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INSIDE

RELIAS MEDIA

Calls for IRB Transparency in a Closed-Door System

Transparency 'benefits would outweigh the cost'

By Gary Evans

It is a common critical observation in human research that IRBs operate in a sort of "black box," making decisions that could greatly affect a general public that remains largely oblivious of their role and function.

"The default rule — permitted by the regulations governing IRBs and demonstrated by the practices of many — has been for IRBs to be closed-door, relatively secretive bodies, making determinations with substantial impact on a wide variety of stakeholders without robust explanation, justification, or transparency," the author of a paper on the subject noted.[1]

This default ought to change toward transparency, both for the good of the research community and to be in line with the increasing calls for publishing research results, reporting all clinical trial data, and sharing consent forms, says **Holly Fernandez Lynch**, JD, MBe, John Russell Dickson Presidential Assistant Professor of Medical Ethics and Health Policy at the University of Pennsylvania. Although her background is in law, Lynch is less interested in indicting IRBs than extolling the benefits of a new age of transparency.

> "IF THERE IS NO REGULATORY REQUIREMENT TO BE TRANSPARENT ABOUT A WIDE VARIETY OF THINGS, IT IS NOT GOING TO RISE TO THE TOP OF PRIORITY LIST."

"I don't think anybody is non-transparent because they are trying to hide things," she tells *IRB Advisor*. "They end up being nontransparent because the focus is on regulatory compliance, doing what you need to do to satisfy the rules, following your procedures, and moving things along. Anything that could

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take longer is kind of frowned on, and that's understandable. People get frustrated when IRBs are slow. Setting up systems of transparency takes some effort."

For example, releasing more thorough documentation of the proceedings beyond the cursory regulatory requirements of meeting minutes may necessitate redacting information for confidentiality protections, she says.

By the same token, "if you open your IRB meetings, you might have people come and ask questions that may be uninformed," Lynch says. "That happens, but that is part of the educational function that IRBs can help serve. I don't suggest that being transparent would be costless, but I think the benefits would outweigh those costs. On top of that, I think it is hard to justify nontransparency in decisions that have huge public relevance about what type of research can proceed or not."

Lynch concludes her paper with the bottom line that "IRBs are rarely required to explain or justify their decisions. Investigators must be given some information, institutions and regulators have full access — to the extent that IRBs record their rationales — but everyone else can be left in the dark."

IRB Advisor asked Lynch to comment further on this issue in the following interview, which has been edited for length and clarity.

IRB Advisor: While you are not accusing IRBs of trying to hide anything, it seems intuitive that closed proceedings could increase the risk of ethical lapses and heighten participant risk.

Lynch: I'm sure you have heard the phrase "sunshine is the best disinfectant." I don't think there is necessarily something that needs to be disinfected, but when you know your records are open, people tend to behave a little bit differently. IRBs may not necessarily agree with this, but I think IRBs have a lot in common with government regulators. For example, they are often at private universities or for-profit companies but they are the ones who get to decide whether research can proceed. That is a huge responsibility that I really think should not happen behind closed doors.

IRB Advisor: You note that probably the most common pushback is not against IRB transparency itself, but the cost of achieving it?

Lynch: IRBs often indicate that they have a lack of resources. They are trying to do everything they can to keep their head above water, maintaining regulatory compliance, and trying to protect human research participants however they can. Anything that is not actively required of them is likely to fall by the wayside. If there is no regulatory requirement to be transparent about a wide variety of things, it is not going to rise to the top of priority list.

The other thing is, frankly, nontransparency can be a way to avoid having people peek into your affairs in a way that might cause trouble down the road. I don't mean to suggest that this is some purposeful and nefarious thing that IRBs do because they are engaged in shady activities. But if you think anecdotally about IRB minutes, they don't often really allow you to piece together exactly what was discussed in the room. They satisfy the regulatory requirements and often provide the bare minimum of the information to do so.

IRB Advisor: Is there a concern that more complete documentation

of discussions and decisions could raise legal liability?

Lynch: That's part of it. If you write things down and then something negative happens, your records [can] get "discovered" in the legal sense. It's probably "better" from the litigation perspective to not have written down a lot of things. But we don't want IRBs to engage in activity that is preparatory to litigation all the time. That is not the best way of doing business, but it is a reasonable worry. It gets to this idea of IRBs being criticized for being more for institutional protection than [research] participant protection. I'm not saying that I endorse that view, but non-transparency kind of falls into that category. [The mindset] is "Don't share information that you don't have to share because it could cause you a headache later."

