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INSIDE

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All of Us: NIH Looks to the Future, Tries to Overcome the Past

'This is one of the most important research programs in history'

By Gary Evans, Medical Writer

Trying to address "big data" threats to privacy and step out of the long shadow of human research travesties, the National Institutes of Health (NIH) recently launched its ambitious All of Us project.

The NIH is seeking 1 million Americans reflecting a broad diversity of racial and socioeconomic conditions to volunteer as research subjects. The Precision Medicine Initiative (PMI) will use whole genome sequencing and other cutting-edge tools to create, aggregate, and analyze individual health data for years into the future.

How high are the stakes? The NIH launched the initiative on May 6, 2018, in multiple cities with a marketing and messaging campaign across the social media spectrum. The NIH is trying to reach out to ethnic and racial minorities that have previously been largely left out of clinical research or directly harmed by it. As **Francis Collins**, MD, director of the NIH, observed in an interview, you better be ready to talk about Tuskegee if you ask an African-American to volunteer for research.

> THE NIH "WILL HAVE TO OVERCOME A LONG HISTORY OF DISTRUST OF MEDICAL RESEARCH AMONG MANY MINORITY COMMUNITIES."

Extending the research into these communities falls in large part to **Dara Richardson-Heron**, MD, the chief engagement officer for the All of Us project.

"Our mission is to find 1 million or more people who reflect the rich diversity of our nation," she said at an opening ceremony in New York City. "We're seeking adults of all ages, races, ethnicities, sexual orientations, socioeconomic, and health statuses to join us in this unprecedented effort. We

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are seeking people from every corner of the U.S. because we know all too well that where a person lives has a tremendous impact to reflect on their overall health."

Many communities have a significantly higher disease burden than others, with health disparities well-known "but not at all well understood. Research has the potential to be a powerful change agent," she said.

The NIH is anticipating that some will view this recruitment with hesitancy, if not downright suspicion.

"There have been unspeakable instances where unethical testing and research was performed often under the guise of 'medical treatment,'" Richardson-Heron conceded. "In other cases, whole communities have not been invited to participate in research. Our program is different. We are fully acknowledging concerns head-on because we must. We are also collaborating with our participant partners to build a program with policies and processes in place to make sure that the transgressions of the past are never, ever repeated."

The program promises to "oversample" communities that have historically been underrepresented in medical research, which is a commendable goal, a human research legal scholar tells *IRB Advisor*.

The NIH "will have to overcome a long history of distrust of medical research among many minority communities," says **Carl H. Coleman**, JD, a professor of law at Seton Hall University in Orange, NJ. "This distrust is likely to be exacerbated by recent revelations about misuses of personal information by Facebook and others, which could make people reluctant to share the kind of data the researchers intend to collect."

Grand Design

In an opening ceremony in New York City, Collins said All of Us is among the most ambitious NIH research projects ever undertaken.

"More than almost anything we have done, this program has the potential to shed new light on how to manage disease and keep people healthy," Collins said. "I know that is a bold statement, but I truly believe this program will be a game-changer for medical research, and ultimately for human health."

Speaking at a similar ceremony in Detroit, Eric Dishman, director of All of Us, was no less enthusiastic.

"This is one of the most important research programs in human history — this has never been done before," he said.

That may not be much of an exaggeration, given the level of medical technology applied to an unprecedented population that is expected to be at least half representative of diverse demographics. In a personal aside, Dishman said access to whole genome medicine essentially saved his life.

"I am alive today because I was lucky enough to be one of the early prototype patients eligible for precision medicine," he said. "At 19, I was diagnosed with a rare form of kidney cancer and told I would be dead within nine months."

He survived the following two decades, undergoing rounds of chemotherapy that did not find its cancerous targets.

"I was eventually running out of options and a colleague of mine helped me get access to whole genome sequencing and to get my complete electronic health record together," Dishman said. "Armed with this new data, doctors could

understand my unique form of cancer and find the treatment that was 'for me.'"

Cancer-free, he became eligible for a kidney transplant.

"I am heathier standing before you today at age 50 than I was at 19," he said. "That's the power of precision medicine."

A former Silicon Valley entrepreneur, Dishman frequently addresses the other major concern about the project: protecting the medical data volunteered by research participants.

