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INSIDE

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Right to Try Law in Regulatory Limbo

FDA 'expanded access' may prevail in the confusion

By Gary Evans, Medical Writer

On May 30, President Trump signed into law the Right to Try Act, which seeks to give patients a new pathway to experimental drugs. The law, however, has been dogged by implementation questions and remains in regulatory limbo.

Given the circumstances, the prevailing thought is that the ongoing "expanded access" pathway to experimental drugs currently in place at the FDA will continue to be the preferred method.

> THE PREVAILING THOUGHT IS THAT THE ONGOING "EXPANDED ACCESS" PATHWAY TO EXPERIMENTAL DRUGS CURRENTLY IN PLACE AT THE FDA WILL CONTINUE TO BE THE PREFERRED METHOD.

"My prediction is that all reputable players — be they doctors, institutions, or companies — are going to decide to stick with expanded access," says **Alison Bateman-House**, PhD, MPH, MA, a professor in the division of medical ethics at New York University Langone Medical Center.

David Borasky, MPH, CIP, vice president of IRB compliance at the WIRB-Copernicus Group in Cary, NC, says his organization is taking a "wait and see" approach to the new law.

"We have always as a company done our best to help anybody that needed expanded access," he says. "We are very comfortable and used to processing the IRB review requirements for the expanded access pathway. In the short-term, we are going to continue to work with anybody [under] the FDA expanded

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access program for unapproved drugs and devices."

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. To be eligible, the investigational drug cannot be approved for any FDA use, but Phase I of a clinical trial must be completed. Under these conditions, FDA and IRB approval would not be required, although institutions and drug companies could seek IRB guidance.

After the law was passed, FDA Commissioner Scott Gottlieb, MD, said the agency's expanded access program would continue to operate alongside Right to Try. Gottlieb said drug companies will still prefer the FDA oversight under expanded access. *(For more information, see the related story in the July 2018 issue of* IRB Advisor.*)* Under

Unresolved Issues With 'Right to Try'

Alison Bateman-House, PhD, MPH, MA, and colleagues at the New York University School of Medicine Working Group on Compassionate Use and Pre-Approval Access (CUPA) recently issued a statement[1] that cited the following unresolved issues on the federal Right to Try (RTT) law.

- How many companies or healthcare institutions will permit use of the RTT pathway?
- Who will oversee the implementation of the law (write rules/guidance) and compliance with it?
- Although the statute references a federal regulation that stipulates that sponsors can charge only direct costs for investigational products, what will this restriction mean in practice? How will companies interpret it? How will it be enforced, and by whom?
- Who will pay for drugs obtained via RTT and the costs of administering them? What about related medical, travel, childcare, and other expenses?
- Are companies' RTT policies subject to the 21st Century Cures Act's transparency provisions that require companies with investigational products in Phase II or later to make their expanded access policies publicly available?
- In the absence of federally mandated FDA and IRB oversight, will healthcare institutions or companies require in-house or other third-party oversight of nontrial use of investigational drugs? ■

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1. Statement on the Enactment of a Federal "Right to Try" Law from the NYU School of Medicine Working Group on Compassionate Use and Pre-Approval Access (CUPA). June 25, 2018. Available at: https://bit.ly/2m5E4oQ.

expanded access, prior IRB approval is waived in emergency situations, but the IRB must be notified within five days of approval.

"I think a legitimate company that has a plan to develop a drug and bring it to market — and has to be accountable to a board, shareholders, and everyone else — will continue to use expanded access. So far, that's what we are seeing," says Bateman-House.

Informed Consent Requirements Unclear

Advocates of the law said one of the primary goals was to bypass FDA regulations and oversight. As a practical matter, the law lacks implementation guidance, particularly on the issue of informed consent.

The law requires that a patient give the treating physician written informed consent and specifies that the FDA's informed consent regulations do not apply, explains **Patricia J. Zettler**, JD, associate professor at Georgia State University College of Law in Atlanta.

"The law basically says that the patient must give informed consent," she says. "That informed consent does not have to conform to the FDA regulations, but then the law gives no additional guidance about what informed consent means. It is not necessarily clear what information physicians should be providing to Right to Try patients. It is unknown at this time."