Change Must Come From Within

IRB Advisor: You mention that regulations requiring more transparency would be one approach, but of course any regulatory changes would certainly proceed slowly.

Lynch: I don't think the regulators are going to be pushing this [transparency] movement if it ever gets some legs under it. I think it is going to have to be driven by the human research community. There are a lot of benefits to transparency. Our default approach ought to be transparency because we have all of these stakeholders in our system. We have investigators that we are beholden to, research participants, and the public. In terms of cost, I think eventually it would be more efficient to be transparent.

If you could share information across institutions that would be huge. As it stands, each institution often has to reinvent the wheel because it is difficult to find policies that you could rely on from other institutions. If you are dealing with a problem at your institution and you have to write a policy about it, chances are some other institution already has that policy. You could use someone else's policy as a jumping-off point. There are some informal mechanisms that have been built up to allow IRBs to share with one another, and that's a great thing. It indicates that the community appreciates the value of transparency, at least with one another. They can build on that, and I would encourage them to go even further and think about how can we be more transparent with our investigators.

IRB Advisor: How can IRBs promote transparency for researchers?

Lynch: I know many IRBs are thinking about, for lack of a better term, "user satisfaction." For researchers, it could be having a better understanding of how IRBs make their decisions. Open your IRB meetings. Have them come see what is discussed and how things work. Make your decision letters more robust and give reasons for your decisions. IRBs are not arbitrary. They have reasons for the decisions that they make, but if you don't explain those to investigators you allow them to concoct reasons that they might disagree with. It is better to explain clearly the IRB's rationale. Then, if the investigator disagrees, there can be a discussion. It doesn't put the investigators in the position of getting frustrated over something that may not actually be true about the IRB position.

The other thing is that often, if I have a conversation with somebody and they ask my opinion on something, I will give my off-the-cuff opinion. Then, I think later "that's interesting, maybe I should write something about that." But when I start writing, I can't justify [my opinion] in the same way I did in the conversation. In the process of justifying something in writing, you are thinking about whether your argument flows logically, or whether there are inconsistencies or holes. This is something that is really important that is not built into the IRB system. We have meetings where people are talking, having conversations, and mostly work off a consensus model. I wonder a lot whether IRB decisions would necessarily be the same if they had to be written down and justified.

IRB Advisor: Can you elaborate on the idea of establishing a repository of IRB "precedents," past actions that could inform future decisions if they are in some searchable format?

Lynch: I have launched an organization called Advancing Effective Research Ethics Oversight (AEREO). We are trying to come up with ways to figure out not only how to make IRBs more efficient, but how can we be sure what IRBs are doing is actively promoting the goals they were created to promote? One of the projects our group has been working on is to think about whether a system of IRB precedents is plausible. You don't have to necessarily be transparent to develop a system of precedents within an institution. You don't have to share the information with anybody else; you could just have internal precedents. But ideally, you would share information across institutions with all the various stakeholders.

Of course, it is easier said than done, but we are trying to think about coming up with some kind

of a summary, after an IRB makes a decision, of the key things it decided and then putting that into a kind of taxonomy. We could sort IRB decisions according to what they were about; for example, whether a study was minimal risk or what was decided about an informed consent waiver. You could build these taxonomies in search categories that would allow you to figure out what your institution had done previously, or ideally, what other institutions have done. We are trying to build on the transparency concept, and one of the things AEREO does is create this safe space for institutions to share information and ideas with one another. ■

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Pragmatic Trials on the Rise as Data Collection Pushes Trend

Privacy, risk remain concerns

By Melinda Young

Several recent changes are driving the pragmatic trial trend nationally, including acceptance from regulators and the growth of big data.

Pragmatic clinical trials measure effectiveness of a study drug, device, or intervention on a wider range of people. Unlike clinical trials that exclude people based on health conditions and other criteria, pragmatic trials study a treatment's effect on a group of people who are more representative of patients in clinical practice and the real world.

"There are a lot of situations where you have two practices and interventions being used, and they've never been tested head to head," says **Scott Kim**, MD, PhD, senior investigator in the department of bioethics at the National Institutes of Health (NIH). Kim is scheduled to speak about the research risks of pragmatic randomized control trials at the Human Subject Protection: I Will Survive! conference on Sept. 5, 2019, in Covington, KY.

