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INSIDE

RELIAS MEDIA

Low Health Literacy Is Major Barrier to Research Participation

Watch for cues that patient is struggling

By Melinda Young, Author

Readability is a continuing problem with informed consent (IC) for research. It especially is a problem when participants struggle with low health literacy.

The revised Common Rule suggests ways to make the informed consent process simpler and easier to understand. But there are many people who still struggle when reading an IC form written with a first-page summary and with sentences understandable to middle schoolers.

Researchers assessing readability of sample informed consent forms approved by IRBs between 2013 and 2015 found that the mean readability was 10th grade. After a plain-language IC template was developed and used, the readability was seventh grade.[1]

"Our federally qualified health center has patients with low health literacy — low literacy, period — and limited English proficiency," says **Parinda Khatri**, PhD, chief clinical officer at Cherokee Health Systems in Knoxville, TN.

> THERE ARE MANY PEOPLE WHO STILL STRUGGLE WHEN READING AN IC FORM WRITTEN WITH A FIRST-PAGE SUMMARY AND WITH SENTENCES UNDERSTANDABLE TO MIDDLE SCHOOLERS.

Researchers may design an informed consent form at a fifth-grade reading level, but even that is too high, Khatri says.

"All of our forms are at a fourth-grade reading level," she says.

Khatri was a co-author of a study of informed consent materials used with people of low or very low health literacy. The study collected data on how IRBs and researchers can refine

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IC materials to suit a low literacy population. *(See story about study, page 15.)*

The findings still are being analyzed, but the experience suggested that people preferred video media with real people instead of animation. Researchers also learned which words and phrases were too difficult for the cohort to understand, and their comfort with technology was very limited.[2]

Research institutions should make an effort to make informed consent understandable to people with low health literacy for the sake of enrolling a more diverse population of participants, Khatri says.

"If we want to have more underrepresented populations involved in biomedical research, we need to tackle this issue," she says.

For example, some people will not understand that a study is referring to medications when it mentions "drugs," she says.

Other medical words they might not understand are "biobank" and "electronic health record," says **Vanessa Barone**, MPH, research scientist at Sage Bionetworks in Seattle. Barone is the low health literacy study's primary author.

"Some people will know the words 'electronic' and 'health' but not 'electronic health record,'" Barone says.

Low health literacy is not always easy to identify. People are clever at hiding their difficulty understanding or reading an informed consent document.

"Some folks will say, 'I left my glasses at home,' or 'I don't have my phone with me today.' This is very common," says **Kathleen Keogh**, LMSW, program manager at HRHCare in Peekskill, NY. Keogh also was involved in the low health literacy study.

"You hear these reasons, and you don't know whether they are unable to read or not able to use the computer, or maybe they did just forget their glasses," she says. "That was something we noticed time and again."

Participants with low technology skills might ask for support or simply say, "I don't like computers or cellphones," Keogh notes.

For these reasons, investigators should watch for cues that a person is struggling reading or understanding the informed consent form, she says.

There's a stigma with low literacy, and people use their glasses as an excuse or ask if they can take the form home and bring it back because they don't want to admit that they are going to have family members read it to them. When researchers hear those words, they might think they are a proxy for low health literacy, Khatri says.

"They might say their head hurts, so can they take it home, and we have learned to say, 'How about if we read this to you and give you a copy to take home?'" Khatri says. "Often, people will say, 'Yes, I will do that if you can read it to me.'"

Other clues of low literacy include participants who just scan the document and sign it. Researchers also can give participants a copy to share with family members or friends, she adds.

Improvements to informed consent's readability can benefit all participants — not just those with literacy issues. One study found that research participants had significantly better understanding of the research when given a simplified informed consent form, compared with those who received a standard form. The study's findings were true for those with typical health literacy, as well as those with low health literacy.[3]

Health Literacy and All of Us

The All of Us Research Program is a National Institutes of Health (NIH) initiative that is building a national cohort of 1 million-plus Americans. People are participating through electronic enrollment and informed consent. Its goal is to extend precision medicine to all diseases. *(Read more about All of Us at: https://allofus.nih.gov/.)*

A recent study about electronic informed consent and readability found that most participants benefited more from e-consent, noting that it was easier to understand and use and more interesting. Some rural participants had accessibility and privacy concerns about e-consent, and some minority participants had computer literacy and trust barriers.[4]

The All of Us Research Program has to use e-consent because it will enroll its 1 million participants online over a five-year period, Barone says.

