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RELIAS MEDIA

Informed Consent Rule Changes Could Help IRBs, Expand Research

But do FDA's proposed consent waivers go far enough?

By Melinda Young, Author

The FDA has issued a proposed rule that some say would provide research institutions with much-needed clarity on informed consent regulations and open the door to clinical breakthroughs.

"I think, personally, anything that is on the side of loosening up the asinine, ambiguous rules is wonderful," says **Susan Rose**, PhD, executive director of the office for the protection of research subjects at the University of Southern California in Los Angeles.

Current FDA regulations allow informed consent waivers only in life-threatening situations or during certain emergency research[1]. But with the 2016 passage of the 21st Century Cures Act, the agency was given the ability to grant exceptions for clinical investigations that pose no more than minimal risk to human subjects and that include safeguards.

> "FOR MANY YEARS, WE'VE HAD ONE SET OF REGULATIONS FROM OHRP FROM THE COMMON RULE AND ANOTHER FROM THE FDA, AND THERE WERE PLACES WHERE THE TWO OF THEM DID NOT MATCH."

The proposed rule, issued in November 2018, would implement Cures Act requirements, more closely aligning the FDA's informed consent waiver provisions with related provisions in the Common Rule. The agency's leader says such change could bring about research innovation.

FDA commissioner **Scott Gottlieb**, MD, said in a statement announcing the proposed rule that the agency had "received feedback from sponsors and investigators that they were not able to move forward

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in conducting important clinical investigations where there would be minimal risk."

Gottlieb said that the proposed change could enable research "addressing significant public health needs without compromising the rights, safety, or welfare of human subjects."

Regulatory uniformity may be another benefit.

"I think the steps the FDA is [taking] right now are useful," says Rose. "It's a good thing if a study is compliant and ethical and the IRB has looked at it and waivers are involved — unless another government agency doesn't allow the same thing."

That point also is emphasized by **James Riddle**, MCSE, CIP, CPIA, CRQM, executive vice president of Kinetiq, a division of Quorum IRB, in Seattle.

"For many years, we've had one set of regulations from the Office for Human Research Protections [OHRP] from the Common Rule and another from the FDA, and there were places where the two of them did not match," he says.

"IRBs and researchers do struggle with how to handle consent and consent activities for FDA-regulated data research — under OHRP, the old rules were you could waive consent, and under FDA, the rule was the intent to exercise enforcement discretion," Riddle says.

With the FDA's proposed rule, IRBs would be allowed to waive or alter certain informed consent elements or waive informed consent altogether — a significant departure from the agency's current system.

These changes would give IRBs a consistent way to approach waivers — with one big exception, Riddle says.

"FDA chose to harmonize against existing OHRP regulations but did not harmonize against the new Common Rule that goes into effect on Jan. 21, 2019," he explains. "The FDA adopted four waiver-of-consent criteria that exist in the [old] Common Rule regulations; the new Common Rule includes *five* waiver-of-consent criteria."

"FDA CHOSE TO HARMONIZE AGAINST EXISTING OHRP REGULATIONS BUT DID NOT HARMONIZE AGAINST THE NEW COMMON RULE THAT GOES INTO EFFECT ON JAN. 21, 2019."

Under the FDA's new approach, informed consent is waived when IRBs find and document the following:

- the clinical investigation involves no more than minimal risk to the subjects;
- the waiver or alteration of informed consent will not adversely affect the rights and welfare of the subjects;
- the clinical investigation could not practicably be carried out without the waiver or alteration of informed consent;
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

And this is the fifth criterion that will be in the new Common Rule — but would not be adopted by the FDA: "If the research involves using identifiable private information or

identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format."

There is no information about why the FDA chose not to adopt the fifth criterion, which would have made harmonization more complete, Riddle says. "We look forward to additional guidance from FDA, or we hope they'll clarify," he adds.

From a practical standpoint, informed consent waivers will not be appropriate for most FDA-regulated research but could be helpful in certain instances, Riddle notes.

"While it's nice to see the FDA harmonizing, this is the low-hanging fruit for them," he says.

"The underlying theme is it is great the FDA is doing the harmonization; it will facilitate more research, and it will reduce burden on IRBs on how to deal with a waiver of informed consent when a regulatory structure didn't exist for the FDA, and now it does."