Thus, bypassing the FDA on this issue is problematic, as the agency would appear to be the most logical entity to clarify informed consent requirements, Bateman-House says.

"Somebody has to turn a vague law into rules or else it's not going to work and no one will be able to use it," she says. "There doesn't seem to be any other reasonable actor — it has to be the FDA. If [politicians] want to hamstring the FDA and say 'you're not going to do it,' then the law is effectively dead."

"IT IS NOT NECESSARILY CLEAR WHAT INFORMATION PHYSICIANS SHOULD BE PROVIDING TO RIGHT TO TRY PATIENTS. IT IS UNKNOWN AT THIS TIME."

Still, she reminds that the FDA is not completely out of the loop, as Right to Try requires the agency to submit an annual report on patients granted drug access under the new law.

"The FDA is removed from reviewing each individual request, but it is not removed from having some role to play overall," Bateman-House says.

Climate of Uncertainty

In the current climate of uncertainty, some institutions are adopting policies saying they will continue with expanded access and not consider Right to Try requests, Bateman-House says.

"I'm hearing lots of backchannel conversations of institutions putting in policies saying that they will only allow these things via expanded access," she says. "If your institution has no such policies, then theoretically a doctor could treat a patient with an investigational product without it ever going past the IRB."

Given liability concerns, institutions may adopt a policy clarifying that the IRB must approve any experimental drug use, regardless of pathway.

"That is speculation. I am not aware of anyone doing that, but I could see an institution saying that just for liability purposes," Bateman-House says.

"They may say as part of the agreement you have to have an IRB review because otherwise who is going to say there is valid informed consent?"

A particular concern to Bateman-House is how the Right to Try Act affects similar laws already on the books in 40 states.

"Lawyers tell me that when a federal law and the state law deal with the same topic, the federal law is paramount," she says. "That is what I am worried about because my understanding is that the things that are not mentioned in the federal law are still valid, on-the-book laws in those states. I think that adds to the confusion."

Some of the state requirements that did not make it into the federal bill are "patient-hostile provisions," she said. These provisions include potentially denying patients home healthcare, hospice, or other insurance if they try an investigational drug.

"There are reasons they didn't make it into the federal law because they are highly punitive, and it would not have passed," she says. "But they are still law in some of those states." ■

Researcher Explains How Data Sets Can Affect Study Privacy

Process can more accurately assess risk

Human subjects research increasingly involves the use of large data sets that allow analysts to drill down to the most specific of details from healthcare records or other databases. This creates challenges in ethical data analysis and information privacy.

Researcher **Hye-Chung Kum**, PhD, associate professor at Texas A&M University in College Station, was involved in a study about this topic, titled "Controlling privacy risk in database studies for human subjects protection via a privacy budgeting system."[1]

The study proposed a privacy budget system for human subject protection, using anonymity set size to define allowable risk in database studies.[1]

Kum explains more about the study and how this privacy budgeting system works in the folllowing Q&A:

IRB Advisor: How do you determine the anonymity set size (n)?

Kum: That should be based on the acceptable policies and practices of the organization and legal restrictions in the application.

For example, I am on a project where the DUA [data use agreement] specifies that aggregate data less than 10 cannot be published. In such situations, when anonymity set size equals 10, then information that represents less than 10 people will pose a risk that needs to be quantified. While, on the other hand, information that represents more than 10 people does not pose risk of identification and no risk is present.

IRB Advisor: Why was this chosen as the way to define allowable risk in database studies?

Kum: I think there might be a misunderstanding. The anonymity set size is not the allowable risk, but rather the threshold where risk needs to be quantified. Information that presents more than the given anonymity set threshold is considered to not have any risk of privacy violation.

> "THERE IS NEGLIGIBLE RISK OF IDENTIFICATION BECAUSE THE EXPOSED INFORMATION REPRESENTS MANY PEOPLE AND, THUS, THE INFORMATION IS NOT SUFFICIENT TO KNOW WHO IT IS ABOUT."