What will help is the use of videos and visual aids.

"The videos are a game-changer," Khatri says. "People watch those videos and then say, 'Oh, now I get it.'"

For instance, a video will show a research participant's blood and what happens to the blood at a biobank.

The videos also ensure consistency in the informed consent process.

"You don't have 1,000 research assistants saying 1,000 different things," Khatri says. "Instead, there is a media aid to enhance understanding and comprehension of the consent process."

As soon as a prospective participant provides contact information online to All of Us, a video plays and moves to the next screen of informed consent. Each screen has some text and a video to elaborate on the text, Keogh says.

"It's a very new program, but from all of our experiences and what we've seen so far, I feel confident about the informed consent," Keogh adds.

"It's not just one long informed consent form with a lot of different words and scientific jargon; there's a real effort to help people who learn in multiple ways — text, video, visual aspect, auditory," she adds. "It's geared to cater to lots of different audiences." ■

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Study Sheds Light on Improving Informed Consent Readability

Many Americans have basic or lower literacy

A small study about improving readability of informed consent examines how investigators and IRBs can make research understandable to people with very limited reading skills.

The NIH plans to enroll at least 1 million people in its All of Us research program over the next five years. People will volunteer online and receive electronic informed consent.

The goal of All of Us is to reach Americans from all walks of life, including populations that are underrepresented in most human subjects research. Investigators decided to study whether the project's electronic informed consent was understandable to people with low and very low health literacy. *(The study, titled* Did I Lose You*, can be found at: http://bit.ly/2LuNIx3.)*

Researchers interviewed 18 people — half individually and half in focus groups. They partnered with four federally qualified health centers, says **Vanessa Barone**, MPH, research scientist at Sage Bionetworks in Seattle and lead author of the study.

"When the All of Us study launched, we knew we'd have to go back and look at informed consent because literacy was an issue," Barone says.

"One in five people in the United States has below a sixth-grade reading level, and we want to make sure the All of Us research program is enrolling a million people and specifically looking at underrepresented populations," she explains. "We want to make sure the program can enroll people from diverse backgrounds and who also have lower health literacy."

This goal of reaching everyone, regardless of their literacy level, is extremely important to the program, she notes.

About 14% of U.S. adults have below basic health literacy. This means they can only read a short set of instructions or identify what they can drink before a medical test. And only 12% of Americans have proficient health literacy, meaning they can use a table and calculate a worker's share of health insurance costs for a year, according to the U.S. Department of Health & Human Services, Office of Disease Prevention and Health Promotion. *(http://bit.ly/2EHtdMZ)*

In most clinical trials, there is someone who helps research participants understand the informed consent document and answers any questions they might have. With the electronic informed consent for the All of Us project, participants will be able to go through the e-consent process wherever and whenever they want without a face-to-face informed consent meeting, Barone says.

The smaller study was designed to find out how well people with low literacy and low technology skills understood the e-consent process.

The low literacy focus groups provided very useful information about this population, including these insights, Barone says:

- low literacy participants sometimes struggled to distinguish between research and clinical care;
- they tended to have low technology use;
- some people with low literacy relied heavily on their families and friends to deal with the barriers created by their lack of literacy;
- there were a number of common research terms they did not understand.

Focus groups also asked questions about blood collections, what participation would cost, whether they could see their lab results, and why investigators needed their blood, DNA, and medical records, Barone says.

"They asked, 'If I participate in this study, who will see my information?'" she adds.

The participants used electronic consent instead of paper consent, and for some people, that was a problem, she notes.

Underrepresented and low health literacy populations often find ways around their barriers to understanding written information, says **Kathleen Keogh**, LMSW, program manager, HRHCare in Peekskill, NY.