"This is one of our biggest concerns and highest priorities to make sure that we safeguard your data and maintain positive trust with you," he said. "If we lose that, we have the potential for losing the whole program."

All of Us uses the PMI Privacy and Trust Principles and PMI Data Security Policy Principles and Framework, he said. The program has entered into a hacker challenge program, where computer experts probe the data set for weaknesses that could lead to a breach, he explained.

"They get what is called a 'bounty' — they get paid for finding holes in our systems that we can then fix," he said.

All of Us is using commercial security systems "that constantly improve as the hackers get better," he said. "We are holding all our partners accountable for security at the same level that we are on our systems."

That said, the NIH program has policies to immediately alert participants regarding any security breakdown or data breach.

"There is no such thing as a 100% guarantee," Dishman said. "If a company or an organization is promising that your data can never be hacked, then they are not being direct, transparent, and completely honest with you."

This, again, is an uphill battle akin to the linked effort to restore trust from some communities, Coleman noted.

"SIMPLY TELLING PEOPLE THAT THESE SAFEGUARDS EXIST WILL PROBABLY NOT BE SUFFICIENT WITHOUT LARGER EFFORTS TO ENGENDER GREATER TRUST IN THE RESEARCH ENTERPRISE OVERALL."

"The program includes strong safeguards to protect privacy and data security, but simply telling people that these safeguards exist will probably not be sufficient without larger efforts to engender greater trust in the research enterprise overall," Coleman said.

The plan is to eventually enroll children, but currently the program is only open to adults 18 and over. Of course, there are scientific and ethical hurdles to clear to involve research on children, including the development of detailed pediatric protocols and addressing the informed consent issues.

Study participants — a term favored over "subjects" in the explanatory language of the project — will be asked to submit basic identification and medical information. Some will be asked to go to participating clinics for physical measurements and a medical workup that could include blood draws and testing needed for whole genome sequencing. According to the NIH, some of the goals of the program are:

- develop ways to measure risk for a range of diseases based on environmental exposures, genetic factors, and interactions between the two;
- identify the causes of individual differences in response to commonly used drugs;
- discover biological markers that signal increased or decreased risk of developing common diseases;
- develop new disease classifications and relationships;
- empower study participants with data and information to improve their own health;
- create a platform to enable trials of targeted therapies.

The large-scale cohort will not be focused on a single disease, but instead will be a broad resource for researchers working on all manner of inquiries.

This year marks the 15th anniversary of the international whole genome project, which spelled out the 3 billion letters in "the human DNA instruction book," Collins said.

What if we could look at the genetics of a million people "and combine that with other information about them, their environmental exposures, diet and exercise habits, and their health histories?" he asked. "Looking at all those factors would enable us to create a priceless resource that would speed up the research needed to deliver healthcare more precisely."

Human research on populations over time has been shown to yield medical breakthroughs, like those

realized by the Framingham Heart Study in Framingham, MA, that started in 1948.

"Researchers have followed several thousand residents for decades," Collins said. "They discovered that smoking, cholesterol, and high blood pressure are major risk factors for heat attack and stroke. Believe it or not, before that we didn't know those things. All of Us will be 40 times larger than Framingham." ■

With Common Rule Delay, IRBs Can Still Revamp Human Research Protection Programs

IRBs have until 2019

Implementation of the new Common Rule was officially postponed until July 19, 2018, and now federal agencies have requested a further six-month delay of its effective date, according to an April 20, 2018, proposed rule in the *Federal Register. (Available at: http://bit.ly/2Jn5gsy.)*

The new effective date would be Jan. 21, 2019, providing more time for human research protection programs (HRPPs) to implement the 2018 requirements.

The extra time will give HRPPs an opportunity to revise and improve their program policies and procedures. For example, an effective HRPP needs sufficient resources and a process for evaluating compliance with the institution's policies and research regulations.

"At a lot of institutions, the terms 'IRB' and 'HRPP' are used synonymously," says **Debra Dykhuis**, executive director of the IRB at the University of Minnesota in Minneapolis.

In establishing an effective and collaborative HRPP, the research institution focused on how human research protection programs include other groups that also touch human subjects research.