There is negligible risk of identification because the exposed information represents many people and, thus, the information is not sufficient to know who it is about. For example, if there are 10 people named "Tom" in the database, there is no way to know which of the 10 people that exposed information is about.

Although this level of detail is not discussed in the poster,[1] the framework has a separate parameter that is set, called allowable risk, as a hard threshold if desired. When the allowable risk parameter is set, then no information is displayed unless information represents more than the allowable risk count. The default for this parameter is set to 1, meaning that any information may be displayed.

IRB Advisor: How does your privacy risk score work? What kind of score is it, and what does it mean when a person in a database has a rare name like "Hye-Chung"?

Kum: Let me answer the second question first. When a person in the database has a unique name, such as "Hye-Chung," this means that the only information that has to be disclosed to know exactly who this person is would be just the first name.

On the other hand, if a person has a common name like "Tom," this means that name itself is not much of a privacy risk since it has very little power to identify a unique person. So "Hye-Chung" has a high risk score, and "Tom" has a low risk score.

All information that is disclosed can be measured (that is, privacy risk measure) in terms of how unique the disclosed information is. So if you have a birthday, 2/29/2000, and you happen to be the only person in the database born on 2/29, just the month and day of your birth is sufficient to identify you exactly.

Now to answer the first question, the score is based on this principle:

The risk score is between 0% and 100%. Where all information is disclosed, the score will be 100%, and 0% represents no information is disclosed. It is an accumulative score for the whole database, so if there are "n" records in all the databases that need to be linked, 1/n% is the score corresponding to one row. Then, for any given information disclosed for the row, it ranges from 0% to 1/n%, "allotted for the row." It is close to 0% if the information disclosed does not uniquely identify the person represented in the row.

On the other hand, if the information disclosed uniquely identifies a person, then it would be close to the max (=1/n%). The actual formula is pretty complicated and takes into account multiple things to meet certain properties (e.g., everything adds up to 100%).

But the most important thing is that most risk is accounted for when unique information is disclosed for everyone. So even if a lot of information is disclosed, if none of the information actually is unique for anyone in the database (for example, if year of date of birth is disclosed for everyone, but it is not unique to anyone, the risk score would be low), then the risk score is low.

IRB Advisor: In your poster,[1] it says that the proposed method has not been implemented, and more time is required to finalize and evaluate the concept. Is anyone planning to evaluate the concept? If not, why not?

Kum: I have a PCORI [Patient-Centered Outcomes Research Institute] project that is working on implementing a prototype and evaluating it.
(For more information on the project, visit: https://bit.ly/2O0F1LG.)

We hope to have initial evaluations done by the end of the project period, and have plans to secure more funding to harden the code. You can see how this works in a user study implementation we did at: https://bit.ly/2uEC8az.

You can see how "percentage of characters disclosed" compares with the risk score when different information is disclosed. The "percent disclosed" is simple to understand, but does not represent actual risk. So for certain information you barely see any movement in the risk score, but other information (such as ID numbers), you see large scores. But in the "percentage disclosed," the score is uniform across all information regardless of the actual risk.

> "IT IS CRITICAL THAT WE FACILITATE ACCOUNTABLE USE OF DATA TO IMPROVE HEALTHCARE AND BENEFIT SOCIETY."

IRB Advisor: If this risk score is evaluated and implemented, how might it change the way privacy is viewed in database studies?

Kum: If the risk score is implemented and used commonly, people would be able to more precisely measure the actual risk of privacy loss in database studies because it would be directly linked to actual risk as opposed to very rough potential of risk when certain identifiers are shared in database studies. It would make it more possible to rely on "expert determination style" of privacy risk management based on real risk, as opposed to safe harbor style which assumes a worst-case scenario, making database studies seem much more risky than they really are.

IRB Advisor: Is there anything else you would like to say about this study and risk score methodology?

Kum: Using and leveraging personal data has inherent risks for information privacy, as it has been proven mathematically that information privacy is a budget-constrained problem. The key to properly manage the risk for legitimate uses of personal data is balancing the utility of data with the privacy risk. In particular, since informed consent in retrospective database studies is not possible, it is important that IRBs learn to balance the risk of harm and benefits to society.

