IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

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RELIAS MEDIA

A Half-Century Later, Guatemala Experiments Still Horrify

Participants' families seek $1 billion in lawsuit

By Gary Evans, Medical Writer

Among the most outrageous transgressions in research ethics were the U.S. Public Health Service's (PHS) sexually transmitted disease (STD) experiments in Guatemala beginning in the 1940s.

Bioethicists recently published a case study[1] of this horrific chapter in human research history after comprehensively reviewing all the records of the Guatemala experiments. The most egregious aspect was that some participants were intentionally infected with syphilis and other STDs.

"It is critical that people like IRB professionals and those of us in research ethics are continually reminded of the reason that we have the regulatory structures and institutional approvals that we do today. I think often people don't quite realize how bad it got," says **Kayte Spector-Bagdady**, JD, MBioethics, chief of research ethics at the Center for Bioethics and Social Sciences in Medicine at the University of Michigan.

> "IT IS CRITICAL THAT PEOPLE ARE CONTINUALLY REMINDED OF THE REASON THAT WE HAVE THE REGULATORY STRUCTURES AND INSTITUTIONAL APPROVALS THAT WE DO TODAY."

Incredibly, after more than a half-century, the books have not been closed on this research debacle. Earlier this year, a federal judge allowed a $1 billion lawsuit to proceed against several groups allegedly involved in the experiments.

"The Guatemala STD experiments still represent an ongoing saga," she says.

On Jan. 3, 2019, a federal judge in Maryland ruled the lawsuit could proceed, denying an appeal by the defendants that a prior Supreme Court

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ruling protected them against international claims in such cases.

According to the complaint, which U.S. District Judge Theodore Chuang allowed to proceed, "Plaintiffs estate of Arturo Giron Alvarez and 773 other Guatemalan nationals have filed a civil action against the Johns Hopkins University and four affiliated entities, the Rockefeller Foundation, and Bristol-Myers Squibb Company. Plaintiffs allege that defendants subjected them or their family members to medical experiments in Guatemala without their knowledge or consent during the 1940s and 1950s, in violation of the law of nations."[2]

Johns Hopkins and others named in the suit denied the allegations and will continue to contest the claim.

Military Readiness

STD research in the 1940s was considered critical because the infections sidelined many military personnel during WWII. With the 1943 discovery of penicillin, the PHS wanted to take a preventive step and develop an STD prophylaxis. Preventing STDs would ensure military readiness and prevent the expense and delays of penicillin treatment. Among the first iterations of this research was a post-exposure wash that could be applied after sexual contact to theoretically prevent STD infections.

"John C. Cutler, a senior surgeon at PHS who later was the lead investigator in Guatemala, believed that before the wash would be ready for widespread use in the U.S. Armed Services, it should be tested via controlled experiments on subjects at high risk for infection," the authors of the case study report.

However, the experiments conducted in 1946-1948 included highly vulnerable populations without informed consent. Disturbingly, these included Guatemalan children, prisoners, and psychiatric and leprosy patients. The experiments with children were apparently to distinguish between congenital syphilis from sexually acquired disease, and the records did not show any children were intentionally infected.

Unfortunately, others were. Here we have the most unconscionable aspect of the experiments, which was apparently done in the name of expediency. Instead of the long-term commitment and ethical standards of a randomized clinical trial, the PHS researchers tested the wash intervention by intentionally exposing some 1,300 prostitutes, soldiers, prisoners, and psychiatric patients to STDs, the authors report.

Many that developed subsequent infections did not receive treatment. Not only are there no records of informed consent, there is evidence that participants were deceived, the authors determined. At least 83 people died during the experiments, but there is little data establishing a direct link to the research. PHS supervisors expressed concern to the principal investigator about the research, but apparently made no attempt to stop it. Although research standards were less stringent, the PHS knew the research was unethical and decided to bury it from the public record, the case study authors concluded.

Decades later, Cutler donated the Guatemala research record to the University of Pittsburgh School of Public Health, where he had been a faculty member, before his death in 2003. The act of voluntarily donating this material speaks volumes to the ethical blind

spot with which the PHS researcher viewed this work.

"He didn't think what he did was wrong, and in fact, wanted people to know," Spector-Bagdady says.

On the other hand, the data had been hidden in the first place because the PHS knew it was unethical, she adds.