"Given the desire for real-world evidence, people want to do trials that are comparing interventions that are actually in use and are accepted as indicated for those conditions," Kim adds.

The goal of a pragmatic clinical trial is to conduct it in a way that tracks what happens in a clinic and in a hospital, Kim says.

"You don't want a highly complicated research apparatus with lots of new elements and eligibility criteria because that won't serve the aim of these studies," Kim says. "You want your research integrated, as much as possible, into every day practice."

The FDA is supportive of these types of trials, says **Mitchell Parrish**, JD, RAC, CIP, vice president of legal and regulatory affairs at Advarra. "The FDA is supporting pragmatic trials in terms of validating that the information gathered from these trials is valuable and important for the development of therapies and adoption of therapies once they're approved," Parrish says.

But the real driver behind pragmatic trials is data. Researchers seek to do more with existing data, accessing data more broadly.

"That's a trend that will not go backward," Parrish says. "With pragmatic trials, you have a component of data collection on a broader scale than what was previously seen in getting data from participants on trial records."

For example, a pragmatic trial might seek a participant's pharmacy records to determine their drug adherence. With that data, they can tell when a person was prescribed a drug and how long it took to get a refill, he explains.

"Having more access to information helps to paint a better picture of how the product is working for each person," Parrish says.

The use of more thorough data can raise confidentiality and privacy concerns. IRBs, researchers, and sponsors should be aware of those risks, Parrish notes.

"Sponsors should provide more confidentiality and privacy sections in the protocol to speak to those safeguards," he says.

From an IRB's perspective, informed consent in pragmatic trials can be problematic.

"The traditional regulatory structure of informed consent creates an obstacle to making these truly pragmatic," Kim notes. "The large apparatus [of regulations] is at tension

with the pragmatic aims of these trials because if you want to do this trial in a doctor's office, how do you do this complicated informed consent?"

The other issue is that risks in pragmatic trials typically are not unknown, so researchers might not desire to go through all the risks as they would if the study involved an investigational new drug or device.

"If you go into your doctor's office and the doctor is going to start you on a different treatment for blood pressure, most doctors will not go through all the possible risks that could happen in taking that drug," Kim explains. "They'll say, 'Here is the drug. It's been in use for X number of years, and you should look for these side effects. Take it like this, and call if you have any problems.'"

But while some people in the human research protection arena do not believe that is adequate for research informed consent, the others believe these types of studies are low risk.

"There is this strong intuition that if you are comparing two accepted treatments, such that if someone uses A, it's a reasonable treatment, and if the person uses B, that's also reasonable, then there isn't great data to say which is better," Kim says. "People in the field say, 'There's not that much risk, even if you randomize it.'"

IRBs need to remain flexible in their thinking about pragmatic clinical trials, Parrish suggests.

"Pragmatic trials are meant to represent and capture a more representative population of who will be receiving a product in the healthcare setting vs. a standard clinical trial, which is very well defined with exclusion/inclusion criteria and studying a small part of the population," he adds.

This is a more representative population that might include people considered vulnerable by IRBs. Pragmatic trial participants could include pregnant women, children, people with economic disadvantages, people who cannot read, and others, Parrish says. *(See story on how IRBs can review pragmatic trials, below.)*

"The thought used to be that you can't test drugs in these vulnerable populations," he explains. "But people realized this was very narrow-minded; you would just end up testing products in a certain subset of the population. You wouldn't know whether they would work in other populations because no one ever gathered data about them in other trials."

Clinicians need drugs for these vulnerable populations, so the FDA has tried to encourage more trials with pediatric populations and enrolling pregnant women, Parrish adds.

Research involving pragmatic clinical trials is an evolving field, Kim says.

"Research ethicists and regulators all are trying to learn and figure out how to do this ethically and efficiently," he says. "I don't think I can give a definitive answer as to what to do, but I would say that at this point we should try to not fall back on rules that are perhaps well-intended, but not sufficient." ■

Tips for IRBs Reviewing Pragmatic Trials

Apply flexibility to informed consent

Flexibility is needed when reviewing pragmatic clinical trials, which typically enroll a broader population of patients and might need more adaptable informed consent than traditional clinical trials.

Researchers have raised questions about how pragmatic trials should be regulated and what IRBs should do to protect participants, but not discourage this type of research.