"One thing I've seen throughout working with these folks is their resourcefulness," Keogh says.

"If they're not learning by reading, they are leveraging social networks, seeking different media, asking questions, and having a really strong foundation of family and friends and other people they can rely on for a lot of the information they need."

This surprised Keogh, who says she didn't realize how strongly people would rely on and trust others to get needed information.

The same resourcefulness was true of people with low technology skills.

"Some people said technology was less of an issue because they had the support of their families, and if they didn't understand something, they could ask their children or someone else about it," Barone explains.

"For people who were more isolated, it was a much greater barrier for them."

The goal is to use these insights to improve the All of Us study's informed consent, she adds.

"The core value of the program is to enroll a diverse population from underrepresented populations," Barone says. ■

Right to Try Off to a Cautious Start

Will law emerge as an alternative to expanded access?

While the federal Right to Try law enacted last year essentially bypassed IRB oversight of patients seeking investigational drugs, research ethics panels and their institutions can codify a requirement for local oversight into their policies and procedures, says **Alison Bateman-House**, PhD, MPH, MA, assistant professor in the Division of Medical Ethics at New York University Langone Medical Center.

Bateman-House and her colleagues at the NYU School of Medicine Working Group on Compassionate Use and Preapproval Access (CUPA) have been following Right to Try closely.

"IRBs are cut out. There is no need for a [Right to Try] proposal to go through an IRB, which is one of the reasons that I'm not in favor of it," she tells *IRB Advisor*.

However, IRBs can make review required at the local level simply by mandating oversight in their institution's standard operating procedures (SOPs) for investigational new drugs sought through the Right to Try pathway.

"Just because the law does not say that an IRB is required, does not mean that you can't put in your own SOP that says it must be [reviewed by the IRB]," Bateman-House says. "I actually think that would alleviate some of my concerns about Right to Try."

Despite the hue and cry accompanying its passage on May 30, 2018, the federal Right to Try Act seems to have had little impact thus far. The Right to Try law is aimed at increasing access to investigational products for those with life-threatening illness who have no other medical options and are unable to join a clinical trial. However, the general consensus after the bill was passed was that the expanded access pathway to experimental drugs currently in place at the FDA will continue to be the preferred method. *(See* IRB Advisor*, July 2018.)*

In addition to the federal law, 41 states have enacted Right to Try laws. Both the state law in California and the federal Right to Try statute were cited in a recent decision by clinicians at the University of California Irvine to administer an experimental drug to a brain cancer patient.

"UCI worked to meet the regulatory and compliance requirements of both the state and federal Right to Try laws before starting treatment," **John Murray**, a public information officer for UCI Health, told *IRB Advisor*.

The university and ERC-USA initiated treatment with the company's investigational compound ERC1671, which is known as Gliovac in Europe. The therapy is being administered to a patient with aggressive brain cancer who did not qualify for an ongoing clinical trial of ERC1671 in the U.S. According to the company, the compound is a vaccine comprised in part of freshly extracted tumor cells and lysates designed to stimulate the immune system to target cancer cells.

Daniela Bota, MD, PhD, medical director of the UCI Health Comprehensive Brain Tumor Program, issued the following statement: "We are gratified to have the opportunity to offer options for this aggressive cancer, as current treatment modalities have proven unsuccessful," she said. "The Right to Try laws may be the only alternative for many patients who may not qualify for clinical trials based on a variety of factors, including progression of disease, comorbidities, existing medications, physical limitations, and others."

In a recently updated Question and Answer section on its website, CUPA states that "as with expanded access, Right to Try does not require companies to grant patients' requests for their investigational products. Furthermore, companies that are willing to provide nontrial preapproval access are able to choose whether to do so via Right to Try, expanded access, or both. … At present, CUPA is unaware of any patients who have accessed investigational medical products through the federal Right to Try pathway."[1]

The law also requires companies to submit annual reports on Right to Try usage to the FDA, and for participating physicians to have liability insurance, CUPA notes.