"It's about our responsibility and how we all have a part to play to bring human research protection to the attention of the institution in a new way," she explains. "We had used the term 'HRPP' for a long time, but we felt there was an opportunity to help create an understanding about what that could mean for us."

It was also about creating a group of various research stakeholders to discuss the issues they have in common and to provide oversight, education, and support of the institution's human research, she adds.

"We knew there was confusion about the meaning of the term 'HRPP' at the U of M, and we did some soul-searching about how we could bring better understanding of the concept to our community," Dykhuis says.

As a result, the organization formed the HRPP advisory committee that includes key representatives from university programs, departments, organizations, and affiliates. Members represent the research community — social-behavioral and biomedical, research compliance office, sponsored project administration, investigational drug services, conflict of interest committee, legal counsel, IRB, healthcare components, and others.

The group of about 30 people meets once a quarter for 1.5 hours, and meetings are consistently well-attended, Dykhuis says.

Their HRPP development model could be replicated by other institutions adopting the same philosophy of effective and successful team management through systematic collaboration.[1]

Here's how the HRPP was developed:

• Establish methods to promote transparency and collaboration. The HRPP committee keeps its members informed through meeting summaries and other information sent to them a few days after the meeting.[1]

Within the first few meetings, the HRPP committee identified areas to prioritize.

"We asked people to tell us what they thought the value would be in pursuing more work in those areas," Dykhuis says. "These often turned out to be an opportunity to work together to share information — not as much a driver of the future."

Committee members prepared for meetings through an agenda distributed several days in advance. Before the first meeting, the agenda asked members to prepare one to three goals for the HRPP to be shared. This ensured that stakeholders would have a voice in the meeting.

The committee realized that it

could build something together, bridging the traditional research silos.

"The mission of the committee is to collaborate, coordinate, and evaluate the university's HRPP with the ultimate goal of ensuring the protection of participants and to uphold ethical standards and improve our practices," Dykhuis says.

For example, the committee has worked on improving IRB performance transparency. One method is to collect metrics and share the information.

"We collect submission volumes and turnaround times and share these with the entire community," she says. "We report on how much of our work is reviewed by an external IRB, and we report on metrics involving our quality assurance program and its activities."

The HRPP committee also has shared with its research community how the organization will address the single IRB requirement under the new Common Rule.

"That touches the IRB, hospital groups, sponsored programs, and the conflicts of interest group," Dykhuis says.

The HRPP committee created a solution to meeting the NIH single IRB review requirement. The institution's investigators, subject to the requirement, can choose to use an independent IRB.

"Until our HRPP can be certain we can properly manage serving as the reviewing institution for multicenter clinical trials, we have elected to provide an AAHRPP-accredited independent IRB," Dykhuis says.

• **Identify, evaluate, and prioritize gaps.** The committee's goal is that each of the groups represented on the committee talks together about the issues that would affect the other members of the group, she says.

"An example of an agenda item we've had that involved this kind of thing was a discussion about ClinicalTrials.gov," Dykhuis says. "We had a high compliance rate with registration, but one of the potential gaps identified is how we can support compliance with the updating of results and ongoing requirements."

"WE HAD A HIGH COMPLIANCE RATE WITH REGISTRATION, BUT ONE OF THE POTENTIAL GAPS IDENTIFIED IS HOW WE CAN SUPPORT COMPLIANCE WITH THE UPDATING OF RESULTS AND ONGOING REQUIREMENTS."

There are some new requirements from ClinicalTrials.gov, including timetables for when researchers must post results. This is more of an HRPP issue than an IRB issue, she notes.

"We're working on how we can work together as an institution to close that gap," she says. "There is no solution in place yet, but we've identified the problem and are evaluating it."

The HRPP committee also kept members on task by developing a meeting management plan that identified who would facilitate the meeting, manage agendas, and take notes.

• **Review and make recommendations.** The vice president for research is a representative on the HRPP committee, so recommendations for changes are readily available to university leadership, Dykhuis notes.

"This provides a link for the committee's discussions to be on the radar of leadership," she explains. "So when things come up from any representative groups, there's awareness already there, and things are not bubbling up for leadership in a vacuum anymore."

