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INSIDE

Gene-Altered Twins Face Uncertain Future

Threat of off-target mutations in controversial experiment

By Gary Evans

Chinese twins born in 2018 face a future fraught with potential health complications after a rogue gene-editing experiment that "basically broke every single principle of ethical medical research," an expert on the case tells *IRB Advisor*.

"This is a cautionary tale for everything that can go wrong scientifically and ethically," says **Kiran Musunuru**, MD, PhD, MPH, a cardiologist and the director of the Genetic and Epigenetic Origins of Disease Program at the University of Pennsylvania. "This experiment on unborn human beings — which is effectively what it was — does not meet the definition of a clinical trial."

Musunuru reviewed a copy of the unpublished research paper obtained by the MIT Technology Review.[1,2] The lead researcher, He Jiankui, announced in November 2018 at a scientific meeting in Hong Kong that he had genetically modified twin embryos. Then, at the Southern University of Science and Technology in Shenzhen, China, Dr. He said he used CRISPR-Cas9 to edit the human genome to confer resistance to HIV infection.

> "THIS IS A CAUTIONARY TALE FOR EVERYTHING THAT CAN GO WRONG SCIENTIFICALLY AND ETHICALLY."

The experiment shocked many in the scientific community, who cited widespread agreement that there were too many unknowns to proceed with CRISPR in human research subjects. Dr. He faced legal consequences from Chinese authorities, but his fate is unknown, Musunuru says.

"His lab was closed immediately, and he was under house arrest for quite a while," he says. "Whether he is still under house arrest is unclear.

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The Chinese government has stated publicly that he violated laws, although it is not clear what he violated and what were the penalties."

Dr. He announced the babies were born healthy in a video posted online but the details are scant. Some remain skeptical of the research and its purported outcomes.[3,4] Based on the genetic information in the unpublished paper, Musunuru says the experiment may lead to downstream harms to the children.

"CRISPR is like fire," he said. "If you are very careful and keep it well-controlled, it can do a lot of good. If it gets out of control, it can cause a lot of harm and damage."

The World Health Organization (WHO) formed an oversight panel in the wake of the incident, calling for a "central registry on human genome editing research to create an open and transparent database of ongoing work."[5] *(For more information, see the story in the May 2019 issue of* IRB Advisor*.)*

"The WHO has convened a committee, and the National Academies of Medicine and Science in the U.S. have convened a commission with international representation," Musunuru says. "Their goal is to create a regulatory framework. Here's the problem: They don't actually have the legal power. It will be up to individual governments to decide whether they want to adopt the recommended regulatory framework into their laws."

Beyond the Pale

IRB Advisor talked to Musunuru about the experiment in more detail in the following interview, which has been edited for length and clarity.

IRB Advisor: The researcher has stated that the experiment, performed in conjunction with in vitro fertilization, was justified because the father was HIV-positive. What was the risk of transmission of HIV from the father's sperm, had the gene editing not been performed?

Musunuru: There was basically zero chance that they were going to get it from the father. During in vitro fertilization, sperm are washed, so there is no possible HIV transmission there. As we all know, HIV is not transmitted through casual contact. Just living with an HIV-positive father is not going to give you any risk of getting HIV. The other issue is that the HIV-positive father was on therapy and his viral load was suppressed. It is not like it was active. You worry slightly more if the mother is HIV-positive. If she has an active virus then there is the possibility of transmitting during pregnancy or more likely in childbirth because there is the exchange of bodily fluids, blood, and so forth (although medication also will suppress viral load and prevent transmission [in that case]).

I would say that if there had not been [gene] editing, the twins' chance of contracting HIV would be essentially the same as the HIV prevalence in China, which is 0.1%. Even if they did get HIV, there is therapy so the chance that it would actually proceed to AIDS and suffering in their lifetimes is very low. There probably will be an HIV vaccine developed during their lifetimes.

There is no justification [for gene editing] because there was very little benefit. That is important because if there is very little benefit, then the whole notion of beneficence gets thrown out the window. You have to ask, do the benefits greatly outweigh the risks? If there is basically no benefit, then any amount of risk is not acceptable.

IRB Advisor: Can you speak to the risk of the gene editing in this case?