"We are trying to give a little bit of guidance based on the drips and drabs that have come out from either FDA or from lawyers," Bateman-House says. "We are still waiting to find out exactly how it would work. But patients have been desperately clamoring, so we tried to update it, explain what it was, and to the small extent that we can, fill in some of the questions."

For example, on a question on

whether Right to Try or expanded access would provide faster access to investigational drugs, CUPA answered:

"It is CUPA's assessment that the slowest part of nontrial preapproval access likely occurs at the company level. Because both Right to Try and expanded access entail waiting for a response from the company developing the investigational product, both pathways will be affected by this time lag. FDA review, which is required for expanded access but not Right to Try, is quick: same day for emergencies and, on average, within four days for nonemergencies. … Regardless of whether Right to Try eventually proves to be a fast pathway, CUPA does not believe that any gain in speed is worth the loss of oversight by independent, expert third parties (the FDA and an IRB)."

To press the point home, CUPA answered a question about the importance of FDA oversight by citing the infamous thalidomide birth defects in the 1960s. The incident "spurred FDA regulations requiring drug companies to prove that their products are both safe and effective before they would be approved. The thalidomide tragedy demonstrated the unexpected yet devastating potential toxicities associated with drug treatment."

For its part, the FDA, which was essentially cut out of the Right to Try Act as well, is providing information on a recently posted webpage. The FDA cites three decades of helping patients through its expanded access program and provides basic information on patient eligibility for Right to Try.

The FDA cites the following criteria for patient eligibility:

- diagnosed with a life-threatening disease or condition;
- exhausted approved treatment options and is unable to participate in a clinical trial involving the drug;
- provided, or their legally authorized representative has provided, written informed consent regarding the eligible investigational drug to the treating physician.

However, the FDA ultimately refers patients to their physicians and to the drug companies.

"If you are interested in Right to Try, you should discuss this pathway with your licensed physician," the FDA states. "Companies who develop and make drugs and biologics, also known as sponsors, can provide information about whether their drug/biologic is considered an eligible investigational drug under Right to Try and if they are able to provide the drug/biologic under the act."

Thus, FDA Commissioner **Scott Gottlieb**, MD, seems to be trying to finesse the issue to some extent, providing information on Right to Try but referring patients to doctors and drug companies if they want to pursue the path.

"The FDA is a political organization, and it has to do what it is told to do by the president or the legislative branch," Bateman-House says. "When the whole Right to Try thing was going down, Gottlieb told the House of Representatives — I was there testifying as well — that it was not a good idea and that he personally didn't think that the FDA was the holdup in people getting access."

Indeed, Bateman-House says both she and Gottlieb advised that pharmaceutical companies were the key stakeholders and control the supply of investigational drugs to patients. Expanding on this point, CUPA's recently updated answer on this question points to what may be the Achilles' heel of Right to Try.

"Many companies see no upside to providing their investigational products through Right to Try," CUPA states on its website. "If a product appears to be safe and/or effective in the expanded access setting, a company may wish to include that information in the paperwork submitted when it seeks marketing approval from the FDA. If a product appears to cause harm in the expanded access setting, a company will want to be able to say that there was FDA oversight of the product's use outside of clinical trials." ■

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FDA Unveils Real-World Data Initiative

'Less intense' clinical trial complements standard research

The FDA recently opened a promising path to capture real-world data and evidence to complement traditional clinical trials and open new avenues of research.

"Framework for FDA's Real-World Evidence Program" fulfills a 2016 requirement in the 21st Century Cures Act that the FDA use real-world data (RWD) and evidence to improve interventions and treatments. According to the FDA report, RWD may "include data derived from electronic health records; medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices."[1]

The idea is to use such data to "develop information and real-world evidence (RWE) that can better inform regulatory decisions," FDA Commissioner **Scott Gottlieb**, MD, said in a statement. "Because they include data covering the experience of physicians and patients with the actual use of new treatments in practice — and not just in research studies — the collective evaluation of these data sources has the potential to inform clinical decision-making by patients and providers."