• **Share accountability and evaluate performance.** The HRPP committee's members include representatives from all areas, so the various research stakeholders share accountability with their respective departments.

Also, the HRPP committee regularly reviews and evaluates its performance on identifying priorities, prioritizing gaps, and in promoting transparency and collaboration. Groups are working together in a brand-new way at the University of Minnesota, to bring the research community and others toward understanding that human research protection is the business of everyone in the research ecosystem, Dykhuis says. "We are a stronger HRPP." ■

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IRB's New Online Learning System Teaches Student PIs About Submissions

Application revisions drop

Research protocol submissions that are missing key information or are written vaguely are a common IRB problem. The new Common Rule focuses on creating a more efficient and streamlined IRB review process. This means the time is ripe for better education on how to submit a protocol.

One IRB improved its submission process through an open site for the IRB on the institution's learning management system (LMS). This made it possible for information to be customized for student researchers, faculty researchers, and faculty sponsors.[1]

From September 2017 through March 2018, the IRB's LMS received more than 21,000 visits and is gaining speed, says **Megan Williams**, MPA, director of research administration at Salem State University in Salem, MA.

Since creating the IRB's site on the LMS, IRB application revision rates dropped from 66% to 25%. With multiple revision requests, it dropped from 23% to 3.8%.[1]

"The learning management system is an open website," Williams says. "We needed to keep it open because we knew that some of our information needs to be transparent to outside constituents."

Initially, the IRB considered using its website for providing more educational content. But there was a better idea: "The more we talked about it, the more we thought the learning management system would do more for us than the website could," she says. "We tested the waters and started out with putting content out there and testing features."

Students were comfortable with the LMS, which they can use on mobile and tablet devices as well as laptops. This helped with the rollout in the 2016-2017 academic year.

For faculty, the change was a little more difficult.

> "IT ALLOWED US TO PROVIDE BETTER SUPPORT RESOURCES, AND TO EXPAND THE CONVERSATION AND TALK MORE ABOUT MINIMIZING RISKS AND WHY WE HAVE AN IRB."

"Initially, the feedback from the faculty was very mixed," Williams says. "They were not comfortable moving away from the traditional website. I think the main reason is that some of the faculty had some challenging experiences with the learning management tool itself — not with the IRB portion of it, but with using it in their classes."

The faculty assumed they'd also have problems with the IRB portion of the system, she adds.

"The students are very accustomed to using it and are accustomed to the online environment. They love it, and the faculty is on board now, although it has taken them a while," Williams says.

Through the LMS, the researchers, students, and the IRB can access documents, hold meetings, and link to other IRB sites, including an online submission site.

"We have online application tutorials and sample applications and exemplars up there with step-by-step instructions or best practices for completing an application," Williams says. "We have created a lot more outreach and support documents."

For example, there is a student IRB FAQ that is designed to tell students how to get their IRB application approved.

The FAQ provides thorough answers to questions about why IRB approval is necessary and what a student needs to do to get his or her IRB application approved smoothly and quickly. The following are a few sample points for getting through the application process:

- Be clear and precise in your writing, providing a clear rationale for your research.
- Do not ask participants to disclose other people's personal information, including mental health status, general health status, substance use, or illegal behaviors.
- Anonymize participation by using an anonymous online survey. Include the actual survey instrument in your IRB application.
- Describe the risks of participation in detail.

Another tool is the list of questions for the IRB application. The following are some of the items

researchers need to include in their application, according to the list of questions:

- CITI certificate uploaded to the applicant's profile.
- Student researcher/principal investigator name, and additional researchers' names and contact information.
- Will the research involve internet data collection?
- Will the research involve the use of transcriptions?
- Will the research involve the collection or study of existing data or documents, and are these identifiable or publicly available?
- Will participants be photographed?
- Are there any research incentives for participants? What are the incentives?
- How will research participants be recruited, and upload recruitment materials?
- Will any information be collected that identifies participants?
- Provide information on how confidentiality and/or anonymity of research participants and their data will be ensured.

When IRBs start new initiatives, it might be time to revise and improve existing procedures and tools, such as standard operating procedures (SOPs).

"We rewrote all of our SOPs," Williams says. "It was a good opportunity to do it, so we also rewrote IRB policy, the procedural manual, and it is far more detailed than it was in the past."