The FDA will accept comments on the proposed rule through Jan. 14, 2019. ■

REFERENCE

1. Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations. *Fed Reg.* 2018;83(221):57378-57385.

HIV Cure Research Includes Tricky Ethical Challenges

What do you do when stakes are high?

A Chinese scientist sparked worldwide controversy in November 2018 when he announced he had used a new gene-editing technique to genetically modify twin embryos. The result was Lulu and Nana, twins born shortly before the announcement. The experiment was intended to make the babies resistant to HIV infection, and the scientist had not published his results at the time he announced his experiment.

Some geneticists compared the work by He Jiankui of the Southern University of Science and Technology in Shenzhen, China, to the pioneering in vitro fertilization efforts that resulted in the birth of Louise Brown in 1978. Many others criticized the scientist for the ethical issues his experiment raised. A local medical ethics board said it would investigate him. *(https://n.pr/2r6Ls5R)*

The researcher claimed to have used Crispr-Cas9 to disable the CCR5 gene that makes the protein HIV needs to enter cells. *(https://nyti.ms/2FFVg0A)*

The CCR5 gene also is the target of entirely different research examining ways to cure people who are HIV-positive. These studies also raise thorny ethical questions — but with less controversy and publicity than the birth of the genetically-altered twin girls.

What Constitutes a Cure?

CCR5 studies into curing HIV are causing hand-wringing across the research community, says **Rowena Johnston**, PhD, vice president and director of research of amfAR, the Foundation for AIDS Research, in New York City.

The foundation is funding research aimed at eradicating the virus and achieving post-treatment control, where the patient can stop treatment and the virus remains undetectable, she says.

"This is a very interesting and rapidly evolving field, and I think regulators in particular are having trouble keeping up with the way new data are affecting research," she says.

HIV cure studies raise a number of ethical questions, including the following:

- Should investigators include regulatory agencies as they initiate these studies?
- How can investigators and IRBs ensure study participants fully understand the study's risks and benefits?
- What is the definition of a "cure" in HIV?

"A person living with HIV in the community might have an understanding that a cure means eradicating the virus," Johnston says.

"In the research community, there is a group of people who would like to eradicate the virus and do what we think of as a cure," she says. "Others say we should aim for post-treatment control, and that seems more attainable."

Of course, from amfAR's perspective, Johnston says, the former would be ideal: "Even if eradication is more difficult, I believe that is a more desirable outcome in the end."

And there is one case in which a man was cured of HIV infection. In 2008, an American man living

in Berlin had HIV infection and a cancer that required a stem cell transplant. "His HIV was doing okay," she says.

The man's physician was intrigued by the discovery that a small number of Europeans lacked the HIV receptor protein CCR5 in their bodies, and they never became infected with HIV — despite exposure that would lead to infection in anyone else, she explains.

The patient's doctor sought to find a stem cell donor who had this CCR5 mutation. He screened people for a stem cell match and CCR5 mutation and found one. "The Berlin patient got the transplant, and since then he has not had cancer, and he no longer needed to take antiretroviral therapy [ART]," Johnston says.

"No one has found any virus in his body through tissue biopsies and blood draws, and he's never experienced a viral rebound," she adds. "He's very active in the HIV advocacy area and goes to conferences to share his experience."

amfAR, which is funding a large consortium in Europe, decided that because the genetic mutation is most common in Europe, it would fund research involving people living with HIV who also have cancer and need stem cell transplants.

"Stem cell transplants are risky procedures, and they should only be done if there is a medically sound reason to do that," Johnston notes. "So this group in Europe has identified the largest cohort of people living with HIV who also received stem cell transplants."

The people enrolled include cancer and HIV survivors who received stem cell transplants from people with the CCR5 mutation (and some without it). Researchers are following them to see if more people are cured from HIV.

"Recently, they published a paper that describes six interesting patients in whom they cannot find any virus after their stem cell transplant," Johnston says.

One of the ethical challenges of reaching a conclusion that the stem cell transplant cured these patients involves the gold standard method for determining whether someone is cured.

"WE'RE ASKING PARTICIPANTS TO PUT THEIR TRUST IN A CLINICAL TRIAL WHERE PEOPLE HAVE TO LET GO OF THEIR LIFELINE AND SEE WHAT HAPPENS."