Here are some suggestions for how IRBs can review pragmatic clinical trials:

• **Assess research risk.** One of the main ideas behind assessing risk in pragmatic clinical trials is this question: "If the two interventions being compared are within the standard of care or are accepted practice, is that a good way to determine the research risk of these trials?" says **Scott Kim**, MD, PhD, senior investigator in the department of bioethics at the NIH.

An IRB's answer to that question will determine what happens with informed consent.

"To waive or alter the traditional requirements, the regulations require the study to be declared minimal risk," Kim explains. "There is a lot of debate about whether these studies are minimal risk."

Unless an IRB determines that the clinical trial is minimal risk, researchers cannot significantly change the way they conduct informed consent, Kim says.

"I think it's quite possible that some pragmatic trials are, indeed, minimal risk," Kim says. "And

for those studies, the regulations allow, if justified, altered informed consent."

To determine risk, IRBs need to recognize the pragmatic trial's purpose, says **Mitchell Parrish**, JD, RAC, CIP, vice president of legal and regulatory affairs at Advarra. "Typically, with a pragmatic trial, you're comparing two treatments that are approved therapies, so it truly is standard," Parrish explains. "But it's a controlled trial, so the physician is not selecting which product is right for you."

Patients are randomized to either treatment, but both are the standard of care, he adds.

IRBs must decide whether this randomization to two different treatments poses any additional risk — even if each is standard care.

"We have to face the fact that using too general a rule to determine the risk of a pragmatic trial, such as the idea that both arms are used in [usual] practice, making the trial minimal risk, is utterly dangerous," Kim says. "IRBs should continue to do specific evaluation of the currently existing evidence about risk rather than just relying on a general rule like that."

This is why it is important for researchers and IRBs to be clear on what usual practice is for purposes of this research, he adds.

• Define and explain usual practice in pragmatic trials. What researchers or IRB members believe is accepted or usual practice might not be usual practice, Kim notes.

"First, you have to prove that the things you are comparing in a trial are truly accepted in practice," he explains. Then, IRBs should consider how the study has been altered to introduce a research element.

The most challenging part of a pragmatic trial might be to explain to participants their relative risks in a study that compares two treatments that have long been used for their condition.

For example, a pragmatic trial might compare treatment A to treatment B. Both have been used to treat patients with a particular condition, and both are considered accepted practice. Suppose small studies have compared the two treatments, and three of the four studies show that treatment A works better than treatment B. This suggests a more thorough comparison trial would be helpful, Kim explains.

"Here's the question: Can the researcher assume that treatments A and B are equivalent? No, they can't, because if they knew the treatments were equivalent, they wouldn't be doing this study," he says. "And you have preliminary, but not decisive, evidence that one treatment might be better than the other."

In that situation, it might be inaccurate to tell potential study participants that if they entered the study, their treatment would be just like going to their doctor with no extra risk, Kim says.

"It is more reasonable to say, 'Well, you were taking A, and were assigned to B, so there is a chance you might be worse off than if you hadn't done the study," Kim explains. "It's complicated."

It is up to IRBs and researchers to anticipate research risk and legitimate potential outcomes, looking at these two factors:

- Even though both treatments in a pragmatic trial are used and accepted, it is inaccurate to say there is no risk to an individual entering the study because their course of treatment might be altered by their clinical trial participation, Kim says.

- Each study and its risks should be evaluated by the best current evidence that exists, as well as for the potential different outcomes a trial participant might face if entered in the study, he says.

When it comes to defining usual practice, this type of consideration is ethically more balanced than just saying that if both treatments in a study are accepted by doctors, then there is no risk in participating in the study, Kim adds.

• Consider the study's vulnerable population. For instance, IRBs should discuss whether the enrollment of vulnerable populations in the study constitutes greater risk in a study that otherwise might be considered minimal risk.

"IRBs should understand the

rationale of why there might need to be more vulnerable populations involved in the trial," Parrish adds. "Once they recognize that rationale, the next thing is to understand, as an IRB, what they can actually offer as an additional protection."

For example, a pragmatic clinical trial that is assessing treatment for Alzheimer's disease likely will enroll people who lose some cognitive ability during the length of the trial.

"You might say this population will at some point lose the cognitive ability to do informed consent," Parrish says. "What can we do to minimize this?"

An IRB might require everyone enrolled in the study to create a plan for if they lose the capacity to decide whether they want to remain in the trial, he adds.