For example, the privacy and anonymity section was expanded.

"We pulled out a couple of pieces that we hadn't before," she explains.

There are many students who want to study physical activity and how exercise can enhance mood. The IRB did not have guidance on how to approach that type of research, and questions sometimes came up.

"We wrote guidance and best practices about screening for appropriate participation, safeguards during the intervention, minimizing risks, identifying minimal risk and greater than minimal risk, and risk to the institution," Williams says.

The IRB's new tutorial and educational information includes screen shots, revised consent templates, and more guidance than was previously available.

"It started as a small site and grew," Williams says. "The more we started to use it, the more guidance we put up there."

Using the learning management system facilitated a more holistic look at IRB support and education for student researchers and other new investigators.

"It allowed us to provide better support resources, and to expand the conversation and talk more about minimizing risks and why we have an IRB," Williams says. ■

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Quality Assurance Project Designed to Improve Good Clinical Practice and Compliance

Key component is a feedback loop

Using a quality assurance process and feedback loop, an IRB improved its good clinical practice (GCP), education, and overall research protection compliance.

Orlando Health in Orlando, FL, built a quality assurance program, including a research education series and GCP audits, around these goals. Research operations used a positive feedback loop to provide tailored education and risk reduction for research records. The feedback loop circles around from internal monitoring findings to education series content to more internal monitoring findings to more education, and an annual competency review.[1]

"We wanted the quality improvement program to link and leverage all strengths together," says **Valerie Danesh**, PhD, RN, CCRP, assistant professor at the University of Texas at Austin. Danesh formerly was a corporate manger of research and clinical grants at Orlando Health.

"We were meeting benchmarks across all of our different areas, regardless of where their intrinsic natural strengths are," Danesh adds. "With this centralization of research, we wanted to make sure everyone was meeting best practices, and we wanted to make sure it was consistent across all different areas."

As a result of the quality assurance focus and feedback loop, the research program has improved engagement and enhanced enthusiasm among research protection professionals.[1]

Internal monitoring, called good clinical practice audits, and audit readiness regulatory reviews are conducted periodically. Peer volunteers conduct the audits.[1]

"It's a highly sought-after role," says **Stephanie Brown**, BSN, RN, CCRP, quality assurance manager of the corporate office of research operations at Orlando Health.

"They are the peer volunteers that act as regulatory reviewers for GCP meetings," Brown says. "There are about six studies selected for each meeting, and they cover different regulatory aspects."

Peer auditors and regulatory auditors can reference the binders, which list all needed information clearly and with an intuitive flow. The binders are designed to be easily referenced and viewed by research professionals and auditors, Brown says.

"The binder has been very well-received with monitors through audits we've had in the past," Brown says. "It provides a nice flow for regulatory binders."

There is a table of contents, so if auditors pull binders, they'll know where to find what they want, she adds.

The QA initiative also includes the following actions:

• Train peer reviewers. "The idea in the beginning was to select documentation as if we went through a recognized FDA inspection or an inspection by any other outside authority," says **Tara Roberts**, CIP, CIM, corporate director of research regulation and compliance at Orlando Health.

Research compliance leaders trained peer reviewers to check documentation, informed consent, delegation of authority logs, training logs, and other information.

Trainees are asked to consider these questions:

- What are GCPs?
- Where are GCPs going well?
- Where do GCPs need to improve?

"A LOT OF TIMES WE GET CAUGHT UP IN THE TERMINOLOGY OF GOOD CLINICAL PRACTICE, BUT IF YOU JUST ADVOCATE FOR THE PATIENT AND FOLLOW PROTOCOL, IT COMES NATURALLY."

• Share GCP across divisions. "We share best practices across the divisions, which has been very helpful," says **Marlene Miller**, RN, BSN, audit and quality assurance supervisor at corporate office of research operations at Orlando Health.

For instance, common factors all research areas share are the need to advocate for patients and to follow protocols, Miller says.

"A lot of times we get caught up in the terminology of good clinical practice, but if you just advocate for the patient and follow protocol, it comes naturally," she says.