"He had supervisors at that time who said, 'No, what you did was wrong, and you need to hide it,'" she says. "This indicates to us that this [case study] is not a retrospective moral judgment, where we say by the standards of today we are judging what people did in the 1940s. Actually, they knew that what they were doing was wrong at the time."

The documents were subsequently discovered by a historian and turned over to the CDC in 2010. Then-President Barack Obama apologized to the people of Guatemala and ordered a fact-finding commission, which in 2011 published a report of the atrocities.[3]

"The passage of more than 60 years between this research and its public revelation not only denied study subjects a remedy for the harms they endured, but also erased any opportunity to modify the research ethics regime as it formed in response to this historical failure," the case study authors concluded.

Acknowledge the Past

IRB Advisor asked Spector-Bagdady to comment further on the Guatemala STD experiments in the following interview, which has been edited for length and clarity.

IRB Advisor: For medical purposes, the National Institutes of Health is conducting the All of Us initiative to obtain DNA of a diverse group of 1 million people. Do you think such efforts can be successful, considering ethical failures like the Guatemala STD exposures?

Spector-Bagdady: It is very valid that members, particularly of minority communities, are suspicious of the harms that have been levied upon them by the medical and research profession. Tuskegee, Guatemala — there are hundreds of examples of the medical and research profession victimizing people. I understand why they would be hesitant to engage. That said, I think the programs like All of Us are doing the right thing by not just saying "how can we recruit more people," but saying "how can we reconceptualize what it is to be a research participant? How can we provide full transparency and engagement to research participants, such that we change the entire system and people feel in control and more comfortable?"

> "WE CAN'T GO FORWARD UNLESS WE ADMIT WHAT WE HAVE DONE ALREADY THAT PUT PEOPLE IN THE POSITION OF BEING RIGHTFULLY SUSPICIOUS."

IRB Advisor: So, revisiting and discussing transgressions like this can actually contribute to more representative research?

Spector-Bagdady: I think it is really important to be honest and transparent about the harms that were done in the past so that we can move forward from a place of mutual understanding. We can't go forward unless we admit what we have done already that put people in the position of being rightfully suspicious. And it is important that we have a diverse group of participants to work with for research. If we don't have diverse communities represented, it means that our research might not be as useful, relatable, or applicable to a diverse set of communities.

This is particularly true for things like genetics research or precision medical work that is so closely tailored to small variations in people's genes. If we don't have a large population from which we can pull the data to do this kind of research, we worry that our findings will be more applicable to certain portions of the community than others.

IRB Advisor: The initial push for this was to protect WWII soldiers, but the intentional exposures to vulnerable populations did not occur until after the war. What drove this unethical research forward in the absence of a wartime imperative?

Spector-Bagdady: Yes, the research was actually started in earnest after the war was over. It wasn't quite as urgent because the U.S. Armed Forces weren't at risk of STDs with the same regularity that they had been during the war. But we prepare for military medicine in times of peace just as in times of war. Because this had been such an incredible problem in WWII, and it was the obvious next step of their work, I think that really drove this research.

IRB Advisor: How would you compare this historical travesty to others like Tuskegee and the "Unfortunate Experiment" of leaving cervical cancer untreated in women in New Zealand?

Spector-Bagdady: Comparing research ethics scandals is a zero-sum game. One doesn't need to be worse than the others for us to learn from them all.

IRB Advisor: When you look into this case, do you consider that this is maybe as much evidence of evil people as unethical science?

Spector-Bagdady: That is a good question. I think it would be too dismissive to just say that these things occurred because of an evil person or a couple of evil people. Because many men — white men at the highest echelons of science — knew what was going on. They knew exactly what was happening, and no one stopped it. This was much broader. Yes, I do think John Cutler was an incredibly immoral and hurtful person. However, there was a system that allowed him to victimize thousands of people. It takes a system. This was sponsored by the Public Health Service. It was funded by the National Institutes of Health. The most important men in syphilisology and infectious diseases knew that this was happening.

IRB Advisor: You mention in the paper an undercurrent of racism that may have contributed to the research mindset.