Or, in another example, the study could be about an antianxiety medication for pregnant and postpartum women. IRBs assessing this study should ask the following questions:

- What do these participants need to understand, and how is it explained in the informed consent document?

- Does the informed consent offer suggestions for participants about whom they can see if they experience postpartum or pregnancy issues?

- Could the sponsor provide more information about the site's plan of care for individuals, including counseling and who to contact if there is a problem?

"IRBs should think about it and be ready to discuss their ideas," Parrish says.

• View informed consent more flexibly. There is no settled agreement on how informed consent might be handled, altered, or waived when it comes to pragmatic clinical trials.

"My impression from reading the literature is that the practice is unsettled and it varies by IRBs and other situations," Kim says. "Even if a study is not minimal risk, there are probably studies — from a purely ethical point of view — where it would be permissible to use an informed consent process that is abbreviated and altered from the current practice," Kim says.

"IT'S NOT GOOD PRACTICE TO USE THE REASONING THAT IF YOU ARE TESTING TWO THINGS ALREADY IN USE IN CLINICS THEN THAT AUTOMATICALLY MAKES THE STUDY MINIMAL RISK."

There also have been some pragmatic trials deemed minimal risk, and informed consent procedures were altered, he adds.

Sometimes, IRBs approve the use of deferred consent, giving researchers flexibility to start a pragmatic trial that compares two existing drugs following a health emergency, such as a heart attack, without starting the informed consent process until treatment is underway. At that point, the patients can decide whether they wish to continue.

The main point is that IRBs should make these decisions case by case.

"It's not good practice to use the reasoning that if you are testing two things already in use in clinics then that automatically makes the study minimal risk," Kim says. "That reasoning is increasingly being put forward in the literature by people who do clinical trials, and I think that is not a good idea."

Informed consent in pragmatic clinical trials is tricky, Parrish says.

"If you have someone enrolled in a trial, you have to get their informed consent, but this will screen out some individuals because not everyone will want to participate," he explains. "And that negates the real-world goal of getting a real-world population, so it's a big issue that has to be resolved."

The debate over informed consent for pragmatic trials will continue, although some studies are employing flexible consent strategies, he notes.

For example, some pragmatic trials use cluster randomization, Parrish says. Cluster randomization can be used to study whether to treat an entire group, such as studying immunization, and it can be used to study drug effectiveness. Instead of analyzing individual results, data are analyzed for the entire cluster. *(More information is available at: http://bit.ly/2SZrNBV.)*

Consent is different in cluster randomization because the trial might be set up to give one certain conventional treatment to every patient with a particular disease who enters hospital A. Then, the same type of patients who visit hospital B would receive a different conventional treatment. The two treatments are compared, but there is no individual randomization, Parrish explains.

"People will have a notification component for individuals who go to this hospital," he adds. "There still is an issue of informed consent, and IRBs will have to think about the issue of people individually consenting, or doing something more generic." ■

Identifiable Data Are Not What They Used to Be

By Melinda Young

IRBs and researchers should change their old habits when it comes to assessing studies for privacy and confidentiality. When HIPAA's privacy rules first went into effect, it was not possible for the average armchair sleuth to drill down to specific people based on little more than some health and demographic characteristics and a study site's location.

Now, it is. Researchers recently showed that de-identified data could be used to find a specific person. Using a mathematical model in databases of more than 200 populations, researchers found they could correctly re-identify 99.98% of Americans, using 15 demographic attributes.[1]

The study authors concluded that even heavily sampled, anonymized data sets are not protected from re-identification, challenging the adequacy of the de-identification release-and-forget model.[1]

"This is astounding information," says **Michele Russell-Einhorn**, JD, chief compliance officer and institutional official for Advarra of Columbia, MD.

Even if identifying individuals is not as easy that sounds, it is far more likely that research subjects' identities could be discovered in 2019 than it was in 1999.

"Today, you have banks with cameras, streets with cameras," Russell-Einhorn says. "If you have Alexa [Amazon Echo] in your house, you have lost privacy protection."

Regulatory language on privacy and the way IRBs view privacy are not adequate for current privacy challenges, she says. "We need to get together and come up with the best language and best approaches for our research participants," she adds. "I'm concerned that the non-research landscape is eliminating privacy and confidentiality, and I think that we need to make a decision about how we want to impact the research landscape."