It is called analytic treatment interruption (ATI), and it involves taking a patient off antiretroviral therapy to see if he or she experiences a viral rebound, she says. *(See story on HIV research and ethical challenges, page 5.)*

"It's the most stringent test we have of whether or not this was a cure," Johnston explains. "If a person only has three viruses left in their body, then how do we find them? Maybe the virus is in the left lymph node but you have sampled the right one; it's philosophically impossible to prove a negative, so the only way to see if it's a cure is to take them off ART and see if the virus comes back."

The HIV/cancer patients were not randomly assigned to stem cell donors with the mutation. They were treated according to their medical needs.

When a patient needed a stem cell transplant, the doctor had to find the best donor possible, regardless of whether the person had the mutation.

"We funded prescreening of several million donors to preidentify the ones with a genetic mutation," Johnston says. "So if the doctor reaches the point of finding someone who is a tissue match, there was information about whether a donor had the CCR5 mutation."

In some cases, the physician had to proceed immediately with a transplant that did not have the mutation, and in other cases there were no matching donors with the mutation, she adds.

The HIV/cancer research participants likely fully understand ATI and the risks of being involved in HIV cure research, Johnston notes. The challenge is that stopping antiretroviral therapy goes against everything HIV patients have learned and experienced, which makes it a difficult choice.

"We've spent a lot of years driving home the importance of taking ART and adhering to it daily, and that it is extremely important. Your life and health depend on those medications," Johnston says.

"So now we're entering into a phase in the history of HIV research and the epidemic where we ask people to stop taking ART, and that's a big ask," she says. "We're asking participants to put their trust in a clinical trial where people have to let go of their lifeline and see what happens."

In addition to the physical risks of stopping antiretroviral therapy, there are emotional risks: "There's really a lot of angst on the part of trial participants in letting go of ART in the name of research in order to find out if they're really cured," Johnston says. "There are competing motivations because people want to know if they're cured." ■

HIV Research Poses Unique Ethical Issues

When IRBs review HIV studies, particularly those aimed at finding a cure to the disease, there are some tricky ethical challenges that might not be seen in other types of research.

The following are some of the chief ethical issues that can arise:

• Participants on analytic treatment interruption (ATI) might miss the tipping point for post-treatment control. Another type of "cure" for HIV is called post-treatment control, which occurs when a patient can stop his or her medication regimen and still remain free of detectable HIV. Researchers have studied participants with HIV to identify and learn from this phenomenon. Investigators also are studying potential treatments that would make it more likely an HIV patient achieves post-treatment control, says **Rowena Johnston**, PhD, vice president and director of research of amfAR, the Foundation for AIDS Research, in New York City.

The way to see whether post-treatment control is working is to take the patient off antiretroviral therapy for some weeks. If the viral load starts to rise and then falls to undetectable levels, or if it never rises, then post-treatment control might be achieved, and the person may no longer need to take daily antiretroviral therapy (ART).

Some of the research being performed with regard to post-treatment control includes a therapeutic HIV vaccine regimen and a short course of an HIV latency-reversing agent. *(http://bit.ly/2ACFNc7)*

"Any number of interventions could bring post-treatment control, and they all would need to go through analytic treatment interruption," Johnston says.

"When ART is taken away, there is a virus rebound, and it can go to a very high level. But the immune system might take over and bring it back down," she adds. "It's a game of chicken to wait for an opportunity for the immune system to kick in."

The ethical dilemma with this type of research involves how to fully inform participants of the risks of taking away their antiretroviral therapy when researchers do not know what will happen to an individual patient. And the study participant could be off ART long enough to see the viral load rise to 100,000 copies, Johnston explains.

"But you may miss post-treatment control if you start the person back on ART too early," she says.

The unanswered question is, "Where is the tipping point?"

"There's not a whole lot of consensus on that issue right now," Johnston says. "There have been trials where the clinician wanted to wait to see where post-treatment control would happen, but the participant got so nervous, they put themselves back on ART."

And there are failures. One study using ATI did not work, and those participants had to return to antiretroviral therapy, she notes.

"It's a shot in the dark," Johnston says. "You don't know how long they'll be off ART or how much they can tolerate."

• Research participants might infect others. Participants must be in cancer remission, and their HIV must be undetectable. But there still is a risk of infecting someone else with HIV if ART is stopped through ATI, Johnston says.