Risk in retrospective database studies can be effectively managed to minimal levels through proper use of secure computing systems and training. Given how common use of personal data is these days, retrospective database studies that use personal data do not pose risks greater than those ordinarily encountered in daily life when such systems and oversight exist.

In addition, IRBs should recognize that authorized access to personal data for research is an important and legitimate use for social benefit. It is critical that we facilitate accountable use of data to improve healthcare and benefit society, just as it is used by the private sector for marketing, campaigning, etc. ■

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1. Ferdinand A, Schmit C, Kum H-C. Controlling privacy risk in database studies for human subject protection (HSP) via a privacy budgeting system. Poster presented at PRIM&R's 2016 Advancing Ethical Research Conference, Nov. 13-16, 2016, in Anaheim, CA. Poster: 17.

Final Common Rule Compliance Date Set

'Burden-reducing' provisions for IRB consideration

The revised Common Rule has been issued in final form,[1] with IRBs allowed to use three "burden-reducing" provisions to prepare for a Jan. 21, 2019, compliance date.

This follows the publication of an interim final rule[2] and delay announcement on Jan. 17, 2018, which was then followed by request for comment on April 20.[3]

"The one exception to this general rule is that institutions will be permitted (but not required) to implement, for certain research, three burden-reducing provisions of the 2018 requirements during the delay period (July 19, 2018, through Jan. 20, 2019)," the final rule states. "Institutions taking advantage of the three burden-reducing provisions must comply with all other pre-2018 requirements during the delay period."

Moreover, the burden-reducing provisions can only be implemented during the delay period with respect to studies initiated prior to Jan. 21, 2019, that will "transition to compliance" with the revised Common Rule.

The burden-reducing provisions include:

- a revised definition of "research," which deems certain activities not to be research covered by the Common Rule;
- elimination of the requirement for annual continuing review with respect to certain categories of research;
- elimination of the requirement that IRBs review grant applications or other funding proposals related to the research.

Given the thicket of regulatory action and delay, *IRB Advisor* spoke to **David Borasky**, MPH, CIP, vice president of IRB compliance at the WIRB-Copernicus Group in Cary, NC.

IRB Advisor: Can you put this issuance of a Final Rule with an effective date of Jan. 21, 2019, in context with the other actions and previous iterations in this process?

Borasky: Six months ago or so, we were waiting for the final rule to go into effect with a Jan. 19, 2018, implementation date. Then within days of the go-live date they issued the first six-month extension. There was a delay until at least July, and then they mentioned the fact that they anticipated an additional delay. People were relieved to know the status, and then during the additional delay the big hope was if it was going to further delayed that they wouldn't wait until the last minute again.

I think in general, the IRB community — whether they wanted the additional delay or not — was happy to know the status fairly early. Since April we have known the status of the delay. It is delayed until January 2019, except for these three burden-reducing provisions.

IRB Advisor: What are the benefits of these provisions?

Borasky: They are sort of a mixed bag. The first was a change to the definition to research. Really, the definition in the new rule is more exclusionary. It is taking things out of the realm of research, like journalistic and scholarly activities, and public health surveillance. I think many IRBs already had cut down the scope [of these], but there was concern from some researchers that their IRBs were engaged in mission creep. I think the regulators purposely called this out as things to get out of there.

I suspect, and this is just my opinion, that they made that one of the burden-reducing provisions because it is pretty easy to implement without much additional guidance. It is what it is. There should be no question that public health surveillance is not research. That was sort of a no-brainer, and a nod to a lot of the nonmedical community who were seeking some relief under the new rule.

IRB Advisor: What about the provision dropping the review of grant applications?

Borasky: That was just sort of a nuisance thing that had crept into requirements for IRBs, probably back in the late 1990s or around 2000. OHRP had made it clear that they expected IRBs to be looking at grant applications, primarily from NIH, to make sure that there was concordance between what the awardees said they were doing in their grant, and what they told the IRB they were doing.

In reality, I am not aware of any time that an IRB found a complete discrepancy between the two, so most IRBs viewed it as a nuisance requirement that we did because we knew there was an expectation to do it. So I think having that go away is also a nice thing.