IT ALSO IS THE IRB'S RESPONSIBILITY TO ENSURE INVESTIGATORS HAVE GIVEN THOROUGH CONSIDERATION TO PRIVACY AND CONFIDENTIALITY.

IRBs cannot lose sight of the fact that research participants are volunteers. "We're faced with the fact that people choose to participate in research. We need to be respectful of their choices, and we need to maintain the public's trust in research," Russell-Einhorn says.

It also is the IRB's responsibility to ensure investigators have considered privacy and confidentiality thoroughly.

"Investigators are incredibly overwhelmed with different responsibilities in conducting research, and they might not think about the exact words they use in informed consent about privacy," she says. "They think they can say, 'We guarantee your privacy and confidentiality, and no one but study team members will ever have access to your data,'" Russell-Einhorn says. "That's simply not true; no one can guarantee this because secondary research could see the data."

If investigators are not thinking through this kind of wording in informed consent and what the implications are, then it is up to IRBs to think it through, she says.

"I don't fault them because they have way too much on their plates," she adds. "But we need organized discussions on how we want privacy and confidentiality handled in research, and we need to include investigators, IRBs, and industry sponsors."

IRBs and investigators also should consider the reality that their past ways of de-identifying data might no longer be adequate.

"If you think about research and data — the diagnosis, height, weight, and lab counts — there's lots of other information that could be identifiable depending on the disease or condition and what's being studied," Russell-Einhorn says.

IRBs should consider all the risks and benefits of a study, including the potential for a breach of privacy. They also should ensure that privacy and confidentiality are not guaranteed in the informed consent, she says.

"The first thing to do is make sure the consent form is understandable and honest," she adds. "The worst thing an informed consent form could say is 'We guarantee your information will never be shared and de-identified' because I don't know how anyone can guarantee that."

Instead, IRBs should encourage language that looks more like: "We'll do our best and set up the research in

such a way to keep your information as restricted as is possible," Russell-Einhorn says.

It also is fine to say in an informed consent form, "Notwithstanding our best efforts, it is always possible that de-identified information will be accessed."

IRBs also could give extra consideration to the risks of de-identification in studies that enroll a very specific minority population, Russell-Einhorn says. For example, a sociobehavioral study that enrolls a transgender population could be at risk of inadvertent de-identification of subjects simply because this population in any given research institution or area could be very small.

"That's where an IRB could say, 'If you put down where the study takes place and you talk about transgender issues, it could be identifiable,'" Russell-Einhorn explains. "If you don't list certain demographic information, then you are more likely to have data that is not identifiable, which — in the case of transgender research — might be a better and more proactive way of protecting those individuals." ■

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Indigenous People Grill NIH on All of Us Protections

'We can never allow atrocities to happen again'

By Gary Evans

Attempting to reassure an indigenous community that has been abused in past research, the NIH All of Us precision medicine initiative is holding a series of meetings and webinars with the National Congress of American Indians (NCAI.) A key part of the dialogue is letting American Indian/Alaska Native (AI/AN) Tribal Nations ask questions and express concerns about the project.

In a June 3, 2019 webinar,[1] Native American leaders outlined the general concerns of their people. **Eric Dishman**, PhD, director of the All of Us research program, fielded questions from indigenous community members. The All of Us project aspires to collect DNA from 1 million people, including populations that traditionally have been exploited and misled about human research. The invitation to participate comes with the acknowledgement of unethical research in the past.

One example of how research on indigenous people can go horribly wrong is the case of the Havasupai Native American tribe in Arizona, which lost their lands to white settlers and fell into mental health and addiction issues. Researchers conducting a study ostensibly on diabetes and other health problems in the tribe subsequently published findings on their high rates of schizophrenia and alcoholism, much to the consternation of the Havasupai. *(For more information, see the December 2016 issue of* IRB Advisor.*)*

"We have been working with community partners all around the country to talk explicitly about historic examples of the absolute failure and wrongdoing of federal and other researchers on tribal communities and other diverse groups," Dishman said. "We put together some materials that train people clearly to understand what new laws and protections are in place so we can never allow those atrocities to happen again."

Indigenous people "have been studied quite a bit. Some of the experiences of that have not been positive," said **Aaron Payment**, EdD, chair of the Sault Ste. Marie Tribe of Chippewa Indians, and first vice president of the NCAI. "Tribal communities are a little reluctant and very skeptical — and rightfully so. Concerns that we have are human samples and how those are used, and the cultural appropriateness of how to approach people in our tribal communities with research. Also, making sure that our data are not just aggregated to expose our vulnerable populations. We must make sure the data are used responsibly."