The reason for this is that if a patient's stem cell transplant successfully put the cancer in remission and the patient then is taken off ART for the HIV infection, there is a possibility that the patient's HIV could rebound and lead to the person infecting someone else with the virus.

"Say you've gone six months without a rebound, and the doctor thinks, 'I'll test you every two weeks and see if you do have a viral rebound' — then your virus might have a chance to go high enough that there's a risk you'll transmit that virus to somebody else," Johnston says.

Potential participants would learn of this complex risk from informed consent, and they would be advised to use condoms. But it raises the issue of informing participants' partners.

• Participants might not inform partners. "Getting partners involved is an ethical issue that people wring their hands over," Johnston says. "They might not have disclosed to partners that they have HIV or have participated in the trial."

An ethical challenge is whether this disclosure should be required when the participant will receive analytic treatment interruption.

"How do you handle this disclosure to partners?" she asks. "And not everyone has one partner. The population living with HIV includes people who might have multiple partners, whose names and contacts they don't know."

One way to prevent HIV-negative partners of HIV patients from becoming infected with the virus is for them to take pre-exposure prophylaxis (PrEP), which is a daily course of HIV medication that can lower their chances of getting infected. According to an HIV

government website, daily PrEP reduces the risk of contracting HIV from sex by more than 90%, and its most common risk is nausea. *(http://bit.ly/2racrxp)*

Researchers have wondered whether they can require participants to ask partners to take PrEP to prevent HIV infection. And should the study pay for their PrEP?

At a consensus workshop, researchers and HIV advocates voted on a proposed course of action. Most voted that PrEP should be discussed and that clinical trial participants and their partners should be made aware that PrEP was recommended, Johnston says.

"The most common thought was that the trial should pay for PrEP, but that puts a lot of burden on funders," she adds. "It potentially adds so much to the cost and risk of a trial that it would be difficult to get as many trials done as we would like to see out there."

• Antiretroviral therapy might not work as well when patients return to it. HIV medications are much more effective now than they were a decade or two ago, but there still is a risk that a patient who has stopped ART will develop drug resistance when returning to the treatment.

"In one trial, a participant was supposed to go back on antiretroviral therapy but was not adherent and didn't disclose to the trial that he was not adhering to ART," Johnston recalls. "He developed drug resistance."

If HIV-infected patients adhere to their medication regimens, drug resistance is not an issue, she adds.

"Drug resistance happens when viral replication happens, and they don't have viral replication in the ART period because it's been a latent cell and it's not producing virus that goes on to infect other cells," she explains. "You need replication to get evolution, and evolution is what leads to resistance."

When HIV trial participants are monitored weekly for viral rebound, typically there is minimal risk of drug resistance. This is because they will detect the viral rebound and ask the patient to return a few days later for a confirmatory test.

"THOSE WHO PARTICIPATE IN HIV CURE TRIALS ARE INCREDIBLY ALTRUISTIC; THEY UNDERSTAND THAT THEY MIGHT NOT DIRECTLY BENEFIT FROM A TRIAL, BUT THEY'RE DOING IT FOR THEIR COMMUNITY."

With only one week of potential exposure to viral replication, there is not enough time for drug resistance to develop, and the person should be able to return to the same antiretroviral therapy used previously, Johnston adds.

• Is it ethical to ask people to make these choices? Before giving research participants informed consent, the studies must be reviewed and approved because there is some public good that might be achieved with answering the research question. Few would dispute that finding a cure to HIV would be a public good. But these studies have risks that are difficult to describe and define.

Johnston says the issue is especially difficult given that HIV research participants tend to be compassionate individuals.

"We're very dependent on altruism of participants," Johnston says. "Those who participate in HIV cure trials are incredibly altruistic; they understand that they might not directly benefit from a trial, but they're doing it for their community."

HIV research participants might know that a particular trial will be part of a puzzle that builds a solution, although not necessarily in their lifetime, she adds.

It is incumbent on investigators and IRBs to ensure participants understand all of the known potential risks. One strategy is to use videos. Another is to interview participants after the informed consent process to probe their comprehension. Investigators could give them a comprehension test about the study, Johnston says.

"There's also an idea that informed consent should not be a one-time thing," she adds.

"These trials tend to go on a very long time, and someone might be given a series of interventions over four to six months. Researchers could check in to see if their understanding is the same as when the person started in the trial."