The FDA action was hailed by a medical ethicist in the Working Group on Compassionate Use and Pre-Approval Access (CUPA) at New York University School of Medicine. CUPA has been pursuing a similar idea in a new project called Ethics and Real-World Evidence (ERWE), says **Alison Bateman-House**, PhD, MPH, MA, assistant professor in the division of medical ethics at NYU Langone Medical Center.

This "clinical trial light" approach for real-world evidence may ultimately provide greater patient access to needed effective drugs and treatments, she says.

> "WE CAN'T FIX ALL OF THIS WITH THIS PARTICULAR POLICY PUSH, BUT THE IDEA BEHIND THIS IS WHAT IF YOU SET UP A CLINICAL TRIAL OF THE PEOPLE WHO DID NOT MEET THE CLINICAL TRIAL CRITERIA?"

"We have been sort of this crazy voice in the wilderness talking about it," Bateman-House says. "The FDA is now saying it looks like it would be useful data. It looks like it is actually happening. I'm sure we will run into some unintended consequences along the way, but I'm personally really excited about it."

It removes an initial hurdle, which is that physicians are much more familiar with clinical trials than with nontrial investigational drug pathways like expanded access and right to try, she explains.

"Clinical trials typically involve payment to the doctors, which expanded access doesn't," Bateman-House says. "So that will knock down another disincentive."

For example, many physicians in the neurological disease community do not seek FDA expanded access "because they don't get reimbursed for their time, and that makes their hospitals unhappy," she says.

The RWD movement has the potential to tap into resources that bring in people typically excluded from clinical trials for various reasons, she adds.

"Sometimes, people are too sick to be in trials — they have comorbidities that keep them from meeting the [inclusion] criteria," she says. Sometimes, they live too far away or face other barriers and obstacles to get into clinical trials.

"We can't fix all of this with this particular policy push, but the idea behind this is what if you set up a clinical trial of the people who did not meet the clinical trial criteria?" Bateman-House says. "A less intense clinical trial, where maybe you don't have to go in for as many clinical scans or have as much bloodwork but investigators still track you and get information."

There appear to be incentives for research companies to support RWE programs, which could bring in research subjects that reflect a broader range of people and may show better product efficacy in the general population after market, she notes.

"One of the huge problems with clinical trials is that with the people who get into clinical trials, you come out with data on blood pressure, for example, and [the product] is approved by the FDA, goes on the

market, and doesn't work," she says. "Unfortunately, we see this all too frequently with approved drugs."

IRBs would still have an oversight role, although the FDA is preparing to use more electronic verification measures as demanded by the various data sources.

"It's set up like a clinical trial, so IRBs would have the exact same role, though the data measures may be less frequent and/or less intensive," Bateman-House says. "For example, instead of going in every two weeks for a blood draw and a scan, maybe these patients would have one at intake and then another at four weeks in."

The use of electronic health records (EHRs) and other "data-capture technology, together with new trial and study designs using RWD, has the potential to streamline and improve the efficiency of clinical studies," the FDA report states. "Nevertheless, these advances may also raise new questions about the applicability of certain regulatory requirements, including requirements for informed consent and appropriate oversight and monitoring."

The FDA has previously issued guidance documents to capture electronic data while "maintaining adequate documentation for FDA to validate the source and reliability of the data," according to the report. "…Additional guidance may be needed to address different study designs using RWD to generate RWE for effectiveness determinations."

Hybrid Design

As described in the framework document, clinical trials may use a hybrid design that could include "collection and analysis of RWD extracted from medical claims, EHRs, or laboratory and pharmacy databases."

The FDA notes that researchers could collect other data using methods typical of a traditional clinical trial. A hybrid trial could use RWD for one clinical outcome, while incorporating more conventional criteria and other endpoints for the more traditional arm of the study.

"Clinical trial designs can also include some elements that more closely resemble routine clinical practice, which are sometimes described as 'pragmatic' elements," the report states. "These pragmatic clinical trials often rely on RWD and have the potential to generate RWE."