Musunuru: We know that CRISPR has a tendency to be messy. It's not easy to control. You can make edits at the place that you want in the gene in question. In this case, that is the CCR5 gene, which, when turned off, confers resistance to HIV. But the problem is it is very hard to control. [Dr.] He put CRISPR into the single-cell embryo, the zygote that was made from the sperm and the egg. It quickly starts to divide into two cells, four cells, eight cells. Different cells can get different edits. You end up with a situation called mosaicism — the body of the child is a patchwork of different cells with different edits. You might think you are protecting against HIV, but some number of cells in the body may not have edits that are protective. HIV could still gain a foothold and cause problems. You don't know that you are actually getting the benefit that you think you are. With HIV, there was no risk anyway, so the point is kind of moot.

The other aspect, which is more worrisome, is that this tool, CRISPR, can be sloppy and edit other genes inadvertently. It's more of a theoretical concern that if you may hit a tumor suppression gene or another gene, the kid is at [increased] risk of cancer, heart disease, or whatever. There can be directly harmful consequences of the gene editing because you are introducing a mutation that causes disease rather than helping. You mix the two — mosaicism and potentially harmful mutations — that makes it hard [to justify]. When the kid is born, you take a blood sample, you scan it with genome sequencing, and you think everything is fine. But, in fact, there could be some cells deep in the body that have harmful edits. They are not present in all of the body, but some are present in some of the body.

IRB Advisor: Are these mutations inheritable?

Musunuru: Some of these potentially harmful edits could get passed on to the next generation. This is a technology that is far from being perfected. To put it lightly, [Dr. He] was both arrogant in thinking he had a full grasp of it, and he was incompetent because, from what we know looking at the information that is available from the embryos, CRISPR was messy. There was mosaicism and off-target effects. The children could still have potential downstream harmful effects. If one of the kids gets cancer as a teenager, is it because of the [gene editing], or were they just really unlucky? We'll never really know. This is the problem if you just go in willy-nilly and do this.

> "CRISPR IS LIKE FIRE. IF YOU ARE VERY CAREFUL AND KEEP IT WELL-CONTROLLED, IT CAN DO A LOT OF GOOD. IF IT GETS OUT OF CONTROL, IT CAN CAUSE A LOT OF HARM AND DAMAGE."

IRB Advisor: You note that CRISPR can create unintended consequences, even if the experiment goes as planned.

Musunuru: Let's say that everything worked perfectly. He turned off the CCR5 gene. They are resistant to HIV even though they weren't any at any particular risk. The problem is that turning off the CCR5 gene has multiple affects. You get resistance to HIV, but you become more susceptible to other viral infections — West Nile, tickborne encephalitis. You may say those are rare, but the other big one is influenza, which is very common. The evidence is that people who have this gene naturally turned off, because they were born with the mutation, are actually more susceptible to having a bad outcome if they get infected with the flu. They can get very sick, or die. If one of [the children] gets the flu — and they probably will because everyone gets the flu at some point — they might die from it because of the [gene] editing.

IRB Advisor: Were these potential adverse consequences addressed as part of informed consent?

Musunuru: None of this was covered in the informed consent document — or the travesty of a document that was called informed consent. There was some potential for harm, and very little potential for benefit. I can't imagine any IRB allowing this to go forward.

The informed consent document reads like a contract. It talks about all the rights the research team retains — publicity, intellectual property, and basically the patients are waiving rights to those things. There is active coercion, as it says if the patients discontinue the trial at any time they have to pay back everything that they received. If they don't do so in 10 days they have to pay the equivalent of a $15,000 penalty, which is higher than the annual average income of a Chinese national. That is beyond the pale. Participants have to be able to withdraw from a study at any time for any reason without any penalty. ■

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Right to Try in Oncology: Gatekeepers or Mercenaries?

By Gary Evans

While the federal Right to Try law passed in 2018 has thus far resulted in little activity, bioethicists expect oncology will be on the frontlines of an anticipated increase in requests for investigational new drugs.

There is concern that increasing patient demand for investigational cancer drugs could lead to an increase in federal Right to Try requests, favoring that route over the longstanding expanded access pathway that includes FDA and IRB review.