One innate problem with informed consent for a study of a cure to a dangerous disease is the participant's sense of exceptionalism.

"One thing that informed consent will never resolve — and you can tell a person until you're blue in the face that the chances of their being cured is infinitesimally small — is the sense that 'I might be the lucky one,'" Johnston says.

That feeling of exceptionalism will exist in every clinical trial involving a disease in search of a cure, she adds. ■

Children's Hospital Improves Assent-Consent With Animation Board Video

Patients and families give feedback

When a children's hospital needed to approach research informed consent and pediatric assent with more creativity and flair, the research office asked children for input.

"We have a research program here, and one of our goals is to increase awareness of our research program amongst the rest of the hospital and our patients," says **Jessica Macha**, CIP, associate director of the office of research integrity and compliance at the Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago.

"We found there is a need to get the right kind of information out to our families and to raise awareness of their ability to take part in research," she says.

Engaging potential research participants in a process to improve informed consent is a very positive trend, says **Ryan Spellecy**, PhD, professor of bioethics at the Medical College of Wisconsin in Milwaukee.

"If we engage potential research participants [and] stakeholders from the get-go and beyond the old model of 'Let's develop it and test it in this population,' that can make for a better process," Spellecy says.

At Lurie Children's Hospital, the available tools and resources were adult-focused. The video was developed as a tool that could help educate the children and their families.

Families helped develop the video. "We designed the video with focus groups and our stakeholders as part of the process," Macha says. "Our group is a mix of people who came together around this idea of wanting to create more educational tools for researchers to use and for our patients to help them understand research."

The hospital has a board of pediatric patients that provides input as needed.

"Our institution has a children's advisory board of volunteer kids who are patients in the hospital, and they give advice on designing rooms, decorations, and more," she says.

A research integrity group created a whiteboard animation video called "What Is Research?" The three-minute video shows hand-drawn pictures illustrating a narration about what taking part in a research study is like. It was designed to be used for both guardian consent and children's assent.

"We targeted the video to children and their families," Macha says. "We expect it to be used as an adjunct in the consent process."

The video focuses on these main areas:

- research is voluntary and a person can choose to be in it;
- researchers keep the person's participation and information private;
- a study is reviewed by an IRB to make certain it is safe and that participants' rights and welfare are protected;
- a person can volunteer to participate in the study but also can leave at any time, and pulling out of the study would not impact the patient's medical care.

Involving potential participants in developing the video is similar to other ways researchers engage stakeholders.

"This is patient-centered outcomes research initiative [PCORI] style," Macha says. "PCORI is an initiative the National Institutes of Health started to make research more tailored to people who would be in the research."

Potential participants are brought in to help with design and research questions, in all stages of research development. "It's a good model to bring in people who will take part in the study, your target audience, and bring them in to be more engaged in the process," Macha says.

The group showed the children's advisory board the video and obtained feedback on character development, how to focus the story, and what kinds of words and language to use in the video.

"We also brought in a family advisory board, so we had feedback from patients and their parents," she adds. "They helped us with feedback on images and timing."

After developing the video script, with the children's help, they partnered with a professional media company to create the animation.

Children offered helpful suggestions. For example, the story was organized around the idea of a very important participant, or VIP. To illustrate these child VIPs, the original storyboard showed them wearing sunglasses, as celebrities might wear in public.

"They were wearing what we adults thought would be cool," Macha says. "Every kid asked, 'Why

are they all blind?'" The sunglasses were scrapped.

The children also helped ensure the video's words were appropriate and that the message was clear.

"As part of the team, we also had health literacy experts and an ethics committee review the script and storyboard," she says.

"We went back to the kids and the other advisor groups after it was done, and they all really liked the video and thought it was great," Macha says. "We showed it to the leadership at the hospital, and the overall perception was good."

Once the finalized video was approved, the research committee was surveyed for additional feedback.

"We did a pre- and post-survey to assess participants' comprehension of principles and ideas in the video," Macha says. "In our convenience sample, we asked people in our cafeteria and in other public spaces whether they would take a short survey before and after watching the video."

Then they were asked questions to assess comprehension. "A statistical analysis found that the majority of people — both children and adults — showed an improvement in comprehension," she adds.