In any case, real-world data could be used to "improve the efficiency of clinical trials" even if it does not reach the threshold of real-world evidence on a given product's effectiveness. FDA examples of this kind of RWD use include:

- "generating hypotheses for testing in randomized controlled trials;
- identifying drug development tools (including biomarker identification);
- assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial;
- identifying prognostic indicators or patient baseline characteristics for enrichment or stratification." ■

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Research Program Closely Monitors ClinicalTrials.gov Compliance

Site turns 19 in February

Compliance with the 2017 changes to ClinicalTrials.gov registration can be time-consuming, as at least one organization has learned over the past year.

"A lot of institutions started to take notice after the update of the existing rule because it appeared that more attention was going to be paid to ClinicalTrials.gov," says **Brian Brotzman**, CIP, senior compliance specialist and ClinicalTrials.gov PRS administrator in the human subjects office of the University of Iowa in Iowa City.

"Before the update to reporting requirements in 2017, there was not a lot of attention paid to ClinicalTrials.gov," Brotzman says. "A lot of what was going on was under the radar, so we had to go back and look at the records and get those up to date and make sure people who were supposed to register knew they were supposed to register."

The University of Iowa put Brotzman in the oversight role

to ensure investigators complied with rules for registering with ClinicalTrials.gov, which opened in February 2000. The results database was opened to the public in September 2008. *(View online at: http://bit.ly/2A6teGc.)*

More recently, the Department of Health and Human Services (HHS) issued changes to a final rule that went into effect on Jan. 18, 2017. *(Read more at: http://bit.ly/2QDe0Tz.)*

The changes include specifying how to submit data and require there to be only one responsible party for submitting information about an applicable clinical trial.[1]

"We're a community that works together," Brotzman says. "When this new final rule came into effect and there was a lot more attention being paid to ClinicalTrials.gov registration, we did our background work. We looked into what the expectations were."

They soon realized compliance work and oversight of more than 200 clinical trial investigators would require team effort. They formed a ClinicalTrials.gov working group with representatives from different departments.

Prior to Brotzman taking on the role of leading the working group, there were few procedures in place. "This was a whole new experience, so we could start from the ground up to get what we wanted, using the resources we had," he says.

The work has paid off. The institution is now compliant with all legacy studies. The records, since the working group started, grew from 162 to more than 400, and most are in compliance. Records are up to date as well, he says.

"We had pretty good success across the board in getting things caught up and maintaining it," Brotzman says.

Here is how the institution's successful registration compliance strategies worked:

• Address departmental concerns. "We identified the current concerns regarding ClinicalTrials.gov registration and identified support from different departments," he says.

Strategically, they approached departments that had researchers with the most studies registered on the government website. Then they asked the departments to nominate one or two people to help with compliance and to cover one or two hours of their time spent with the working group.

THE INSTITUTION IS NOW COMPLIANT WITH ALL LEGACY STUDIES. THE RECORDS, SINCE THE WORKING GROUP STARTED, GREW FROM 162 TO MORE THAN 400, AND MOST ARE IN COMPLIANCE.

Department heads were eager to learn more about the initiative and contribute to the program, he notes. Those nominated would be members of the ClinicalTrials.gov working group.

"We worked with them and trained them on using the ClinicalTrials.gov system, and since then, they have been an invaluable asset," Brotzman says.

Working group members educate researchers in their departments about the registration and provide help when asked, he adds.

"They're training researchers that we otherwise would not be able to reach on a regular basis," Brotzman says.

• Provide training on using the system. The working group's initial training was on how to use the system, enter data, and respond to system users.

"We spent three months getting everybody trained and up to speed," Brotzman says. "We met monthly after that to address ongoing issues and to continue to provide training as needed."

Training included case examples. The working group also discussed ideas and solutions as they met, including any updates or news from ClinicalTrials.gov.

As working group members trained others on how to be compliant with the government website's registration policies, they listened to feedback from investigators and reported on what they learned at the monthly meetings, he says. Working group members also stay in touch between meetings.