IRB Advisor: What about dropping the annual continuing review with respect to certain categories of research?

Borasky: This one is the most

interesting. I would say that is the biggest immediate change that we could make. We have the ability now to not do continuing review for certain activities. I think institutions will be eager to start doing that, taking things off the plate of their IRB administration.

Probably the biggest one is that under the new rule, studies that start off as expedited review don't have to come back for continuing review. There are also some specific carveouts in the rule itself.

IRB Advisor: Is there any downside to IRBs adopting these burden-reducing provisions?

Borasky: The questions I have been getting are whether institutions and IRBs should implement these burden-reducing provisions. The hiccup in it is if you decide to do that with a protocol now, then in January you have to apply the rest of the new rule to any protocol you approved using the burden-reducing provisions. For example, if you had a grant come in and you wanted to approve it without reviewing the grant application, then by January — when the rest of the rule goes into effect — you have to build in all of the new consent form requirements and required elements of consent.

I know there is some chatter among my colleagues on IRBs about whether they want to do that. If they do implement now, should they go ahead and implement everything they can implement now? Because that would save you approving something now in August 2018, and then coming back in January and making the researchers make changes to conform to the rest of the rule.

IRB Advisor: You note that at some point the FDA will have to harmonize its requirements with those in the Common Rule.

Borasky: The thing to remember in the regulated community is that until the FDA is clear about where they can harmonize, these new burden-reducing provisions to exempt something from continuing review — those are not allowed by the FDA regulations at this time. So if you had an FDA-regulated study, you couldn't start using the continuing review provision because that is inconsistent with the FDA regulations — at least until the FDA comes out with a statement about how they are going to harmonize. It is a little bit of a wrinkle that gives some people pause.

I think it is going to be institution by institution. Part of it will depend on an institution's research portfolio. We receive a lot of FDA-regulated studies, so we are careful about not implementing something that currently does not meet FDA regulatory requirements.

If I was at an institution that had largely NIH-funded studies, it would make a lot of sense to just start applying these things now. It will be interesting to see the uptake of these burden-reducing provisions.

IRB Advisor: There has been a lot of activity and uncertainty. Do you expect this to be the final iteration of the Common Rule going forward?

Borasky: I think the OHRP has been pretty clear. I would never say never, but what we are going to see next January is the implementation of the final rule as it is written now — as it would have gone into effect this past January. I don't anticipate any more tinkering with the rule itself or any more extensions.

In reading the preamble to this additional delay, I was personally curious to see how they responded to comments. Nearly half of the people that submitted comments really just said, "You should implement the whole rule now." I think people are tired of waiting and are ready to go — or as ready as they are going to be. This additional six months does allow OHRP to write guidance and probably for the FDA to figure out where will be their pain points in trying to harmonize with this.

IRB Advisor: OHRP has been criticized for a lack of implementation guidelines. Is that situation changing?

Borasky: OHRP has been pretty clear in some of their public comments that they are working on guidance. They know the areas that probably will require the most guidance because there are new aspects of these new regulations that are whole-cloth new. There is nothing about them related to the old regulations — categories of exemptions and so forth. They are working on those. ■

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Studies of Insects as Food Now Heading to IRBs

Many could be exempt as 'wholesome foods'

Research participants recently were asked to taste test chocolate chip cookies. One version was slightly darker and had a distinctive aroma. Researchers needed to know what they thought of their cookie's appearance, taste, smell, and texture. The IRB reviewing the study wanted to know how exactly people were told that their cookie might be made from crickets.

"It presented a unique situation to our IRB, which we had to manage through," says **Alyssa Joy Bakke**, PhD, a research technologist at Pennsylvania State University in University Park.

"What we were testing was looking at chocolate chip cookies, both ones with and without cricket flour in them," Bakke says. "Can we make a food that has cricket powder in it and it's still acceptable, and what are people's perceptions of the product and what are some of the intrinsic personality characteristics that impact people's liking of a novel food?"

During informed consent, researchers told participants that some products would contain crickets, but half of the subjects participated in blinded tests in which they didn't know whether they were tasting the cricket cookies or regular cookies. The other half knew whether their cookies contained cricket flour.