"At a minimum, oncologists who are considering certification of patient eligibility should not make themselves available for doctor-shopping or as a rubber stamp," the authors of a recent paper emphasized.[1] "[C]ompanies may emerge to offer the services of physicians willing to certify Right to Try eligibility for a fee. The idea of physician mercenaries is problematic because it makes a farce of the gatekeeping role that Right to Try preserves for certifying physicians."

Lead author of the paper is **Holly Fernandez Lynch**, JD, MBE, assistant professor of medical ethics and health policy at the University of Pennsylvania. "The question of mercenaries came up in the context of what we have seen in these online pharmacies, where you can get a prescription from some nameless, faceless physician who doesn't really know the patient," she tells *IRB Advisor*. "For Right to Try, you have to have a physician certify the eligibility criteria. It's possible that could be some physician who doesn't know the patient."

Under such conditions, physicians may not be able to steer patients toward the established expanded access path, which should occur whenever possible, Lynch says.

"I think that physicians have a professional obligation to make sure patients are only pursuing Right to Try if it really is a reasonable pathway for them," she says. "If you have a personalized relationship with the patient, you can help them understand why it may be a bad idea. If you are just signing off on anybody who has the eligibility criteria, I'm not sure you are satisfying your professional responsibilities."

The paper includes several recommendations for oncologists on Right to Try issues, including considering the FDA's Project Facilitate call center, to speed access to investigational new cancer drugs. *(For more information, see the July 2019 issue of* IRB Advisor*.)*

"The first point they should consider is, can you get your patient in to a clinical trial?" Lynch says. "If you can't, can you pursue expanded access rather than Right to Try?"

Other recommendations by Lynch and colleagues for oncologists include:

- Understand that Right to Try may be inappropriate for a patient even when eligibility criteria are satisfied. Physicians can say no;
- Seek guidance from FDA and others regarding the risks and benefits of unapproved products;
- Collect and report information about patient outcomes if certified for Right to Try;
- Counter misinformation, and do not overpromise;
- Engage in shared decision-making with patients. Consider whether pursuing unapproved interventions is likely to advance their goals.

IRB Oversight Role

As opposed to expanded access, neither FDA nor IRB oversight is required with Right to Try.

"There has been some debate about whether IRB oversight is even necessary in the context of expanded

access, given that you have FDA involved," Lynch says.

A recently published survey of IRB members found that 78% of respondents agreed that it is important for IRB review of single-patient expanded access requests. Eighty-seven percent of respondents said their IRB is prepared to review expanded access cases.[2]

"IRBs also do things that FDA is not doing," Lynch says. "They take a close look at the informed consent to make sure that the patient really understands what is going on in expanded access. They are able to oversee the physician to make sure they are not conflicted and to make sure they have the right expertise with the particular drug product."

Likewise, the IRB can ensure that their institution has the right capabilities, resources, and support to oversee such cases. "You can debate whether their role is duplicative with expanded access, but with Right to Try I think the role of IRB review is important because you are losing FDA oversight," Lynch says.

No such involvement is required under the law, but institutions and IRBs are free to set their own conditions if they are asked to take on a Right to Try case, she says.

"Institutions can decide whether they want to engage in Right to Try at all," Lynch says. "They also are permitted to add whatever additional protections they think are appropriate." ■

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Money Matters: Payment to Research Participants 'Haphazard'

Outlining payment policies in study results could help

By Gary Evans

The authors of a new study on payment to research participants underscored concerns that "undue influence" of higher payments may be overemphasized in compensation to human subjects.

"Considering whether payments are too high should be secondary to considering whether payments are so low that they are exploitative," the researchers reported.[1]

They found wide variation of payment practices across studies in the same region and populations, suggesting a "haphazard" approach to compensation for research participation.

"We recommend that study authors describe their reasoning behind the payments they provided in their peer-reviewed manuscripts," the authors noted. "Currently, rationales behind payments are seldom, if ever, reported, and few institutions may have formal and standard payment policies based on study type and contextual factors of the research setting."