• Monitor registration compliance. One of the most common compliance problems involves investigators not registering as required on ClinicalTrials.gov, Brotzman says.

"This is probably consistent at other universities, as well," he notes. "Another problem is when those who have registered are not keeping their records up to date and accurate."

The 2017 final rule states that a responsible party has to register the clinical trial within 21 days after enrolling the first human research participant. The registration must include descriptive information, recruitment information, location and contact information, and administrative data elements.[1]

ClinicalTrials.gov also keeps a

list of problems. Any registrations where the date has passed are automatically generated on the list. If an investigator has not updated the record within the past year, the research institution receives a notice, Brotzman says.

"As administrator, I oversee the entire registration for our institution," he explains. "Anytime I see an issue come up, I communicate directly with the working group member who will take it to the department and address it there."

Brotzman sends working group members daily messages, if needed. "Anytime a registration is not submitted on time or is not fully addressed, it is put on the problem list," he says.

The working group found compliance problems that involved registrations that were accurate, but the researcher had not reported results as required. There were noncompliant studies completed years earlier and the investigators were no longer at the institution, he says.

"We had to track down the data and get everything back on track," Brotzman says.

While the problem list typically has 50 to 60 records, most are for minor problems that can quickly be addressed, he adds.

• Submit checklist to IRB. The institution has a clinical trial checklist form that researchers complete and submit to the IRB with their research application after obtaining a ClinicalTrials.gov departmental liaison signature.

"It's a robust form for the IRB to review before making their decision," Brotzman says.

The following are some sample items from the University of Iowa's form, which was adapted from ClinicalTrials.gov material:

- Is the study interventional (a clinical trial)?
- Is there at least one study facility located in the United States or a U.S. territory?
- Is the study conducted under a U.S. FDA investigational new drug (IND) application?
- Does the study evaluate at least one drug, biological, or device product regulated by the FDA? ■

REFERENCE

1. Clinical trials registration and results information submission. *Fed Reg.* 2016;81(183):64982-65157.

Earning the Trust of Research Subjects

Overcoming the past to improve health in the future

With the long shadow of past atrocities hanging over human research, IRBs and their partners must act with intention to cultivate trust in subjects. By engendering all aspects of the program with this trust, they can aspire to be acknowledged as a "trustworthy" institution, a bioethicist explains.

Achieving trust in human research can be challenging in an age of precision medicine that calls for long-term relationships and potential unintended consequences far beyond a simple informed consent document.

Q&A

Stephanie Kraft, JD, a bioethicist at Treuman Katz Center for Pediatric Bioethics at Seattle Children's Research Institute, wrote two papers[1,2] last year on the subject of trust in research. She discussed her findings with *IRB Advisor* in the following interview, which has been edited for length and clarity.

IRB Advisor: Part of your research included focus groups with racially and ethnically diverse people, who have certainly been subjected to historical abuses.

Kraft: We have a long legacy of not including or in many cases mistreating patients from minority groups. We are at a point now where we really need to be actively thinking about ways to build trust — to make sure we are not just building trust, but being trustworthy. We need to make sure we are earning the trust that researchers are asking patient participants to put in them.

We often think of research ethics in terms of informed consent. Consent is good and important, but it is not enough. It is not sufficient to really rebuild that trust and demonstrate it over the long-term. The consent form does not tell research subjects what they need to know to put trust in an institution.

IRB Advisor: What are the implications for restoring research trust for IRBs?

Kraft: This is really about oversight broadly — not just in terms of the IRB, although that is certainly part of it. What sort of structures does the IRB have in place? Do they have patient representation on their committees to oversee the research

and make sure that it is being done in an appropriate way? Have they vetted the researchers who are going to be doing future projects? These are some of the messages we heard from folks. It is not just, "Did I technically give permission to have my data used in the future?" Are there protective measures in place so that even if I don't fully understand what those future uses are, I know that [the data] will be used in an appropriate and trustworthy fashion?

IRB Advisor: You recommend addressing the role of history as part of restoring research trust. With the launch of the NIH All of Us Research Program, director Francis Collins, MD, observed in an interview that you'd better be ready to talk about Tuskegee if you ask an African-American to volunteer for research.