"The goal of the video was to improve understanding and decision-making and not to say 'yes' to participating in research," she notes. "There seemed to be more interest in learning what research was after viewing it."

Once rolled out, the goal is to make the video available on the hospital's internal circuit television and to upload on iPads for study coordinators to use in clinical research, Macha says.

The video's broad information about research makes it useful for any clinical trial consent and participation.

"Study coordinators seemed interested in the video and thought it might help with study recruitment," she says. "It's short enough they could use it to answer questions."

The next step would be a video library to explain other research topics, such as randomization and biobanking, Macha notes.

"Videos could be available during the study or consent process, and we've had groups reach out to us within the institution about creating clinical videos as well," she adds. ■

IRB Overhauls Its Minutes Template, Saving Time and Reducing Words

New process saved two days

The IRB's meeting minutes process was too long, too wordy, and inefficient.

That was the conclusion reached by the office of research/responsible research practices at The Ohio State University (OSU) in Columbus.

"Our minutes' process was exceedingly lengthy, especially when compared with other institutions we had talked to," says **Paul Montesanti**, CIP, senior IRB protocol analyst at OSU.

The IRB and research office decided changes were needed.

"We convened a working group, and the first thing we did was take a look at the regulations," says **Erin M. Odor**, MA, CIP, quality improvement specialist at OSU.

The working group also consulted guidance from the Association for the Accreditation of Human Research Protection Programs (AAHRPP). They checked records of site visits and warning letters of deficiencies by regulators.

"We reached out to peer institutions, including commercial IRBs and other institutions," Odor adds.

The revised minutes template was completed before an AARHPP visit in fall 2017. The IRB took into consideration the accrediting organization's feedback, which was mostly positive, she says.

After revising the template IRB meeting minutes, the median time between when the IRB meeting took place and when the minutes were sent to investigators declined by about two days.

"This is a really good improvement from the investigator's perspective," Odor notes.

Before, the minutes of the Monday meetings might be written and sent to the IRB chair for approval by Friday afternoon. This meant that investigators would not receive a copy of the minutes until the following week.

"Once we got the draft's time down to a median of two calendar days, we got correspondence out the same week," Odor explains.

Before the revision, 23% of

minutes were sent out within the same week as the IRB meeting, Montesanti says. Now, 63% of minutes are sent out during the same week.

"If our IRB chairs took no more than one business day to review the minutes, we could get 90% sent out in the same week," Odor says.

The following are the main changes to the minutes template:

• Switch from narrative to table format. "The old version of the minutes was prose narrative with several sections of prose that described different parts of regulator findings that we wanted to include in the minutes," Montesanti says. "We moved it to more of a table format, considerably stripped down when compared with the original one."

The new format contains some prose, including one section that describes the board's discussion and another that outlines specific regulatory criteria for waivers, he says.

This change eliminated long summaries of research, which are contained in other IRB records, and duplicate summaries of requested changes. Also, the main determinations were simplified to a couple of words, instead of whole sentences.

But most of the new format is in simple tables. Average total word count is 2,000 words — 20% less than the old format.

The change also made senior staff review of minutes unnecessary and reduced staff time spent writing information into the minutes before meetings.[1]

• Meeting minutes follow a summary of required elements. Most of the regulatory information to which the IRB might refer in a board meeting is documented in other paperwork and not included in the meeting minutes, Odor says.

The working group created a summary of required and recommended elements of IRB meeting minutes, including items that are required by federal agencies, recommended by federal agencies, and required by AAHRPP. Asterisks after an element indicate this item might be documented elsewhere in IRB records.

Here is a sample of the required and recommended elements related to actions taken by the IRB:

- approve, require modifications to secure approval, disapprove, suspension, or termination of IRB approval;
- actions related to review of events requiring prompt reporting;
- basis for requiring changes, disapproval, or suspension/termination;
- separate deliberations for each action;
- effective date of approval;
- approval period (initial and continuing review);
- process to ensure conditions/modifications are met.

• Simplify input for meeting minutes. The OSU IRB uses a Word template that is completed after meetings, Montesanti says.

"We take notes during the meeting, and then after the meeting, we finish composing the minutes in the Word document," he explains. "We also have a data document we make that includes all of the studies on the meeting list, and we also use that to create minutes."

One early hope was to create a template that was so simple it could be completed during the meeting, Odor notes.