The researchers analyzed 100 IRB-approved sociobehavioral research protocols at a large research university in Southern California. "The proportion of studies that paid participants differed significantly by type of research and study population," they wrote. "The average payment amount also differed significantly by study population and type of participation (in-person vs. remote). In addition, studies that required more visits and more time paid significantly more than studies with fewer and shorter visits, respectively."

The lead author of the study is **Brandon Brown**, MPH, PhD, associate professor in the department of social medicine, population, and public health at the University of California, Riverside. *IRB Advisor* asked Brown to comment on the implications of the study in the following interview, which has been edited for length and clarity.

IRB Advisor: Based on your findings, you note that concerns about undue influence have been overemphasized, and that considering whether payments are too high should be secondary to whether they are exploitatively low. Can you elaborate on this point?

Brown: Too much attention has been paid to undue influence — which might happen rarely — while we are not spending enough time on

underpayment. We can ask the question: Would it be unethical to pay someone $1,000 to take a 30-minute survey? What about $1,000 to test an experimental treatment in a Phase I trial? When would it be undue influence? Whether research is low or high risk, lack of compensation can be exploitative and disrespectful of participants' contribution to research, including their time, effort, and their disclosure of information we use as data.

IRB Advisor: Is there some perceived formula that the higher the risk to participants, the greater the compensation? Or, would that raise ethical concerns of undue influence?

Brown: From the IRB's perspective, payment is not to be used to evaluate the risk/benefit ratio of a study. This is regardless of the fact that participants themselves may view payment as a benefit of participation. I would assume that a simple, anonymous survey study would pay less than a clinical trial, but that doesn't need to be the case, and may depend on the individual study budget. I also would expect a study with a high level of risk to pay participants more, which can raise ethical concerns of undue influence, depending on the risk and payment. Unfortunately, we have little sense of low or high payment dependent on risk.

IRB Advisor: Your findings suggest that payment decisions are made by study type, participation type, participant type, time, and number of visits. Does your research or review of the literature suggest that payments for biomedical research are similar?

Brown: Yes, our data from sociobehavioral studies at UC Riverside suggest this is how payment decisions are made, due to statistical significance between payment and the variables listed above. We have no idea if this will be the factual case for biomedical research, but it makes sense that payment may differ by study type, participation type, participant type, time, and number of visits for any type of study.

IRB Advisor: You recommend that study authors describe their reasoning behind the payments they provided in their peer-reviewed manuscripts. Is this something that individual IRBs and researchers should emphasize to better inform future decisions and overcome the dearth of data?

Brown: Definitely. We need data to understand how people make decisions; otherwise we will continue making decisions on a case-by-case basis. As a member of my own institutional IRB, I often ask how these decisions are made, and oftentimes there is no specific reason apart from perceived norms. In a perfect setting, we can collect this information in a systematic way so that each institution can formulate norms for payment to study participants based on the numerous factors.

IRB Advisor: SACHRP recently approved some guidelines on the unusual situation where participants pay to be part of research. *(For more information, see the December 2019 issue of* IRB Advisor*.)* Can you comment on this from the perspective of your research?

Brown: First, I agree that therapeutic misconception is more apparent in pay-to-participate studies, since people usually pay for things or services rather than to be experimented on. Also, it is true that populations without the ability to pay will be excluded, when they otherwise fulfill all other inclusion criteria. It also may contribute to the historical focus of research on white populations. An obvious risk of joining the pay-to-participate studies is loss of money. Certainly, this is obvious to the participant who must pay to join. But since IRBs do not consider money gained to be a benefit of research that pays participants, they also should not consider money lost as a risk. I personally do not believe that participants should be required to pay to participate in research, unless the potential benefits to the individual are so high that the amount they pay is well below the benefit. ■

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Need Researchers to Pay Attention? Try Experimenting With Engaging Content

By Melinda Young

At one time or another, IRBs have ignored some part of the website content, simply adding new information rather than revamping educational pages and instructions. This can lead to redundancy and waste. A better long-term solution is to replace older educational information for researchers with more engaging content.

"My main goal is trying to reach out to researchers in ways that show them what information we want them to have, including how to submit studies and IRB policies," says **Mercedes James**, MPH, IRB analyst at the University of Texas at Austin.