"We had interesting results," Bakke recalls. "People tended to be more accepting when they knew it had crickets in it, saying, 'OK, this is pretty good for a cricket cookie.'"

It is still unusual for IRBs to receive protocols involving insect-derived food, but it can and does occur, so they should be prepared.

Bugs as food is a growing enterprise, with cricket farms, university "bug bowls," and "insect delis" cropping up in recent years.

"For several years, when I was at Purdue, there was an annual bug bowl event," says **Kristine Hershberger**, CIP, director of the human research protection program at the University of Tennessee in Knoxville.

A professor brought awareness of insects with edible insects and cricket spitting, she recalls.

Likewise, Penn State holds a fair in which the public is invited to try chili-encrusted crickets and other insect delicacies, Bakke says. "It's for kids, and they get a bug sticker when they go through the line."

Also, as people increasingly travel or meet people from international communities, they find that insect-derived food is commonplace in some other locales, says **Harry McGee**, MPH, IRB chair at Michigan State University in East Lansing.

"I worked in the Congo, Zaire, and Bangladesh, and in the Congo, eating insects was very common," McGee says. "I ate these flying termites that tend to harvest during the rainy season and palm grubs, which are larvae of beetles that attack palm trees."

Larvae are high in fat, so these can cook in their own fat, and termites are high in protein. In taste the palm larvae could be compared with shrimp, he says. "These are really good."

Because of these types of edible bug exposures, Hershberger was not too surprised when an investigator recently submitted a protocol involving roasted crickets. "It was surprising that it's taken this long."

The IRB had some additional questions for investigators, and the review process is ongoing, Hershberger says.

"Our IRB chair brought the study to my attention, not really knowing if there were any requirements, so I said I'd do some digging to see what I came up with," she explains.

Hershberger asked a question about insect food studies on the IRB Forum, and she researched it online.

"But all I could find were references to how many parts of insects were allowed in prepackaged foods, and the European Union had recently passed some legislation, and I found something about that with regards to edible insects," Hershberger says. "And the U.S. FDA has been funding some projects in cricket farming."

As IRBs receive inquiries about unusual studies and deal with new regulations about exemptions, institutions will need to update policies and processes to handle research that doesn't fit the usual categories.

For example, insect food is food. But can IRBs really treat it like they would beef?

One U.S. code that might apply to insect-derived food studies is 42 U.S. Code 1791, the "Bill Emerson Good Samaritan Food Donation Act." If the edible item is an "apparently fit grocery product," meeting all quality and labeling standards by all applicable laws, then it's food. It also could be "apparently wholesome food," meaning the same thing.

If it's food, then a taste test would be low risk and might qualify for exemption from IRB review.

Investigators of the cricket cookies found the most difficult part of the IRB process was finding a regulation that matched their investigational product, Bakke says.

"Under the Food, Drug and Cosmetic Act, bugs and insects are considered food, if that's the intended use," she explains. "Specifically, it has to be raised as human food and not for pet food."

A study involving whole insects that were properly cooked might be of less concern to an IRB than would insect-derived foods, McGee says.

"For instance, if there's a product with deriving material from insects, I'd want to know how they're doing that in order to make the derivative material safe," McGee says. "And how is it going to be prepared safely?"

Research of taste-testing that involves unusual foods like insects might be exempted under the wholesome food category, but sometimes researchers will seek IRB review if there's a specific ingredient that might raise questions, Bakke says.

For example, research involving extracted, pure capsaicin, a compound that makes chili peppers spicy, might not be exempt research, she says.

"We might need to work with the IRB to make sure we're not giving it at too high a level," Bakke says.

Another risk could be food allergies. Less is known about insect food allergies, although some research suggests that people with shellfish allergies could be susceptible to problems with crickets and other insects, Hershberger says.

According to www.edibleinsects.com, people with shellfish allergies might be allergic to the chitin, the insect's exoskeleton, which is similar to the chitin in crustaceans. Pesticides and herbicides also could be a problem with insects gathered in the wild and not on a farm for human consumption.

So the best strategy for handling insect-derived food studies might be to ask questions about the origin of the insect product and to make certain informed consent lists all potential risks.