"It turned out that wasn't feasible. There still is clean-up work required, especially with lengthier discussions," she says. "We are able to do some of the work ahead of time, and we do some of the writing at the meeting."

Also, IRB staff can manually copy information from the electronic system, including the study title, principal investigator's name, sponsor, and changes requested, into the template using an autofill process, she adds.

"Our hope is that our meeting electronic system down the road will be smart enough we can do a report and check these boxes in the meeting, so we don't have to do it manually," Odor says. "We're not there yet, but we're moving in that direction, and that's one of our long-term goals." ■

REFERENCE

1. Odor EM, Montesanti PM. Every minute counts: improving the IRB minutes process. Poster presented at the 2018 PRIM&R conference: Poster 44.

IRBs Can Learn to Deal With Medical Innovation Ambiguity

The lines between research and medical innovation can be blurry. When does a new surgical practice cross from case study to a study that must adhere to human research protection regulations?

"This issue has hit our IRB," says **Stephanie Solomon Cargill**, PhD, associate professor at the Center for Health Care Ethics at Saint Louis (MO) University.

"We've had several situations where we get minimal risk, retrospective studies coming into the IRB, and they were doing pretty risky and outside-of-standard-of-care procedures," Cargill says. "But they were doing these studies under the auspices of medical innovation."

When physicians say their procedure is medical innovation and then they later want to evaluate their results retrospectively, they are not scrutinized by an IRB because it is a retrospective study, Cargill says.

"A lot of times when retrospective studies come to IRBs, they don't make a big issue out of it because it's minimal risk," she says. "But it's unclear how an IRB would know if medical innovation were happening clinically."

For example, if a researcher tells a journal that the submitted paper describes a prospective study, but the researcher received approval from the IRB for a retrospective study, then this is a discrepancy that needs to be resolved, she says.

IRBs do not want to be too restrictive, forbidding physicians from going outside the standard of care and engaging in medical innovations. But they also do not want researchers to take advantage of IRBs by submitting studies that clearly should have been subject to full board review as retrospective studies, Cargill says.

Those kinds of cases show that IRBs should have policies and procedures in place that clearly state how and when researchers can use medical innovation and retrospective studies when sending their protocols to the IRBs.

"We've reviewed literature of surgical innovation, and we've noticed it happening in radiology and other areas that are not just surgeries," she says.

If a physician has performed an innovative procedure once or twice, then it is feasible and legitimate to consider this a medical innovation. The physician could write these examples as retrospective review or case studies that do not require IRB review.

Suppose the physician performed the medical innovation with multiple patients over a long period of time and wants to publish results as though these were clinical research outcomes. This is different and probably should not be submitted to the IRB as a retrospective study. Instead, the physician should submit the procedure for IRB review prospectively, Cargill says.

"Can we distinguish between having a legitimate space for clinicians to work things out and then saying, 'Hey, let's write this up as a study,' as opposed to their thinking, 'We know we want to get published for this, but we don't want to go through the study and tell patients what we're going to do,'" she explains.

Clinicians might think their medical innovations are low-risk when there is very little evidence for that view. These procedures are not endorsed by their profession, she says.

For instance, surgeons can access surgery innovation committees before performing a procedure that is further outside standard of care. This provides checks and balances.

"There should be some extra level of oversight," Cargill says.

IRBs need to have some guidance on procedures performed for clinical purposes, benefiting a patient, or for research purposes when it might establish the effectiveness of a procedure, she adds.

The goal is to develop documents that help clinicians assess whether their procedures constitute medical innovation or research, Cargill says.

"We're a working group with members that include a general counsel, a surgeon, an IRB staff person, and someone from compliance," she says. "We sat down together to work on coming up with policies and recommendations that work for our institution."

"We give the guidance to department chairs, telling them that if someone in their department is doing those procedures, then here are the questions they should ask them," she adds.

"There are two paths: medical innovation path, which doesn't have to be research, but there needs to be specific informed consent, and then there's the research path."

When an institution writes a policy to distinguish between medical innovation and research, the policy should be promoted as a way to enhance institutional and clinician legal protection and provide human research protection.

"Without any kind of oversight, if something goes wrong with a medical innovation and a patient sues, there's no malpractice protection," she says. "So it's about whether they are consenting patients so patients know what they are getting into."

Also, clinicians should have limits placed on what types of studies they can publish without proactive IRB review.