Prior to focusing on improving its educational content, there was little evidence that investigators paid enough attention to the material. "There were no channels interesting enough that people would try to learn this information," James says.

The IRB modernized its brand identity, created more interesting and visual IRB content, and minimized the volume of educational material. It also conducted a survey to assess attitudes toward the content.[1]

"I'm a visual learner, and I tried to figure out ways to reach out to researchers and provide them with deliverables that are informative, interesting, and contain all the information they need," James explains.

The changes have been positive. "People are engaged with the new efforts we're doing," James says. "We've revamped our identity and have a new logo."

Another tactic is to simply listen to researchers' concerns, making the IRB office available whenever they might have questions, suggests **Ximena Levy**, MD, MPH, CIP, associate director of research integrity, division of research, at Florida Atlantic University.

"One of the main problems is a lack of understanding from both sides," Levy says. "Usually, it takes time to clarify what the IRB wants."

Here are some ways an IRB can improve its educational and informational content:

• Create a monthly newsletter. The UT Austin IRB began distributing a newsletter in January 2019. "We do a newsletter every month with three to nine pages," James says. "Each newsletter issue had three or four topics, and it's in PDF format, uploaded to UT-Box, containing links to click on for more information or to contact the IRB."

For instance, a link might take someone to a page on the IRB's website or to a government website, where the researcher could obtain more information on the topic.

"The newsletter has a lot of visuals," notes James, who creates each month's newsletter. "Each issue has a link that people can share with anyone; it's open to the public."

Increasingly, people are downloading the IRB's newsletter and asking about IRB workshops. "We've gotten good feedback about the newsletter," she adds.

• Run interactive workshops. Another method to engage researchers is through workshops. The UT Austin IRB held a series of workshops last year, focusing on the new Common Rule regulations. Typically, each workshop attracts 30 to 50 attendees, as well as 20 people who watch online, James says. "We recorded the workshops so we could have them posted to our website," she explains.

The workshops were held in February and May in a conference room. "We try to make the workshops interactive, and have questions and answers sessions," James says.

Using PowerPoint and the Poll Everywhere app, the workshop leader can ask people to indicate their choice of answers to several poll questions, she explains.

"There is a login link, and before the webinar, we have that information available on a whiteboard or the PowerPoint slide," James says. "People can pull out their phones and click on their answer when there's a poll question."

An example of a poll question is "What does informed consent mean?" After people have completed the poll, the workshop leader goes over the answers to show how many people selected the correct answer and the incorrect answers, James says.

"It's real-life education within the PowerPoint, and it's more engaging because they learn something on their own, as opposed to just seeing it on a slide and having to retain it," she explains.

For the Q&A, attendees can write their questions on paper. Eventually, the sessions might include a way to ask questions within the app. The workshop leader asks people to keep their questions general and of interest to everyone. If they have a question about a study, they can wait until after the workshop to discuss it.

"Right after the workshop, we

make ourselves available within our offices to interact with researchers," James says.

• Listen to researchers and educate them during the review process. "One of my recommendations is to limit the message to what they need to know," Levy says. "Sometimes, we want to give them the whole education of IRB and ethics, but when they're asking questions, just give researchers what they need to know."

For example, it is unnecessary to recite an entire section of the federal regulations when all that is needed is a complete answer to what the investigator is asking, she says.

IRB staff should practice listening skills and communicate the criteria for good responses to their requests. They also should make education a chief goal in communication with researchers.

Levy says the take-home message is:

- Simplify by using easier-to-understand language;
- Justify by providing an understandable rationale;
- Emphasize that requests are directly related to the protection of human subjects;
- Be complete by providing thorough and detailed information of what investigators are missing;
- Maintain consistency of the information provided in each protocol and across the study.

"It is good practice to try to summarize what the IRB is requesting," Levy says.

For instance, IRBs can ask investigators if they understand what the IRB wants, and what changes the IRB has suggested. "After the IRB has reviewed a proposal, instead of just sending a letter or making a phone call, offer to help the researcher clarify whether they understood what the IRB said," Levy explains.

Researchers appreciate these educational or clarification moments, and it helps build rapport. "Since implementing these practices two years ago, we've only had two complaints," Levy says. "We take time to talk with investigators, and that changes their whole perception of the IRB. They thank us for taking time to talk with them."