"The potential for an allergic reaction would be my greatest concern, and it's the biggest safety issue I can think of," Hershberger says.

For Bakke's cricket cookie study, investigators told participants in the informed consent that the cookies might contain crickets and that people with known shellfish allergies have reacted to insects in the past.

"We screened out allergies in the inclusion and exclusion, and we put it in the informed consent in case someone slipped through the cracks," she says. "But that was the only risk. The way we worded it was that the risks are no greater than what you would encounter in daily living because there is a specific IRB exemption carve out for wholesome foods tests." ■

Report Examines How Research on Donated Organs Can Be Ethically Performed

Thousands of available organs discarded annually

More than 115,000 transplant candidates are on a waiting list for organs — but only about 33,500 organs were transplanted in 2016. These numbers tell an unfortunate story: every year, thousands of people die waiting for an available organ.

"We are all aware of the substantial gap between organs that are needed and organs that are available. There is a huge gap between supply and demand," says **James F. Childress**, PhD, John Allen Hollingsworth professor of ethics and emeritus/founding director of the Institute for Practical Ethics and Public Life at University of Virginia in Charlottesville.

Much of the discussion to date has centered on how to increase the number of organ donors. Few people are aware of the need to improve the quality of the organs that already are available.

"Many in the transplant community have proposed that we research ways to improve donated organs for transplantation in order to improve transplant outcomes and reduce the gap," says Childress.

Almost 5,000 organs from deceased donors were discarded in 2015 because they were deemed unsuitable for transplantation.[1] Some donated organs are used solely for research because they don't meet the criteria for transplantation. "Research is needed on how to best

optimize organs for transplantation," says Childress.

Interventions on the organs while they are still in the donor's body or shortly after removal could improve the chances of a good outcome for the recipient. "Some research has been done, with some good results. But there are some perceived obstacles to doing this research," says Childress.

A Delicate Balance

In 2016, The National Academies of Sciences, Engineering, and Medicine assembled an expert panel to examine the ethical, legal, regulatory, policy, and organizational issues related to research in the United States involving deceased organ donors. The committee looked at how this important research can be performed ethically, in adherence with the regulatory and legal rules currently in place.

"Our task was to determine: Can this research be conducted ethically, within those frameworks? And if so, how? It's a delicate balance," says Childress, chair of the study committee.

The resulting October 2017 report, "Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation," offers recommendations for conducting organ donor intervention research in a way that maintains high ethical standards, ensures dignity and respect for deceased organ donors and their families, and provides transparency and information for transplant candidates who might receive a research organ.[2,3]

Trustworthiness of the organ donation system, and of research involving human subjects, is heavily emphasized. "We depend on the public to donate organs and to participate in research to generate knowledge and benefit others," says Childress. Some of the committee's recommendations include the following:

- The Uniform Anatomical Gift Act should be clarified to allow people to understand that donated organs might be used for research and transplantation.

"It's not a single purpose, but a combined purpose," says Childress. "People need to understand as much about this as possible so they don't end up feeling that their trust has been violated."

- Donor registries and departments of motor vehicles should use consistent language to communicate about this type of research to potential donors and surrogates.
- Recipients of organs that have been subjected to research interventions and are now being studied for their function, efficacy, and safety should be treated as research participants.

Deceased organ donors are not characterized as research subjects because federal regulations for research protection only apply to living individuals.

"Nevertheless, it's important to respect individuals and surrogates in making decisions about organ donation, and to determine if they are willing to donate for this purpose," says Childress.

The committee contended that under most research protocols, patients who receive organs that were subject to a research intervention are research subjects. "This raised a lot of issues," says Childress. "For instance, research informed consent may be very difficult to obtain when organs need to be transplanted quickly."

Realities of Transplantation

A robust clinical informed consent process that includes specific regulatory requirements already exists for transplantation, says **Alexandra K. Glazier**, Esq., president and CEO of New England Donor Services in Waltham, MA.