Spector-Bagdady: All of the experiments involved vulnerable populations including women, children, minorities, and people with mental disabilities. It involved psychiatric patients and prisoners, and the people who populated those institutions were largely from the indigenous communities in Guatemala. They were sort of doubly vulnerable. They did not speak the English the Americans were speaking, but they also did not speak the Spanish that the Guatemalans spoke. ■

REFERENCES

1. Spector-Bagdady K, Lombardo PA. Case Study: U.S. Public Health Service STD Experiments in Guatemala (1946-1948) and Their Aftermath. *Ethics and Human Research*; 20 March 2019, 41: 29-34.doi:10.1002/eahr.500010.
2. *Estate of Arturo Giron Alvarez et al v. The Johns Hopkins University et al.* U.S. District Court of Maryland. No. 1:2015cv00950 - Document 204 (D. Md. 2019) Civil Action No. TDC-15-0950. Jan. 3, 2019.
3. Presidential Commission for the Study of Bioethical Issues. *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948.* Washington, DC: Government Printing Office, 2011.

Electronic Informed Consent Platform Enhances Education and Engagement

Problems are quickly fixed

By Melinda Young, Author

E-consent can help research institutions check all the boxes on their consent process goals: efficient, readable, comprehensible, engaging, and trackable.

"It can improve participant engagement and comprehension," says **Michael Buckley**, MS, MBA, manager, enterprise innovation, clinical research informatics, and technology at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City.

MSKCC has been rolling out its e-consent process for a couple of years. The organization started with institutional biospecimen banking protocols and clinical genetic protocols, he says.

"We've been working with high-volume protocols we want folks to consider participating in," he adds. "We wanted to start with them because the number of patients consenting to them is so high, and we wanted feedback from folks using that protocol to do iterative enhancements to the electronic IC [informed consent] module."

Plus, the genetic research protocols already had a video for participants to view. With the electronic IC module, the video can be embedded in the web browser, saving time, Buckley says.

User feedback surveys at MSKCC suggested investigators saved an average of 10 minutes per informed consent, he says.

"It freed investigators from administrative tasks of printing out informed consent documents, putting names on each form," Buckley says. "They can spend more time having engaging discussions with potential participants about the protocol."

With the paper IC process, the hard copy is scanned into the electronic medical record (EMR), a process that can take 24 to 72 hours to complete. With the electronic version, the information is entered into the EMR in less than two

minutes, and it goes right to the patient portal for the patient to see.[1]

Since implementing the electronic IC process, thousands of research participants have consented electronically, increasing at a rate of about 500 per month, Buckley says.

About three out of four people surveyed liked the electronic informed consent process better than the paper process, and most liked the user-friendly interface of the electronic IC, he adds.

MSKCC's electronic consent process uses embedded educational videos. For example, there is a video of a principal investigator discussing the study and describing potential study participants, Buckley says.

The electronic consent process could provide videos that show how the technology used in a study works. For instance, there could be a video of a surgical protocol that uses a robotic arm. Participants find the electronic consent process engaging. There are drop-in images and graphics or flowcharts with protocol timelines, test dates, and clinic dates, he adds.

"If investigators are taking surveys after particular visits, we take words from the informed consent and put these in a visual, showing what you have after your first visit and second visit," Buckley explains. "It makes it easier for the patient to digest, and it makes for a better consenting experience — improving comprehension of the protocol."

Electronic informed consent documents are less work than paper IC forms for IRB staff. They also have improved informed consent audit trails, Buckley says.

Researchers can add visual elements to the electronic IC by simply using their smartphones to film procedures that are sent to the IRB for approval.

"It takes lifeless words on the paper, puts in images and videos, and shows someone talking to the participant about the protocol," Buckley says. "The research literature says visual aids help improve visual comprehension."

Researchers can write informed consent documents in the web browser, which has an embedded document authoring system that allows them to see track changes without reliance on emails, he adds.

SINCE IMPLEMENTING THE ELECTRONIC IC PROCESS, THOUSANDS OF RESEARCH PARTICIPANTS HAVE CONSENTED ELECTRONICALLY, INCREASING AT A RATE OF ABOUT 500 PER MONTH.

"It's like Google Docs but with all the controls and information for tracking," he explains.

Participants have direct access to the IC form. Once they read and authenticate it, the form is automatically sent to the patient portal at MSKCC if the patient has a portal there, Buckley says.

"The patient portal is a secure portal messaging account that patients can use to talk with clinicians and to receive secure documents," he says.

Research participants can choose the electronic consent form or a paper form, but they also can keep a hard copy of the electronic consent after they have signed it.

"It's an agile system," Buckley notes. "Our overarching goal is to continuously improve and update the informed consent process."

The electronic IC platform features a number of useful features, including the following:

• It is web-based and browser independent. "It's an in-house, standalone application that is web-based, agnostic, and browser independent, meaning you can use Chrome, Safari, Firefox — any type of browser," Buckley says.