• Collaborate with departments on webinars. The IRB works with different departments and institutions to create webinars on IRB topics that they would like, James says.

"They might provide the content, and I would do a flier and event," she says. "With one of our last webinars, five people hosted it and planned it."

The webinar was seen by about 70 people, linked to virtual attendees via a webinar platform. "The topic was on how to deal with HIPAA rules under the revised Common Rule," James says. "We worked with a webinar production company that specifically does research-related topics."

• Ask for feedback on engagement. After publishing two newsletters, James asked for feedback via survey. "I wanted to get a general understanding of how people are engaged with the IRB," she explains.

This first survey attempt was a missed opportunity. Too few people took time to answer the survey questions, she says. "This let us know people need to be engaged, and didn't take the bandwidth of time to do the 10-question survey," James says. "We're trying to improve that."

Another way the IRB is asking for feedback is through reaching out to departments and letting people know the IRB is available to help researchers. The IRB has asked some researchers, who have worked with the IRB over time, to be ambassadors.

"If we can get researchers and departments on board, they can share information with their colleagues," James explains. "This is how we can get more people interested in what we have to say."

For instance, the IRB can ask the ambassadors to tell their colleagues about the IRB's workshops and newsletter. "The more people who have access to IRB information, the more we'll be able to learn about what they need," James says. "We're trying to improve on these efforts." ■

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Study: Research Subjects Might Consent to Records Use, But Want to be Asked

Useful technique is democratic deliberation

By Melinda Young

Researchers and IRBs could learn a lot about what research participants want with informed consent and privacy if they ask.

One way to find out what research subjects think is called democratic deliberation. Using this technique, researchers found that most patients want someone to ask them before deidentified medical records are used for research.[1]

"It is an innovative technique used when we need to generate an informed and considerate consensus opinion from our fellow citizens," says **Reshma Jagsi**, MD, DPhil, Newman Family professor, deputy chair of radiation oncology, and director of the Center for Bioethics and Social Sciences in Medicine at the University of Michigan.

"Think of democratic deliberation as a citizens' jury," Jagsi says. "We can't reasonably engage every single patient in the community in understanding some of the complexities in policy decisions. We learn by engaging a representative group of patients and give space to their deliberating with peers."

In the study, the democratic deliberation process led to investigators learning that people want more control over their data than some researchers might think. "A first step is to have a better understanding of what patients desire in this context," Jagsi says.

The researchers found that participants with cancer were most comfortable with their health information in secondary uses for purposes of university research about cancer or local hospitals using the information to ensure cancer patients received the right treatments. They were least comfortable with insurance companies using their information to determine which cancer treatments are eligible for coverage, or for hospitals using the information to market itself to cancer treatment patients.[1]

The goal is to include people in the deliberation that are representative of research participants undergoing informed consent. It is not a focus group, Jagsi says.

"It's a unique process and distinct," she explains. "It replicates a jury by presenting a case and information, and jurors have a chance to talk before rendering a verdict."

Using the democratic deliberation process, Jagsi's recent study saw results consistent with prior studies that used traditional techniques, such as surveys and interviews with patients. "What was striking about our findings was that a substantial proportion of the participants, even after deliberation, really did desire some degree of patient consent beyond notification," Jagsi says.

"The argument has been that if patients really knew about the complex tradeoff involved, the quality of databases would suffer," she says. "Many patients wanted to be asked for permission; they told us that they fully intended to give permission, but they wanted the opportunity to provide their permission."

The study authors enrolled more than 200 patients with cancer. Those involved in deliberative sessions attended day-long educational events, small-group discussions, and completed several surveys. Investigators surveyed patients' comfort with secondary uses of health information. Participants learned of several scenarios involving secondary use of electronic health information. They rated their comfort level with this use on a four-point scale.[1]

The democratic deliberation sessions used this setup:

- Attendees were randomly assigned to tables of four to eight people and one trained facilitator;
- Deliberations included an educational presentation and two small-group discussions;
- Researchers recorded, transcribed, and deidentified discussions;
- Participants heard presentations on "Disclosure and Consent," and "Data Protection, Use, and Governance;"
- Facilitators asked participants to discuss the issue and vote to choose a corresponding policy;
- Participants were encouraged to defend their position on a policy, explain the rationale, and think like a citizen in a community about which policy would be best for society.