• Use shared regulatory binders. "When we've used this shared binder experience, I've had auditors provide feedback that they love the setup," Roberts says. "It's easy for them to find the documents they are looking for, and when they see that kind of nice organization, they feel more confident about how things will flow at the organizational level."

Roberts recalls how two investigators thumbed through the binders quickly, saying it was easy to find what they were looking for. "It helps them focus on what they need to focus on, and the binder gives it a nice flow," she says.

"We are sharing this across all of our divisions because it's been successful in our audits," Roberts adds.

• Design a monthly education series. Orlando Health's entire research enterprise may participate voluntarily for most of the monthly educational sessions. A few sessions are mandatory. Attendees include research staff across all research divisions, as well as fellows and others involved in human research.

"We cover hot topics, and sometimes we might see that there has been a deficiency in an area," Roberts says.

Educational themes have included audit readiness, data management, GCP, regulatory issues, patient recruitment, research billing, research ethics, and privacy/confidentiality practices.[1]

"Sometimes topics are generated by a team that goes to an investigators' meeting or to a conference," Roberts says. "We try to support the sessions with credentials so staff can earn credits toward their credentials."

Leadership led the educational sessions for the first 10 months, and then peer volunteers took over.

"I would say it really is wholly team member-led with leadership

guidance," Danesh says. "There are no prepackaged materials."

• **Develop GCP audit readiness.** "Regulatory coordinators and others involved sit in on sessions and they provide documents for review, and we meet to discuss and review further," Brown says. "That's where feedback is developed."

Study selection for audits is random for each division, Brown notes.

• **Apply the feedback loop.** The feedback loop that ties together education, internal monitoring, and annual competency reviews is applied to all quality assurance programs, Danesh says.

"They've built a beautiful culture where it's an expectation that an external agency, like the FDA, will provide feedback, and the organization learns lessons," Danesh explains.

Problems identified in reviews and internal monitoring are resolved through education and the quality assurance process, she adds.

"We route all quality assurance through the process and provide continued education hours," she says. "We make it a continuous feedback loop from FDA inspection to QA program, and shared with everyone through continuing education."

• **Provide annual competency review.** The annual review assesses each research team member's content knowledge. It's a closed-book exam with multiple choice questions. There also are two interactive skills stations. ■

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Baby Blood: Suit Alleges Michigan Lacked Informed Consent

Blood testing, research use challenged

In the immediate aftermath of the birth of his son in September 2017, **Philip L. Ellison**, MBA, JD, was more a proud father than a crusading lawyer. Things quickly changed.

"The whole reason I am involved in this is because of my son," he tells *IRB Advisor*.

An attorney in Hemlock, MI, Ellison is suing the state for its practice of routinely taking blood samples from newborns for testing and medical research. Alleging that the blood spots already are taken before any consent is given, the suit asks the court to declare that the program as currently structured violates the Fourth Amendment right to privacy and protection from illegal search and seizure.

"The main thing is, we are not trying to stop newborn blood screening," Ellison emphasizes. "If parents want to consent to the state, that is their business — but they should be given full information and a choice beforehand, not after the fact."

When his son was admitted to a neonatal ICU shortly after birth to resolve a blood sugar problem, Ellison waited with the angst known to any parent in such a crisis. He was shocked that in such a moment he was asked to sign off on the routine use of his son's blood for testing and medical research.

"As a father at that point — less than 24 hours in — I don't care about medical research. Why are we even talking about this?" Ellison says, recalling his reaction. "They said 'no, no these are the blood samples we send to the state.' I'm a lawyer who sues the government for a living. I said, 'Wait — what blood samples did you send to the state?'"

As he researched the subject after the hospital experience, Ellison says he was "horrified by how expansive this was — the profiteering, and basically the lack of disclosure that was given."

Ellison is suing for his family in a state case and filed a similar motion in federal court representing a group of nine newborns and their parents.

"We asked for both equitable relief and monetary relief, but in reality, this case is really more about this program and whether it can continue in its current form," he says.

Ellison reasoned that the average person dealing with the birth of a child is in no position to grant informed consent in a meaningful way.

"Everyday citizens are not told anything, and they would never think to ask," he says. "Who would think

that Michigan was running a program where they are secretly extracting blood samples and storing them in a warehouse? It's like a science fiction story. The whole point of this is to bring some sanity of consent to this process."