Users can login through a security link on desktop computers, laptops, and tablets. Participants sign it with their finger, a stylus, or a mouse.

"Our clinical research informatics and technology group at Memorial Sloan Kettering created that for us," Buckley says.

The electronic IC platform improves efficiency, reduces redundancy, and provides cleaner data, improved quality, and greater innovation, he adds.

"We're not forcing people to use electronic consent, but we're offering that as an option," Buckley says. "We want to create a nimble system."

• It is designed by an innovation team with user input. "We have a strategic planning and innovation design group," he says.

The team works with physicians, study coordinators, and others to see how the electronic informed consent process is working for study participants.

"We get feedback in real time," Buckley says. "There is a survey to get direct feedback. The design innovation team does facilitated interviews with new-to-informed-consent-process users to hear how things are going and to get feedback on what can be improved."

The fluid nature of electronic IC has helped them figure out where bottlenecks are in the IC process and to fix issues.

Research participants helped to inform the development process, identifying large themes of what should be enhanced in informed consent. For example, one theme was for participants to choose how they would like to receive their finalized consent document, Buckley explains.

"They might want an electronic copy in the MSK portal account or to receive a hard copy," he says. "We give participants a choice in how they would like the copy."

• Videos and images enrich the IC process. In addition to embedded videos, the electronic IC uses various educational tools including colorful images.

"It makes for a richer consent discussion, we think," Buckley says.

Often, health system patients who are considering participating in research have spent long periods of time in a clinic, waiting for treatment, and this is very taxing, he notes.

If researchers were to review informed consent while they are in the clinic, the electronic version with its videos and illustrations would be a nice change of pace from the usual consent documents they encounter, he adds.

Also, the electronic IC form is not just an electronic version of a paper document, like a PDF file, Buckley says.

"It's separated by sections and has tabs on the left side, like serious adverse events that they can scroll through," he explains."It's more digestible, and it's quick to adapt it."

• The electronic IC process is more efficient and has fewer errors. When investigators used the electronic informed consent, their data entry was 4% more compliant and complete than when paper documents were used.[1]

For example, the electronic IC form would direct users back to missing fields.

"If someone didn't put in a name, address, or telephone number — which are required fields — we have smart tools in there to guide folks back to that section," Buckley says. "If a word is spelled in an unusual way or if an address doesn't look real, then smart technology surfaces and asks them if they are certain."

If the electronic IC document is amended by the investigator and approved by the IRB, the changes can be implemented that same day, he says.

"We have a lot of automated systems letting us know if there is a fail point in any transfers of information," he says.

"We get an automatic alert on our dashboard right away, and we can go back to the study team to rectify that issue." ■

REFERENCE

1. Buckley M, Lengfellner J, Koch M, et al. MSK electronic informed consent (eIC) platform for clinical trials; an operational model and suite of tools for obtaining informed consent and managing consent documents. Presented at PRIM&R's 2018 Advancing Ethical Research Conference, Nov. 14-17, 2018, in San Diego. Poster 17.

Should IRBs Set an Incentive Pay Limit?

Is $50 too little — or too much?

Not all IRBs and research institutions specifically address limits to how much researchers can compensate study participants.

But allowing these limits to default to what is reportable to the IRS as income could be a mistake, one IRB chair says.

"We did a survey and found that only 10% of research institutions actually had a policy about incentive payments," says **Michelle DuBois**, PhD, associate IRB chair and associate professor of biology at Seattle University.

"Some institutions did not allow any incentive payments, but those were few and far between," she adds. "When we went through research online, we found that limits ranged widely."

Allowing researchers to offer some kind of payment for participation in a study is extremely reasonable, DuBois says.

"Some people argue for larger incentive payments for some studies," she adds. "It really comes down to what kind of study is being done and what kind of population is involved."

Studies mainly encourage someone to participate under the theory that the participant's time is worth compensating.

"Is there a reason why someone should give two hours for an interview when they don't have to?" DuBois says. "Is it worth $20 for

their time? Is it worth $50? Those are the kinds of questions researchers come up against."

Other incentive questions involve how incentives should be provided. Should they be in cash, gift cards, or products? A $10 T-shirt also is an incentive, and transportation passes or tokens are incentive payments even if they are used to reimburse participants for travel to the research site, DuBois says.

And everything that is an incentive payment, whichever form it takes, counts toward an institution's incentive limit.