"We've discussed requiring any publication of results to be limited to structured case reports, proof of concept articles, or retrospective case studies — if under five cases," Cargill says.

The goal is to not make patients unwitting research participants. "If it's being sold to patients as something that is the best thing for them, and 'I'm acting as your clinician,' that's a big ethical question," she explains. ■

OHRP Issues Guidance on Public Health Surveillance vs. Research

The Office for Human Research Protections (OHRP) recently published new draft guidance to clarify the difference between human research that might require IRB review and public health surveillance that is not defined as research.

The OHRP recommendation is that activities supported by the U.S. Department of Health and Human Services (HHS) and initiated on or after Jan. 21, 2019, comply with the revised Common Rule. There are additional categories of nonresearch activities under 45CFR 46.102. *(The guidance can be found at: http://bit.ly/2AyK1RX.)*

The research definition remains the same: "A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

HHS recognizes that the requirements of 45 CFR part 46 should not impede a public health authority's ability to accomplish its mandated mission to protect and maintain the health and welfare of the populations for which it is responsible, which is why this type of investigation is excluded from the definition of human research, according to **Julia G. Gorey**, JD.

"While the 2018 requirements retain the pre-2018 research definition as 'a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge,' public health surveillance activities is one of the categories of activities that have been explicitly deemed not to be research, to clarify that they do not fall within the scope of the regulations," adds Gorey, public health analyst in OHRP's division of policy and assurances and executive director of the Secretary's Advisory Committee on Human Research Protections.

The new draft guidance is intended to resolve uncertainties that existed in the regulated community concerning whether such activities were considered research, she says.

The guidance spells out four categories of activities that are deemed explicitly to not be research, providing clarity over what might have been ambiguous before the Common Rule changes:

• **Public health surveillance activities.** These include the collection and testing of information or biospecimens when conducted or authorized by a public health authority. This might be necessary for monitoring, identifying, assessing, or investigating disease outbreaks, public health trends, risk factors, disease patterns, and other conditions important to public health. These activities might be associated with a public health crisis following a natural or manmade disaster.

• **Scholarly and journalistic activities.** These include oral history, journalism, biography, literary criticism, legal research, and historical scholarship.

OHRP guidance, effective July 19, 2018, states that scholarly and journalistic activities often are conducted in fields that focus on the specific individuals about whom the information is collected and not to draw generalizations about other individuals or groups. *(This guidance can be found at: http://bit.ly/2P964DK.)*

• **Collection and analysis of biospecimens, records for criminal justice activities.** Activities involving the collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order, solely for criminal justice or criminal investigative purposes, are not defined as research.

• **Intelligence operations.** Authorized operational activities, determined by each agency, in support of intelligence, homeland security, defense, or other national security missions are not defined as research. *(More information is available at: http://bit.ly/2RoONIS.)* ■

IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **The FDA's recent proposed rule regarding human research includes four criteria from the Common Rule that stipulate when an informed consent waiver is allowable. Which criterion did the FDA exclude?**
   a. If research involving identifiable information or biospecimens cannot practicably be carried out without using such information in an identifiable format.
   b. If the clinical investigation involves no more than minimal risk to the subjects.
   c. If the waiver or alteration of informed consent will not adversely affect the rights and welfare of the subjects.
   d. If the clinical investigation could not practicably be carried out without the waiver or alteration of informed consent.

2. **Which of the following is an ethical question raised by HIV cure clinical trials?**
   a. Should investigators include regulatory agencies as they initiate these studies?
   b. How can investigators and IRBs ensure study participants fully understand the study's risks and benefits?
   c. What is the definition of a "cure" in HIV research?
   d. All of the above

3. **Which of the following is not a needed element of meeting minutes?**
   a. Require modifications to secure approval, disapprove, suspension, or termination of IRB approval
   b. List of outcomes of similar studies
   c. Actions related to review of events requiring prompt reporting
   d. Basis for requiring changes, disapproval, or suspension/termination

4. **OHRP recently published draft guidance to clarify the difference between human research that might require IRB review and other, nonresearch activities. Which nonresearch activities might involve monitoring, identifying, assessing, or investigating disease outbreaks?**
   a. Scholarly and journalistic activities
   b. Criminal justice activities
   c. Public health surveillance activities
   d. Intelligence activities