The attorney likens the timing of the informed consent to asking somebody to sign something right after they have been in a car accident. "I would have signed any form and done anything necessary to get my son out of the NICU," he says.

As outlined in the lawsuit, the key allegations include:

• the state of Michigan failed to obtain express or informed consent from the newborn and/or his or her legal guardian, or to secure a warrant from a neutral, detached magistrate before taking the blood into the permanent custody of the state government;

• parents in this legal action had no knowledge of blood or blood spots being drawn from their newborn child while in the care of hospital staff, which were then being turned over to the government for its permanent custody and/or permanent seizure, and use by said government or those third parties granted possession/custody.

The state disputes the charges and has already filed one motion to dismiss the case.

Lynn Sutfin, public information officer for the Michigan Department of Health and Human Services (MDHHS), could not comment on the case, but provided background information on the program.

The newborn screening program (NBS) is required by the state to detect rare diseases that warrant immediate treatment, she explained in an email.

"Under Michigan law, parental consent is not required to perform NBS," Sutfin stated. "Every year, the program identifies approximately 250-280 babies affected by one of the 54 blood-spot-testable disorders included on the NBS panel."

For example, of 111,725 babies screened in the state in 2015, 270 were diagnosed with one of the disorders — a rate of about one in every 414 babies. The program uses a paper card with designated areas for blood spots, using five to six drops of blood drawn from the heel.

"All of the blood spots are not always needed for screening," Sutfin stated. "One blood spot from the newborn screening card is reserved for uses authorized by the baby's parent, such as medical testing or identification. Parents are also given the opportunity to allow future use of their child's de-identified blood spots through the BioTrust for Health program, which makes them available to qualified researchers."

Since 2010, parents in Michigan have been able to choose if they want their infant's de-identified blood to be used for medical research.

"Spots collected prior to May 1, 2010, can be used for de-identified medical research unless a parent submits a request to mark their child's spots as unavailable for research," she states. "Adults can make this request on their own behalf."

Research requests to use de-identified blood spots are submitted to the BioTrust, where they undergo multiple levels of review, including by the MDHHS IRB, she noted. The review process is designed to ensure that the research has scientific merit, is conducted by qualified researchers, and the human subject data are protected.

The research using the Michigan blood spots has resulted in improved testing for spinal muscular atrophy and Niemann-Pick C Disease, Sutfin explained. The program also has contributed to research in the link between cancer and environmental exposure.

"The NBS process and storage of dried blood spots includes many layers of security to protect the dried blood spots," Sutfin stated. "The dried blood spots are also protected under the law. MDHHS is only permitted to use dried blood spots for quality improvement and test development of NBS disorders, parent- or guardian-directed medical research, crime victim identification, and de-identified medical research."

That said, Ellison is confident he has a case, expressing a willingness to take the federal version to the U.S. Supreme Court if need be. We asked him to comment further on the situation in the following interview.

IRB Advisor: These programs are run in other states. What is different in Michigan?

Ellison: In Michigan, when they designed their system, it did not build in the requirement of getting informed consent before extracting the blood, storing it, and selling the blood later on. The only time they have actually gotten some form of consent is after the blood has been drawn and it's at the lab. They give a form to parents that says, 'Can we use your infant's blood for medical research?' The form does not give all the details, and what the program is doing today is different from what the form says. My position is that even if the actual consent form is signed, the actual options being consented to have been far exceeded at that point.

IRB Advisor: You say the key is that the informed consent is not given until after the fact.

Ellison: I equate it to the state coming in and taking your car from the parking lot of where you work. They do a bunch of tests on it, and say we have your car. We didn't ask you

before we took it, but we are going to use your car to deliver Meals on Wheels. Well, that helps the greater good, but they should have asked you before they took the car for that purpose. Michigan is one of a handful of states that don't get consent beforehand. In my opinion, Michigan has done a poor job in designing a system that fulfills the obligation of consent.

IRB Advisor: At least some of these blood samples are then available for distribution and research?