For donor research where the transplant recipient does not fall under the regulatory definition of human subject, the clinical consent model — rather than the consent model used for human research subjects — best balances clinical innovation, transparency, and protection of patients, she argued in a recent paper.[4]

"The ability to conduct research trials to evaluate interventions on the deceased donor, or donor organ, remains complicated and fraught with regulatory ambiguity," says Glazier, who co-authored the paper.

Characterizing recipients of organs that have been subjected to a research intervention under existing regulatory requirements is one example. "The need for a precise legal and ethical analysis that maps the regulatory language and the complex process of donation and transplantation was needed," says Glazier.

Facilitate Informed Consent

Much of the discussion in the field regarding deceased donor intervention research has been predicated on the assumption that

recipients of these organs are human subjects — even if no research intervention or interaction will take place after transplantation. "The implications of that conclusion are numerous," says Glazier.

Regulatory requirements for IRB review and human research subject informed consent emphasize beneficence, autonomy, and transparency. "While these goals are appropriate, the process required does not comport with the realities of transplantation," says Glazier.

Many ethical concerns will not be resolved merely by categorizing transplant recipients as human subjects. For example, the time-critical process of organ offers and the transplant candidate's health status greatly reduce the ability for effective informed consent. Many individuals are incapacitated at the time of organ offer.

"Requiring human research subject informed consent at the time of organ offer could raise issues of undue influence, when the ability to receive an organ transplant is predicated on consent to participate in human subject research," says Glazier.

Glazier would like to see changes that allow for vital research to be conducted, while addressing recipient informed consent in an ethically meaningful and realistic manner, given the complexities of the transplantation process.

"Although we conclude that transplant recipients of research organs may not be human subjects if no research intervention or interaction will take place, the need for effective informed consent remains ethically paramount," says Glazier.

To expedite organ donor intervention research, the committee recommended that a centralized review process with a single IRB be used. "This would eliminate the need to have a separate IRB for each transplant center sign-off on it," explains Childress.

To reduce delays, the committee recommended the following two-stage process of disclosing information to potential transplant recipients:

• The first stage would consist of informing potential recipients, at the time of intake or listing, about the possibility of being offered organs that were part of a research project, the different levels of risk associated with such organs, and the risks of declining an offer of a research organ.

Potential transplant recipients can indicate at that time whether they would be willing to consider a research organ, if offered. "Or, it could be more nuanced than that. For instance, the person might be willing to consider a minimal-risk organ," says Childress. If a potential recipient declines, he or she will not be notified when a research organ becomes available.

• Transplant candidates who have agreed to consider research organs will be notified when a research organ becomes available, and will be informed about its risk level.

Giving patients the option of accepting a research organ mirrors the ongoing debate regarding older organ donors.[5] "This is another factor like that, but in the research setting," says Childress.

Currently, if a person wouldn't consider a research organ at all but is offered one without anyone knowing the person's preference, the organ is declined. The transplant team has lost a lot of time — and the organ is likely to be discarded.

"What this proposal does is reduce the chance that someone will decline an available organ when it is offered," says Childress. ■

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CME/CE QUESTIONS

1. **Patricia J. Zettler, JD, said the informed consent provision of the federal Right to Try law reverts to what is required by individual state laws.**
   a. True
   b. False

2. **The federal Right to Try law will allow people access to investigational drugs under which of the following circumstances?**
   a. The drug has completed Phase I clinical trials but is not approved or licensed for use, and the patient has a terminal illness or condition.
   b. Patients have a serious physical or mental health condition.
   c. Emergency use of the experimental medication is approved by an IRB in a special session.
   d. None of the above

3. **How might human research protection risk be managed to minimal levels in retrospective database studies, according to researcher Hye-Chung Kum, PhD?**
   a. IRBs can prohibit use of data that poses any risk of deidentification.
   b. Investigative teams can use secure computing systems and training to minimize risk.
   c. IRBs can designate all database studies as exempt.
   d. All of the above

4. **David Borasky, MPH, CIP, said institutions should be careful in applying temporary burden-reducing provisions in the Common Rule because the changes have not yet been harmonized with requirements for research regulated by the:**
   a. National Institutes of Health
   b. Food and Drug Administration
   c. Centers for Disease Control and Prevention
   d. The National Research Council