IRB ADVISOR

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INSIDE

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Right to Try Law Raises Questions About FDA, IRB Oversight

'IRB review may be more necessary for patient protection'

By Gary Evans, Medical Writer

The FDA "remains committed" to reviewing and approving investigational drugs through its expanded access "compassionate use" program, which will continue in conjunction with the recently enacted federal Right to Try law, according to FDA Commissioner **Scott Gottlieb**, MD.

"Those suffering from a terminal illness who've exhausted available options should be able to access promising treatments being studied in clinical trials, or products under active review by the FDA," he said in a May 30, 2018, statement after the law was passed. The FDA will "implement this legislation in a way that achieves Congress' intent to promote access and protect patients … so that patients facing terminal conditions have an additional avenue to access promising investigational medicines."

> "SEVERAL STAKEHOLDERS RAISED CONCERNS THAT FDA IS NOT CLEAR ABOUT HOW IT USES EXPANDED ACCESS ADVERSE EVENTS DATA IN ITS REVIEW OF DRUGS BEING CONSIDERED FOR SALE AND MARKETING."

There was some question whether the law — which opens a new path for terminally ill patients to receive experimental treatment directly from pharmaceutical companies without being in a clinical trial — would effectively bypass the FDA process and render the agency review moot. However, Gottlieb said in an interview that the FDA's "compassionate use program will sit alongside 'Right to Try.' Nothing's

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going to change about our current approach. [Drug companies] will still want to offer drugs through the expanded access pathway because they see value in having FDA affirmatively adjudicate these individual patient requests."[1]

Gottlieb made the comments recently at the American Society of Clinical Oncology Annual Meeting in Chicago, where he updated other FDA actions. *(For more information, see related story on page 83.)*

The issue is far from resolved, as one of the backers of the bill emphasized in a letter to Gottlieb that the intent was to minimize FDA oversight, not to enable it to issue more guidelines or regulations.

"This legislation is fundamentally about empowering patients to make decisions in cooperation with their doctors and the developers of potentially life-saving therapies," Sen. Ron Johnson, R-WI, wrote in the letter. "This law intends to diminish the FDA's power over people's lives, not increase it. It is designed to work within existing FDA regulations, definitions, and approval processes."[2]

On the other side of the political debate, former FDA associate commissioner Peter Lurie, MD, MPH, said the legislation was "heedless of the facts, driven by emotion, mindlessly anti-regulatory, and certain to be exploited for political purposes despite its failure to solve anything."[3]

This Right to Try law amends the Federal Food, Drug, and Cosmetic Act to establish a new pathway 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. Either an FDA marketing application must have been submitted or the drug must be in a clinical trial aimed at establishing an efficacy claim. Under these conditions, FDA approval would not be required.

The FDA's compassionate use path already allows patients with life-threatening illness to use investigational medical products outside of clinical trials through its "expanded access" program. Prior IRB approval is waived in emergency situations, but the IRB must be notified within five days of approval.

This process has been considered onerous by some, but with Right to Try on the books IRB oversight may become more critical, says **Kelly McBride Folkers**, MA, research associate in medical ethics at New York University (NYU) School of Medicine.

To the extent the FDA is cut out of the process, there may be more support for IRB review as a patient safety assurance, she notes. While the Right to Try law does not require IRB review, many institutions may keep ethics oversight in place for patients seeking access to experimental therapies through this new pathway, Folkers explains.

"Without the FDA review and the fact that a federal Right to Try law is giving terminally ill patients and their clinicians the ability to make a direct interaction and transaction with a pharmaceutical company without this regulatory oversight, it appears that IRB review may be more necessary for patient protection," Folkers tells *IRB Advisor*. "It is unclear whether institutions will still require IRB review with the Right to Try pathway."

The law firm of Verrill Dana, LLP, in Westport, CT, weighed in on the

nuances of this point, noting that law "removes the FDA and IRB from the process, permitting — but, notably, not requiring — manufacturers to make certain 'eligible investigational drugs' available to certain 'eligible patients' without preapproval by the FDA or IRB oversight. … Written informed consent to the treatment is also required, but unlike in the context of expanded access the elements are not specified."[4]

Wide IRB Variation

Moreover, there is wide variation among IRB policies currently following the FDA compassionate use path to consider expanded access for qualified patients, Folkers and colleagues found in a recent study. Analyzing publicly available IRB policies, they concluded it is "difficult to find, interpret, and understand IRB policies on expanded access."[3]

The researchers reviewed 95 policies, finding that 88 of them contained language referencing non-emergency expanded access and/or expanded access for emergency requests for a single patient.

"Of the 88 policies that mentioned expanded access in non-emergency situations, 11.5% did not explicitly specify whether full IRB review was required, as was the rule at that time," they noted. "There was considerable variation in other aspects of these policies, including charging patients for use of investigational products and the use of data from expanded access."

