "My worry is that it's not practical to have to go to the literature and comb through dozens of studies to find out what you need to do," Hey shares. There is no searchable online resource for investigators to plug in the parameters of their intended trial and find answers to relevant ethical questions. "That would be really compelling and valuable," Hey says. "That's the guidance and support that's missing right now." ■

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CME/CE QUESTIONS

1. **How might IRBs change their operations after the COVID-19 pandemic?**

   a. IRBs might run their offices virtually.
   b. IRBs might add one or two infectious disease experts to their boards.
   c. IRBs might continue holding virtual meetings.
   d. IRBs might cut staff due to fewer studies.

2. **The Food and Drug Administration's COVID-19 guidance, published in March 2020, discusses which aspect of clinical trials?**

   a. The guidance requires research sites to use data safety monitoring boards during the crisis.
   b. It provides guidance on how sponsors, investigators, and IRBs can determine if research participants' safety is best served through changes to a trial.
   c. The guidance asks investigators to use personal protective equipment in all subject encounters.
   d. The guidance outlines criteria for shutting down a study.

3. **What should research organizations consider when deciding which studies to continue, pause, or modify?**

   a. What is the study design? Are there study sites in locations where COVID-19 is causing a medical emergency or surge?
   b. Does the study involve HIV patients? Does it involve hepatitis C patients?
   c. Is the study sponsored by a pharmaceutical company?
   d. What description of study activities was listed in the informed consent document?

4. **Which is true regarding clinical trials during a pandemic?**

   a. Rigorous evaluation in randomized, controlled trials is no longer appropriate.
   b. There is an ethical obligation to dispense of the need for equipoise.
   c. The use of unproven interventions for COVID-19 outside of ongoing clinical trials is ethically problematic.
   d. Protocols that establish a single approach for testing multiple interventions across different clinical centers are unethical.