"I find that democratic deliberation is a very useful method, but I don't suggest that everyone should use this method," Jagsi says. "It's very labor-intensive and expensive."

The technique likely would not be practical for investigators or IRBs to employ on a regular basis, she notes. "It's not realistic to expect individual researchers, planning particular use of data, to engage in full-on democratic deliberation," she adds. "The point of this study was to inform large national databases, in this regard."

Democratic deliberation could be useful at institutions that see multiple studies proposed for secondary usage of patients' medical record data. "If you are seeing medical records used repeatedly from the same type of user, it certainly is important to get the public perspective on this use," Jagsi says. "It's important to understand that patients do feel quite strongly about this." ■

REFERENCE

1. Jagsi R, Griffith KA, Jones RD, et al. Effect of public deliberation on patient attitudes regarding consent and data use in a learning health care system for oncology. *J Clin Oncol* 2019;37:3203-3211.

IRB Chairs Can Run Better Meetings by Following These Tips

By Melinda Young

The most important way to improve IRB meetings is through preparation. "It's a moving target," says **Francis J. DiMario, Jr.**, MD, MA, CIP, professor of pediatrics and neurology at the University of Connecticut, and associate chair of academic affairs, department of pediatrics, and medical director, human research protection program, at Connecticut Children's Medical Center. DiMario also is IRB chair at Connecticut Children's Medical Center.

"The IRB chair has to have a sense of what's coming up on the agenda, and anticipate an important discussion point," DiMario says. "You don't always have control over how the conversation evolves, so just have people put their thoughts on the table."

DiMario makes these suggestions for improving IRB meetings:

• Reduce redundant debate. IRB chairs can guide people to state their positions succinctly, and without restating someone else's opinion.

"I don't want to cut off people too much, but it's important to limit them in making their point," he says. "If more people chime in with the same point of view, but say it in a slightly different way, then the chair can say, 'Yes, we've heard this already,' and move the conversation forward."

When a discussion or point is not clear, DiMario asks people to reframe it: "I say, 'Please help me understand what you're saying.'"

If someone has taken five minutes to state their point, it usually could be reframed within seconds, he adds. "Rephrase it in a succinct statement, and they all agree that they understand what was just said," DiMario says.

• Let people disagree. "People don't have to always agree. You don't need consensus on every point," DiMario says. "It's nice to get complete consensus, but we should move toward a consensus."

Most of the time, IRB members will agree on a study approval, but sometimes a member will have a different point of view, he adds.

"They might want to stand by that point, and that's OK," he says. "It's important that if they disagree with the general group decision that everyone understands why that is. It's not appropriate for people to take a vote and not hear why."

Any IRB members who disagree with the general group decision, particularly if they feel strongly, should explain their thoughts, he adds.

Chairs also should keep in mind that there could be multiple solutions to any minor problems with a study. "Trivial problems do not need optimal solutions," DiMario says. "It doesn't have to be perfect. The discussion should center around how the study meets or does not meet the criteria. Even if it's not optimal, it's still acceptable."

Similarly, if board members argue over a point, the chair can insert a phrase to get them on the same plane.

"Say, a procedure is being done, and some people are uncomfortable with it, while others argue that it's not the procedure, but the duration that it takes," DiMario says. "The chair can ask, 'What does or does not meet approval criteria?'"

If the disagreeing parties agree the study meets approval criteria, then that settles the dispute.

• Encourage board members to talk. "The folks we work with are pretty trusting of each other," DiMario says. "I make a point to always ask their opinion on everything, even if they're quiet."

It is important to gain each board member's insights. The more the IRB chair works to include everyone, the more often people will speak up, he says.

"If you don't listen to them, they won't say anything, but if you engage them, they're more likely to speak up," DiMario adds. "As chair, I try to speak last, letting everyone else have their input, and I don't want to be the primary decision point."

One way to engage members is to ask them direct, simple questions, such as:

- Do you agree with this?
- Does this make sense to you?
- Does this sound understandable to someone reading these descriptions?
- Do you do this in your job?