With those considerable caveats, Payment expressed a strong interest in the All of Us research, both individually and in its potential to improve the health of indigenous people.

"I share this personally; I have an Indian and mixed physiology," he said. "I exercise and I am vegan, and I still have elevated blood pressure

and cholesterol. I am very keenly interested to figure out what it is specifically that I need to do to live my best healthy lifestyle. I have chronic disease in my family and I am doing my best to try to fight that off. I think precision medicine is really going to help us pinpoint what exactly we need to do."

Spero Manson, PhD, co-chair of the Tribal Collaboration Working Group of the All of Us Research Program, said tribal sovereignty must be recognized and respected if indigenous people are to participate. The working group released a report[2] that remains under review as the NIH moves forward cautiously in light of past mistakes.

"We know that the All of Us program has a single, dedicated IRB, but many of our tribal nations have their own institutional review boards that serve a wide variety of different purposes," Manson said. "We feel strongly that these review boards ought to have equal footing with the All of Us program's dedicated IRB. These considerations need to be taken into careful account as work unfolds in reservation lands."

Further, the Indian Health Service has jurisdiction in off-reservation programs where its staff, resources, or facilities remain involved in any matter related to recruitment of Native Americans, he emphasized.

"Also, there has been an enormous amount of discussion about the care and safeguards that need to be taken to address the unique aspects of the storage and access to biospecimens [from] native communities," Manson said. "Lastly, the notion that the protections and benefits accrue not only to the individual but to the tribes themselves. There is a real responsibility to engage our communities in ensuring that the kinds of questions that we believe are a priority are carefully considered and are part of the research agenda."

Nearly a quarter-million people have joined All of Us since it began May 6, 2018, Dishman said. That includes some 150,000 people who have completed the initial protocol, with 80% of them from historically underrepresented groups in research. However, the program is not currently recruiting AI/AN participants. People may sign up individually, but the NIH is holding off on active recruitment in tribal communities until the ongoing meetings and discussions reveal an ethical path forward.

Removing the Stigma

Dishman gave the following interview for *IRB Advisor*, which has been edited for length and clarity.

IRB Advisor: Regarding minimization of risk for stigmatizing research, what will be your power to terminate research that is determined to be unacceptable? Also, will a tribal representative serve on the board that evaluates what is stigmatizing?

Dishman: The Research Access Board — which you will hear us call the RAB — will include AI/AN representatives from our consortium. We are just starting to form that group now. They have been working on policies for a while. There are many ways in which this program is different, but one of them is the nature of requiring the researchers to really post details about their research before they get started with it. Our RAB will be able to stop research or take access away in an extreme case if someone is performing inappropriate research. But because all that is public, anybody could come along and say, "I do not really understand what this researcher is doing" and ask our board to review the research more closely. That is the kind of transparency that we want to make sure is out there so that anybody can look, see that something just does not make sense, and the RAB can take a look.

IRB Advisor: Who performs research audits? Will they recognize the cultural sensitivities to flag if the research has the potential for cultural harm?

Dishman: The RAB will perform audits. Many of them are experts in ethics and in issues pertaining to stigmatizing research. This is going to be something in itself that we want to certainly hear from tribal groups as well as other racial and ethnic minorities who also have been harmed by the federal government and research in the past. What should we be looking for? Computer algorithms also will look for keywords to audit the materials to make sure that something inappropriate is not occurring. This is a great opportunity in our consultation process to seek help from tribal communities. How do we know stigmatizing research when we see it, and what are the characteristics we should look for?

IRB Advisor: It is a lot of work for one person to maintain good relations with the tribes, especially for a national research program. Do you think it is possible to hire more than one tribal liaison?

Dishman: I am open to all kinds of arrangements. There is no doubt that we need a village of people — some who are feds and some who are consultants and experts in the field. We are going to build a team that is much larger than one across all those different kinds of capabilities. I can tell you that in my experience that it can be very challenging to hire into the federal government, so we need to be open to other ways of hiring

people and getting that expertise on board. I completely agree this is far more than one person's job.

IRB Advisor: How does the research benefit each tribal member if you did not have researchers accessing the data?