IRBs also should learn more about their state's laws when an incentive payment involves a drawing or raffle. There generally is a $600 threshold for reporting the winning prize to the IRS. *(More information on reporting is available at: http://bit.ly/2LkEabx.)*

Research institutions often default to the $600 threshold, DuBois notes.

"They say, 'We don't have a limit in terms of reporting, but the IRS does, and as a result, that is what we have for our policy,'" she says.

But there also could be state laws that prohibit raffles, DuBois says.

"That's something for IRBs to note: Make sure the incentives aren't breaking state laws if they are lotteries, raffles, or drawings," she says.

Incentive payments also count toward the IRS reporting threshold of $600 in payments to individuals. What this means is that anytime an institution pays someone $600 or more, the institution must obtain the person's Social Security number (SSN) and file IRS form 1099-MISC. *(For more information, visit: http://bit.ly/2UYmzWf.)*

Asking research participants for their SSNs can be awkward, which is partially why it is very unusual for research participation incentives to exceed the $600 limit. Individual institutions can make their own policies more stringent. For instance, Seattle University offers a $50 incentive payment limit before the investigator has to ask for participants' SSNs.

"In terms of minimal-risk projects, researchers need to talk with people and maintain privacy," DuBois says. "If you report Social Security numbers, people are less inclined to participate."

Seattle University reached its $50 limit after trial and error and collecting data on incentive payments.

For a while, the university allowed no incentive payments. That policy was unpopular, so the institution enacted a $25 maximum payment without disclosure of an SSN, she explains.

After reviewing incentive payment policies at other institutions, they decided to double the limit to $50.

"We coordinated with our controller's office and the office of sponsored projects to come up with our limit of $50, which is the trigger amount at which a Social Security number needs to be reported," DuBois says.

The $50 trigger would apply to any collective payments to a single research participant. For example, if a participant is given $10 bus ride cards to reimburse for travel each time he or she visits the clinic, then the fifth visit would amount to $50, the payment limit before an SSN is collected.

"If it's over $50, it needs to be reported to the controller's office," DuBois says. "At Seattle University, we primarily have minimal-risk protocols, and these are not the kinds of studies that would merit hundreds of dollars in payment for participation."

The institution tries to balance what seems reasonable with regard to the payment, study, and population being targeted, she explains.

"We encourage researchers working with various types of vulnerable populations to take into consideration how those types of environments might impact participants receiving an incentive payment," DuBois says. "Those types of considerations are the ones the IRB examines for each protocol." ■

Diverse Populations Joining NIH All of Us

Moving to the 'right side of history'

Nearly a quarter of a million people have joined the National Institutes of Health's (NIH) ambitious All of Us precision medicine initiative — with a large response from racial and ethnic minorities who have been historically victimized or ignored by human research.

"Almost 80% of the participants so far are from communities that typically have been underrepresented in research, and 50% are racial and ethnic minorities," said **Francis Collins**, MD, director of the NIH. "Too often, such diverse communities have been left out of research, and therefore left behind when cures are discovered."

The NIH recently held a symposium marking the one-year anniversary of the project launch, which aims to collect genetic information and other health data on 1 million participants. NIH researchers will use whole genome sequencing and other cutting-edge tools to create, aggregate, and analyze individual health data for years into the future.

"More than 230,000 people across this country have started the process of joining," Collins said. "More than 142,000 have completed the full protocol that includes answering surveys, electronic health records, giving measurements and giving biosamples, and linking to [trackable, wearable] data."

The project began with a goal of "oversampling" minority and ethnic populations to restore research representation of these communities. By doing so, the NIH project is imbued with a quality of justice that resonates beyond the research possibilities, which at this point are difficult to overstate.

All of Us foretells an "inevitable cultural revolution," said **Deven McGraw**, JD, chief regulatory counsel for Ciitizen, a medical data company in Silicon Valley. "Doing the right thing before you're forced to do the right thing will always put you on the right side of history."

Overcoming Tuskegee

NIH project leaders have engaged in outreach and opened frank conversation to acknowledge and overcome the mistrust generated by past research atrocities such as the Tuskegee Experiment, where African-American men were studied for untreated syphilis rather than administered penicillin.

"The first thing to getting people involved — which was a brilliant move by this program in particular — is to not deny that the past happened," said **Robert Winn**, MD, director of the University of Illinois Cancer Center in Chicago.

Noting that those in the Tuskegee experiments were essentially used as a "control group," Winn has talked to African-American men about overcoming unethical research of the past for the sake of future generations.