Ellison: Rather than keeping [the blood spots] as part of the state system where there is at least political oversight and transparency under government open-records laws, [the MDHHS] transferred the blood to a private entity that sells and distributes the blood samples to fourth parties. From my research, I have discovered that several university programs across the country have used Michigan blood samples. They are probably doing some good, I will give them that, but they didn't ask before they took it all.

IRB Advisor: You note that the program began on a minor scale, but so much more is possible now with whole genome sequencing of human DNA.

Ellison: The blood program in Michigan started in the 1960s. So about from the mid-1960s to 1984, they were taking a blood sample and testing for a handful of things. Of course, as science progressed, we are up to some 60 different things they are testing for now in Michigan. Some of my opponents thought I was crazy until this whole story of the Golden State Killer came out recently. The DNA was not even from him — it was from family members. The police basically searched private medical data of a bunch of individuals to find this connection. I think this is a classic example of the law not keeping up with the science. If you are going to use it for something more than what you originally got permission for, you have to go back and ask again. ■

FDA Moves to Shutter Stem Cell Clinics

The FDA recently filed complaints in federal court seeking "permanent injunctions to stop two stem cell clinics from marketing stem cell products without FDA approval and for significant deviations from current good manufacturing practice requirements."[1]

The action on May 9, 2018, was taken against U.S. Stem Cell Clinic of Sunrise, FL, which the FDA alleges was using manufacturing practices that "could impact sterility" to create products that were not approved by the FDA.

"The FDA is taking this action because U.S. Stem Cell Clinic did not address the violations outlined in a warning letter to the clinic and failed to come into compliance with the law," the agency said in a statement.[1]

The FDA also moved against the California Stem Cell Treatment Center in Beverly Hills and Cell Surgical Network in Rancho Mirage. These affiliated firms have some 100 for-profit stem cell clinics.

Last year, the FDA issued warning letters to a number of stem cell clinics after highly publicized issues of patient harms and bizarre treatments that included the use of the vaccine for smallpox, a pathogen that has been eradicated in the wild. *(For more information, see the October 2017 issue of* IRB Advisor*.)*

"Cell-based regenerative medicine holds significant medical opportunity, but we've also seen some bad actors leverage the scientific promise of this field to peddle unapproved treatments that put patients' health at risk," FDA Commissioner **Scott Gottlieb**, MD, said in a statement on the most recent action. "In some instances, patients have suffered serious and permanent harm after receiving these unapproved products. In the two cases filed today, the clinics and their leadership have continued to disregard the law and, more importantly, patient safety." ■

REFERENCE

1. U.S. Food and Drug Administration. FDA seeks permanent injunctions against two stem cell clinics. May 9. 2018. Available at: https://bit.ly/2jKs0YC.

Correction

The March issue of *IRB Advisor* featured a story about plain language informed consent with an incorrect reference. The correct reference is as follows:

Hadden K, Moore T, James L, et al. Understandable to the subject: Plain language IRB informed consents for research. Poster presented at the Public Responsibility in Medicine and Research (PRIM&R) Advancing Ethical Research Conference, Nov. 5-8, 2017, in San Antonio. Abstract: 26.

IRB ADVISOR

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

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CME/CE QUESTIONS

1. **What landmark study of a human population was the NIH's All of Us compared to?**

   a. Minnesota Twin Family Study
   b. Framingham Heart Study
   c. National Health and Nutrition Examination Survey
   d. Seattle 500

2. **In designing a monthly human research protection education series, which of the following topics would *not* be appropriate to include?**

   a. Audit readiness
   b. Data management
   c. Guidelines for animal welfare protection
   d. Good clinical practice

3. **Which of the following items would be helpful in student researcher FAQs about the IRB submission process?**

   a. Be clear and precise in your writing, providing a clear rationale for your research.
   b. Do not ask participants to disclose other people's personal information.
   c. Anonymize participation by using an anonymous, online survey.
   d. All of the above

4. **The central issue in a research-related lawsuit in Michigan is:**

   a. conflict of interest.
   b. evidence of bias.
   c. falsified results.
   d. informed consent.

CME/CE OBJECTIVES

The CME/CE objectives for IRB Advisor are to help physicians and nurses be able to:

1. establish clinical trial programs using accepted ethical principles for human subject protection;
2. apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
3. comply with the necessary educational requirements regarding informed consent and human subject research.