IRB chairs can quickly learn what to expect from board members. To keep people focused on the IRB's review goals, the chair can remind people that their questions should address the approval criteria — not tangential issues.

"Is it a good-enough project, and is it meeting our approval criteria?" DiMario says. "Scientist board members get excited about making a better project, but that's not what you have to determine; you have to make sure it's safe and reasonable."

The IRB can overlook the improvement part, unless it is an absolute necessity, DiMario says.

• **Encourage diligence.** Occasionally, IRB chairs deal with members who slack off a little in their summaries or reviews of submissions. One way the chair can encourage greater diligence and less slacking is through feedback during meetings. The chair can say, "Yes, that's a good summary," or "That was well put together," when the reviewer does a good job, DiMario says.

When the summary is lacking, the chair could amplify what was not put together well. DiMario might comment that he was not clear about what the reviewer said, and ask the person to restate it.

"I would point out something that was not put together clearly, saying, 'As I read through this, these are some points I thought were important to consider,'" he says. ■

OHRP Gives IRBs a Break With Single IRB Review Exceptions

By Melinda Young

The Office for Human Research Protections (OHRP) is making implementation of the revised Common Rule a little easier for IRBs with two exceptions to the single IRB review requirement.

IRBs can continue to use multiple IRBs, instead of a single IRB, in these cases:

• Cooperative research conducted by or supported by the U.S. Department of Health and Human Services, where the IRB initially approved the research before Jan. 20, 2020;

• Cooperative research conducted or supported by the National Institutes of Health (NIH) when the NIH single IRB policy does not apply and the research was approved by an IRB before Jan. 20, 2020, or when NIH excepted the research from its single IRB policy before Jan. 20, 2020.

Before OHRP's announcement, some IRBs would have had to revisit some studies, entering into cooperative agreements after the fact. OHRP's announcement clears up confusion over deadlines per the revised Common Rule.

"When OHRP released this new information, I was completely relieved," says **Alayna Nest**, IRB coordinator at Oregon Public Health Division/Multnomah County Health Department IRB in Portland.

Nest realized in 2019 that some studies that were approved by a single IRB in 2019 would require a cooperative agreement under the revised Common Rule. This would have required the small IRB to backtrack and enter the cooperative agreements for those five to six studies. This was frustrating because it would have been easier to enter the agreements from the start if OHRP had made that intention clear, she explains.

"Why in the world would we backtrack a year when we could have done this from the get-go?" Nest asks. "If they were going to require us to go back to 2019 in the first place, they should have made it the same effective date as the rest of the regulations."

The announced exceptions for research approved before Jan. 20, 2020, takes away that headache, she adds.

"OHRP's announcement is very sensible," she says. "Now, my concerns are gone." ■

IRB ADVISOR

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CME/CE QUESTIONS

1. **According to Kiran Musunuru, MD, PhD, MPH, the Chinese twins experiment "turned off" the CCR5 gene to confer resistance to HIV. As a result, the children may be at higher risk of severe:**

   a. antibiotic-resistant infections.
   b. autoimmune diseases.
   c. hemophilia.
   d. influenza infections.

2. **The federal Right to Try law requires patient eligibility be certified by:**

   a. the FDA.
   b. a physician.
   c. an IRB.
   d. the drug manufacturer.

3. **What is democratic deliberation when used in the context of research?**

   a. A focus group votes on phrasing used in an informed consent form.
   b. When investigators vote to select sample informed consent phrases.
   c. When a study sponsor performs an online survey, asking the public to select which answer to a study's ethical dilemma would be most acceptable.
   d. A technique used to generate an informed and considerate consensus opinion from citizens about a complex research policy and/or ethical decision.

4. **Which method might an IRB chair employ to improve IRB meeting efficiency and effectiveness, according to Francis J. DiMario, Jr., MD, MA, CIP?**

   a. Guide board members to state their positions succinctly and without restating someone else's opinion.
   b. Prevent board members from disagreeing by encouraging a full consensus.
   c. Use a stopwatch to keep debating points to 45 seconds.
   d. Ask board members to submit their chief concerns about a study to all members 24 hours prior to the meeting.