He conveyed this message to a meeting of 250 men, who expressed interest in learning their ancestry and providing data that could help African-American children now and in the future, Winn said.

"Men [said] in the town hall we had with them, 'I may not be helped, but how will this help others?'" he said. "That is a recurring theme."

Minorities will participate, but NIH researchers must "show up" every day with ethical intentions if the endeavor is to be successful. "How we gain trust is by showing up, being honest, and being consistent," Winn said. "There are a million reasons why this program might not happen, but I'm going to plead to you that it has to. Hopefully, it will bring out the best in us."

All of Us is getting people engaged in communities that have never participated in research, and these groups are excited about the access to medical science.

"When I go to the barber shops and the churches, people are wondering about the disparities that are happening now, and how to get people involved," Winn explained. "All data matters, big and small, and in a rush to get big data, hopefully we don't make communities invisible."

For example, Winn said in extending a radius out three miles in any direction from the Cancer Center, he found communities with life expectancy ranging from 69 to 85 years.

The granular data that will be generated by All of Us could shed great detail on how socioeconomic conditions affect individual health.

Indeed, after only one year, All of Us has already "managed to become one of the largest, most diverse research resources in history," Collins said.

Now that participation is growing, Collins said, the NIH is creating a "researcher bench and

research tools" that can be used with the project data in the upcoming winter of 2019-2020.

"The precise timeline is dependent on outcomes of usability and security testing," he said. "When that research work bench is made available, it will include data from upwards of 200,000 participants. It will include survey results, measurements, and electronic health record data — hundreds of thousands of data points."

The goal is to add genomic information and data collected by wearable devices by 2020, he said.

"All of Us is operating under a very bold timetable," Collins said. "Most research programs of this scale don't release data until several years after they've completed enrollment of the last participant. Our attitude here is very different. We have a higher responsibility to consider."

A critical aspect of that responsibility is securing the data and privacy of research subjects, and the NIH is subjecting the project to rigorous testing and hacker-like probing on an ongoing basis.

Diabetes and Dementia

An early benefit is expected to be detailed health data on diabetes and prediabetes, Collins said. About 30 million Americans — roughly 10% of the U.S. population — have Type 2 diabetes. Another 84 million people have prediabetes and are at risk of developing full-blown disease in the future, he said.

At full participation, All of Us research would be following some 90,000 diabetic patients and three times that amount with prediabetes, he said.

"Since this program aims to follow participants for at least a decade, if not longer, some people may develop diabetes while enrolled and others may be able to avoid the condition due to early diagnosis and effective treatment," Collins said. "With access to the electronic health record, researchers may be able to explore early signs and symptoms and compare the effectiveness of various prevention strategies."

> "TOO OFTEN, SUCH DIVERSE COMMUNITIES HAVE BEEN LEFT OUT OF RESEARCH, AND THEREFORE LEFT BEHIND WHEN CURES ARE DISCOVERED."

The database also will include environmental data, which when combined with genomic data should give researchers insights into risk factors.

"I am willing to predict that we will be able to demonstrate that what we call Type 2 diabetes will be made up of several subtypes, each with different factors for vulnerability and resilience and with different responses to treatment," Collins said.

The idea is to go beyond a data set and build a "community of participants," giving other researchers the opportunity to recruit diabetic or prediabetic participants to join follow-up studies.

"This could give clinical researchers an opportunity to test health interventions to see if they may be effective in early detection and treatment of prediabetes, or in trying new interventions for those diagnosed with the disease, including such things as the artificial pancreas," he said.

Another promising area for the research project is Alzheimer's disease, as genetic sequencing and family health history can help identify those predisposed to the disease. Part of the data gathered to inform researchers about Alzheimer's and other health conditions will be wearable devices that record exercise and sleep. Surveys and diet diaries will be used as well to assess variables that influence an individual's risk for developing a condition.

"We might even use smartphone-based assessments of voice and speech to see if they can help us predict the onset of Alzheimer's," Collins said.

"And, as with diabetes, when new treatments for individuals emerge, All of Us will be in an excellent position to enroll quickly and efficiently."

The project also will empower research on areas such as cancer, infections, mental health, hearing loss, kidney disease, pain, and addiction. "I invite all of you to imagine the ways in which this resource can speed up your own research studies," he said.