Kraft: Tuskegee is certainly something that comes up a lot, and not just among African-Americans. Many people have heard about Tuskegee and are aware of it. That legacy lives on beyond the African-American community in other people as well. Minority groups and nonminorities are aware that researchers have done really bad things in the past. This might give them pause when they are thinking about enrolling in research.

Tuskegee is one of many ways that we have mistreated people. [We need] to say we know that, we recognize that, and we are actively trying to overcome that — not to hide it or make false promises, but to say we are aware of that and here are the specific steps we are taking to move forward.

IRB Advisor: In that regard, in your research you also recommend addressing cultural values and communication barriers, and integrating "patient values and expectations into oversight and governance structures." Is this essentially a call for transparency?

Kraft: Absolutely. We are finding in a new study that there can be conflicts. You might talk to patient advisors and they will give recommendations and have certain perspectives on the best way of doing something. But then when you talk to the IRB, they may have a different perspective.

I think we could do a better job collectively of making sure that what we are doing from a regulatory perspective integrates with what patients are saying that they need and want. Not that we are necessarily going to say, "A patient said this, so therefore we have to do it." But I think we need to hear what patient preferences are.

To the extent that we don't think that we should follow those preferences, we need to make a strong ethical justification. In some cases, that might require revisiting and rethinking about the way we have done things from a regulatory perspective.

IRB Advisor: You use the word "deontological" to describe acting in good faith regardless of the outcome, which I interpret to mean research ethics are hardwired into the institution. You write that "a research institute must not merely generate patient/participant trust, it has a duty to be trustworthy." How can that designation be earned?

Kraft: A big part of it is the intentionality behind the activities that you do. Whatever you or the institution are doing to build trust needs to come with the intention of being a trustworthy institution.

It's hard to measure, but it is not about a marketing campaign to make sure that people trust us. It is the institution itself actually engaging in those values.

We can tell patients that we care about decreasing health disparities and increasing diversity in research participation. We can build up trust in that regard by saying lots of nice things, but on an internal basis, we have to make sure that our policies align with the goals we are putting forth. Are we taking the steps necessary to make sure as an institution that we are allowing and encouraging the steps to be taken to reach those goals? ■

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1. Kraft SA, Cho MK, Gillespie K, et al. Beyond Consent: Building Trusting Relationships with Diverse Populations in Precision Medicine Research. *American Journal of Bioethics*, 2018;18(4)3-20. DOI: 10.1080/15265161.2018.1431322.
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COMING IN FUTURE MONTHS

- Monitoring program helps use board members more efficiently
- Clickable outline improves IRB workflow, training
- Using plan-do-check-act to improve IRB application
- Enhance relationship with community through use of oversight board

IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **According to the U.S. Department of Health & Human Services, what percentage of American adults has below basic health literacy?**

   a. 5%
   b. 11%
   c. 14%
   d. 21%

2. **Which of the following is *not* required for a patient to be eligible under the Right to Try law?**

   a. Diagnosed with a life-threatening disease or condition
   b. Exhausted approved treatment options and is unable to participate in a clinical trial involving the drug
   c. Seeking a drug that has been approved by the FDA
   d. Provided written informed consent regarding the eligible investigational drug to the treating physician

3. **According to the FDA, real world data could improve the efficiency of clinical trials by generating hypotheses for testing in randomized controlled trials.**

   a. True
   b. False

4. **The National Institutes of Health issued changes in a final rule about ClinicalTrials.gov that went into effect on Jan. 18, 2017. Which of the following is a change it made to the existing registration for the website?**

   a. The changes include specifying how to submit data and require there to be only one responsible party for submitting information about an applicable clinical trial.
   b. The changes include requiring IRBs to submit every clinical trial they review to ClinicalTrials.gov, regardless of funding source.
   c. Having each research institution governed by ClinicalTrials.gov to provide at least 10 hours per year of staff time to overseeing and monitoring the website's submissions.
   d. All of the above