Dishman: Our hope is to work with and through this consultation process and work with the [Tribal Assistance Coordination Group] to develop a way where many tribes would feel comfortable with active recruitment in their own communities and nations. At that point, you would want the database to reflect that we had people signing up who not only self-identified as AI/AN but also were validated by their tribe. That is another great question to address during this consultation process. What would it take for us to do tribal affiliation correctly, to do some sort of validation? At that point, if we can figure those things out, it will be very important to include that individual's information in the research.

IRB Advisor: There is a challenging issue regarding big data sets and the possible identification of individuals based on other available data. How do you plan to protect the identification of tribes and individuals in the data set?

Dishman: We have an entire security and re-identification team as part of what we call our DRC, the Data and Research Center. The team continues to develop anti-identification strategies across many issues, not the least of which is ZIP code, for example. You might have noticed that ZIP code, first of all, would only be accessible if you are in Tier 3 of data access as a researcher. That is the most secure area of data access. We are developing a set of not just policies but also algorithms and human-audited activities to make sure that re-identification is not occurring. It is a bit like security and hackers. People and techniques for re-identification get better, and then we develop better techniques to keep them from re-identifying. Staying on top of that science and that technology is paramount to our success over time. We have got some of the best people in the country working on that issue. As technology changes and new data types come along, we will know how to continue to focus and not let re-identification happen.

IRB Advisor: Historically, issues regarding unauthorized, secondary data use have resulted from investigators who share data with other investigators, including students, without notifying the tribes. How will this level of data use and sharing be monitored and prevented?

Dishman: That is a great concern, and one that has driven the decision to require all researchers to come to our secure domain to be able to do their research. You can imagine that is going to limit, in some cases, researchers who say, "I wanted to pull all of your data into my own tools at my university." We are trying to put as many common tools in place so we will not have that problem. If we did not require everyone to come to the data, then the risk that the question talked about grows higher and higher. The key decision right away was to protect all of these data in an enclave where it can be monitored by both humans and algorithms to make sure the right thing is happening and the wrong thing is not happening.

IRB Advisor: If, after the consultation, tribes only want their data to be available in the Tier 3 or controlled circumstance and do not want any American Indian data available publicly, is that something the All of Us Research Program could accept?

Dishman: I think that is certainly the discussion that we ought to have. Infrastructure-wise, we have some of those capabilities now and others could be built. That is partly what we want to understand, and how, in particular, if we are doing active recruitment on tribal lands, that is a very different scenario than somebody signing up and self-identifying as American Indian/Alaska Native. We should always make that clear, as the working group report recommends. These people are sort of self-identified. I think at the point in which we are engaging tribes to recruit on tribal lands — which means you are separate, sovereign nations — we should have discussions about the things you want to see in place to facilitate that. ■

REFERENCES

1. National Congress of American Indians. NIH All of Us Research Program Overview Webinar. June 6, 2019. Available at: https://bit.ly/31iYyN5.
2. Malerba L, Manson S, Brilliant M, et al. Considerations for meaningful collaboration with tribal populations: The Tribal Collaboration Working Group report to the All of Us Research Program Advisory Panel. April 4, 2018. Available at: https://bit.ly/2C66FDA.

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IRB ADVISOR

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CME/CE QUESTIONS

1. **Holly Fernandez Lynch, JD, MBe, said IRBs could develop a system of "precedents" to:**

   a. use past decisions to inform current ones.
   b. establish legal protections against litigation.
   c. expand decision letters to investigators.
   d. comply with the final version of the Common Rule.

2. **How are pragmatic clinical trials different from typical clinical trials?**

   a. Pragmatic trials involve fewer participants than typical clinical trials.
   b. Pragmatic clinical trials measure effectiveness of a study drug, device, or intervention on a wider range of people.
   c. Pragmatic clinical trials do not require informed consent since their treatments already are used by physicians.
   d. Pragmatic trials do not require IRB review unless they involve greater than minimal risk.

3. **A new study shows that researchers, armed with access to 15 demographic attributes, could correctly re-identify what percentage of Americans?**

   a. 48.53%
   b. 62.3%
   c. 79%
   d. 99.98%

4. **Spero Manson, PhD, co-chair of the Tribal Collaboration Working Group of the NIH All of Us Research Program, said tribal IRBs:**

   a. will cede authority for final decisions to the All of Us IRB.
   b. are actively recruiting tribes to join the NIH project.
   c. should have equal footing with the All of Us IRB.
   d. want the NIH to formally apologize for past research atrocities.