Returning to a recurrent metaphor, Collins said All of Us will be like the landmark 1948 Framingham (MA) Heart Study writ large. Following thousands of people for decades, that study revealed some of the first definitive data about the risks of smoking, cholesterol, and high blood pressure for heart disease.

"If a study of just 5,000 people could contribute to a 67% decrease in deaths from heart disease in the past several decades — and that's what's happened — I think it's safe to say that the potential for All of Us is almost boundless," Collins said. ■

Next Challenge for IRBs: Nanomedicine Research Risks

Paper suggests existing laws work

IRB members soon will see — if they haven't already — protocols involving medical therapies with materials that are so tiny that a human hair is 80,000 times their width.

"There are lots of studies now where people are exposed to nanomaterials," says **David B. Resnik**, JD, PhD, bioethicist and IRB chair at the National Institute of Environmental Health Sciences (NIEHS) — part of the National Institutes of Health (NIH) — in Research Triangle Park, NC.

Nanotechnology involves designing materials that are 100 millionths of a millimeter, called 100 nanometres. Nanomaterials have been used in drug delivery, diagnostics, and regenerative medicine. *(For more information, visit: http://bit.ly/2VbYDDR.)*

Resnik recently authored a paper addressing ways in which engineered nanomaterials should be regulated. He concluded that existing legal frameworks sufficiently minimize and manage risks of engineered nanomaterials.[1]

Policymakers should regulate nanomaterials through existing laws and support research on risks posed by nanotechnology, he wrote.[1]

Seven years earlier, more than two dozen researchers in a multidisciplinary, NIH-funded project group addressed the nanomedicine research field and potential for additional oversight. The project group recommended a coordinated approach to federal and institutional oversight of nanomedicine human subjects research. They called for a focus on strengthening existing oversight and avoiding new requirements unless they were found to be necessary.[2]

So far, nanomaterials research has not set off alarms. "As far as I know, right now, the nanomaterials they are using in research are not very risky," Resnik says. "It might be, in the future, that there are things that are riskier that we need to be aware of."

For example, one of the most promising uses of nanomaterials is in drug delivery, he explains.

"There are cancer treatments now that use a nanoshell to deliver chemotherapy, and the shell attaches to the cancer cell and delivers chemo to the cancer cell but doesn't deliver it to the rest of the body," Resnik says.

The NIEHS IRB, which Resnik chairs, has reviewed a study that uses inhaled nanosilver to look at lung function.

"They wanted to know how nanosilver would affect the microbiota in the lung, the lung's bacteria," he says. "Silver is used as an antibacterial agent, and nanosilver is widely used in wound dressings."

The research examined the risks of inhaling nanosilver. The IRB wanted to know about prior nanosilver research and studies, Resnik says.

"We also wanted to know something about the manufacturers and their quality control and how they're making the material," he adds. "Since people were already using nanosilver, and there were no reports of adverse events coming out of it, we assumed it was relatively safe — especially given the small amount we'd ask people to inhale, and the duration."

When the IRB reviewed the study, members were unaware of any safety warnings by the FDA, but there still could be risks, he notes.

"Safety issues often take time to emerge; you don't find out about things until something has been on the market for years," Resnik says.

A chief risk of nanosilver is that it might interfere with the body's microbiota, which studies show is important to human health.

"When you use an antibiotic, you cause an imbalance in microbiota, and people can get sick because their flora in their body is out of balance — you kill off the good bacteria you need," Resnik says.

One of the outcomes being addressed in the nanosilver study was whether the product killed off some of the bacteria in the lungs and interfered with lung function, he adds.

The European Commission also examined safety, health, and environmental effects of nanosilver, concluding that more research data are needed. *(More information is available at: http://bit.ly/2GVEKqx.)*

When IRBs review nanomedicine protocols, they should assess the risk of introducing nanomaterials into the body, and they should approach this with a degree of skepticism, Resnik says.

"Researchers probably owe IRBs some proof of safety of the materials, based on prior animal studies or laboratory studies," he adds.

For instance, IRBs might view nanomaterials research in the same way they approach review of a Phase I study that tests a new chemical

in a human or a new gene therapy procedure, he suggests.

"You have to do a proper risk assessment before you use this new therapy in humans," Resnik says.

Some nanotechnology might pose risk to people who work with the material, such as carbon nanotubes, which are nanocarrier systems used in engineering and science. In 2010, the U.S. Department of Health and Human Services (HHS) published a 284-page paper about the occupational health and other risks of carbon nanotubes and carbon nanofibers. The paper described rodent studies that showed adverse lung effects from the nanomaterials, and HHS recommended exposure limits. *(For more information, visit: http://bit.ly/2Y2ElcW.)*

"They've done studies in animals where when they inhale carbon nanotubes, the lung produces an immune response to it, which is not surprising and can interfere with lung function," Resnik says. "So there are definitely concerns about nanotubes and immune response."

The risk of inhaled carbon nanotubes has to do with manufacturing the material — not research, he notes.

"The studies we've looked at have been in animals, and no one I know of is asking people to inhale carbon nanotubes," he adds. "So it's more of a risk for people manufacturing carbon nanotubes, where they can get loose in the environment or in dust."

When carbon nanotubes are inhaled into the lungs, they act like asbestos, Resnik says. ■

REFERENCES

1. Resnik DB. How should engineered nanomaterials be regulated for public and environmental health? *AMA J Ethics*. 2019;21(4):E363-369.
2. Fatehi L, Wolf SM, McCullough J, et al. Recommendations for nanomedicine human subjects research oversight: an evolutionary approach for an emerging field. *J Law Med Ethics*. 2012;40(4):716-750.

New Tool Helps With Study Recruitment

Department of Energy (DOE) researchers developed a new tool to connect cancer patients with clinical trials. The tool uses a Netflix-style of analytics to recommend studies that would be a good fit for particular patients.

This technological solution could help improve trial enrollment in several important ways, says **Ioana Danciu**, MS, biomedical scientist, engineering and computing group at the Health Data Sciences Institute of Oak Ridge National Laboratory (ORNL) in Oak Ridge, TN.

The approach improves trial matching by using natural language processing techniques on the unstructured eligibility criteria to extract certain data elements such as labs. It also clusters clinical trials that are similar, using an approach called agglomerative clustering — similar to what Netflix uses for movie recommendations, Danciu explains.

"The approach also improves matching by adding this information into an exascale knowledge graph that connects data from disparate sources, such as electronic health records, medical ontologies, and public datasets," she adds.

ORNL's SmartClinicalTrials capability builds on an existing collaboration between the DOE and the National Cancer Institute, Danciu notes.

ORNL researchers are leading a pilot effort to expand cancer surveillance capabilities and build statistical models that are capable of predicting the clinical course and outcomes for different types of cancer, she explains.

"As part of The Opportunity Project, we collaborated with data owners from the National Cancer Institute and the Department of Veterans Affairs," Danciu says.

The tool has artificial intelligence (AI) capabilities as it can store data, continuously add new information, and allow for computational analysis and knowledge discovery.

"We are using natural language processing in the context of AI to understand the unstructured inclusion criteria, group similar trials together, and perform exascale graph analytics," Danciu says.

ORNL's AI Initiative helped make development of the tool possible, accelerating scientific research breakthroughs.

It is a benefit to cancer trial enrollment because eligibility data often are unstructured in nature, whereas the use of an artificial intelligence tool helps to improve the process of matching cancer patients to clinical trials, Danciu notes. ■

COMING IN FUTURE MONTHS

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IRB ADVISOR

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CME/CE QUESTIONS

1. **After one year, the National Institutes of Health's All of Us initiative has enrolled approximately what percentage of racial and ethnic minorities represented in research participants?**

   a. 15%
   b. 25%
   c. 50%
   d. 70%

2. **Francis Collins, MD, director of the National Institutes of Health, predicted that the research data generated by the All of Us project will show which of the following diseases is comprised of subtypes?**

   a. Prediabetes
   b. Alzheimer's disease
   c. Parkinson's disease
   d. Type 2 diabetes

3. **If investigators propose giving research participants incentive payments of $600 or more, what must they do, according to federal law?**

   a. Report the payments to the FDA.
   b. Collect the participant's Social Security number and file IRS form 1099-MISC.
   c. Give the IRB evidence, derived from a pilot survey, that such a payment would not be coercive.
   d. If the $600 is in cash, they must report it to the IRS, but gift cards or other gift items only should be reported to the IRB.

4. **What is nanotechnology?**

   a. It involves designing materials that are 100 millionths of a millimeter, called 100 nanometres.
   b. Nanomaterials are used in space exploration to help recycle astronaut waste.
   c. Nanotechnology refers to the development of auditory processes in manufacturing and medicine.
   d. Nanotechnology involves the study of shrinking cells for purpose of one day transporting inanimate objects rapidly across space.