Providing some historical perspective on this issue is the Government Accountability Office (GAO). In congressional testimony last year, **John E. Dicken**, GAO director of healthcare, said, "Several stakeholders we spoke with, including the selected manufacturers we interviewed, raised concerns that FDA is not clear about how it uses expanded access adverse events data in its review of drugs being considered for sale and marketing in the United States."[6]

However, Dicken gave the FDA credit for reviewing some 5,800 expanded access requests from Fiscal Year 2012 to 2015, saying 99% were allowed to proceed.

THE CASES WHEN FDA BLOCKED EXPANDED ACCESS WERE PRIMARILY DUE TO INCOMPLETE APPLICATIONS, UNSAFE DOSING, DEMONSTRATED LACK OF EFFICACY OR THE AVAILABILITY OF ADEQUATE ALTERNATIVE THERAPIES, AND INADEQUATE INFORMATION.

"Almost 96% of these requests were for single patients — either emergency or non-emergency — while the rest were for multiple patients," he said. "FDA typically responded to emergency single-patient requests within hours, and responded to all other requests within 30 days."

The cases when FDA blocked expanded access were primarily due to incomplete applications, unsafe dosing, demonstrated lack of efficacy or the availability of adequate alternative therapies, and inadequate information provided in the application on which to base a decision.

Folkers is a member of the NYU working group on Compassionate Use and Pre-Approval Access (CUPA), which was founded in 2014 to address ethical issues involving investigational products prior to FDA approval. In a group email to academic colleagues and supporters, CUPA said the following are some of the central unanswered questions in the immediate aftermath of Right to Try (RTT) passage:

- how and whether stronger informed consent requirements will be implemented over and above the new law's provision, which is much vaguer than the FDA's;
- whether manufacturers and/or healthcare providers and institutions will require IRB oversight of right to try requests in the absence of a provision for it in the law;
- what role the FDA, or any regulatory body, will play in enforcing the law's adverse event reporting requirements and interpreting its other provisions;
- how and whether manufacturers will allow access to their drugs in development via that pathway. Drug manufacturers/sponsors are in the best position to answer questions about investigational products' availability via RTT. CUPA has heard that several companies plan to consider requests only via expanded access;
- how and whether healthcare institutions will allow the RTT pathway to be used by their employees, in their facilities. CUPA knows of two universities that have stated that the expanded access pathway must be used;
- whether patients/physicians will

use the law to try to seek access to other types of unapproved agents; for example, medical marijuana. ■

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Prepare Contingency Plans for Transferring Oversight

OHRP/FDA guidance now finalized

IRBs should create a contingency plan that would go into effect when a natural disaster or a major problem disrupts operations.

Animal protection committees have long had to create contingency plans, but the requirement for human research protection programs (HRPPs) is new, says **Fanny K. Ennever**, PhD, CIP, research compliance officer at Boston Medical Center.

IRBs might not have given contingency plans and disaster planning much thought before Hurricane Katrina caused major disruptions to New Orleans and the region in 2005.

Then, in 2009, an independent IRB had to close its doors after a federal sting operation revealed sloppy human protection oversight. Coast IRB of Colorado Springs, CO, had been targeted by the Government Accountability Office (GAO), which sent several independent IRBs a fake protocol from a fake medical device company. The investigators listed on the protocol had phony credentials, and the proposal was filled with red flags. Two of the IRBs rejected the fake study, but Coast IRB approved it, committing violations of HRPP laws and regulations. *(For more information, see the story in the July 2008 issue of* IRB Advisor *at: http://bit.ly/2svL4hw.)*

When the IRB abruptly closed, all of its existing protocols and studies were left in limbo until investigators could find an alternative IRB to conduct reviews. This was the type of disruption the new contingency guidance is designed to prevent, Ennever says.

The U.S. Department of Health and Human Services Office for Human Research Protections (OHRP) and the FDA issued their final joint guidance, titled "Institutional Review Board (IRB) Written Procedures," in May 2018. *(The guidance can be found at: http://bit.ly/2LNuJ0r.)*

Item 51 in the written procedures checklist simply states, "Contingency plans for transferring oversight of one or more studies to another institution or IRB in the event the IRB is unable to continue oversight of the study (e.g., the IRB closes, suffers loss due to fire, natural disaster)." *(See FDA Q&A on new guidance, page 78.)*

OHRP and FDA provided no template or examples of how to create a contingency plan, Ennever notes.

"There were not many comments on the draft guidance," she says. "We wrote a comment, asking for some guidance on the contingency plan."

But the Boston Medical Center IRB didn't wait for an answer. The organization created its own IRB guidelines, updated in May 2018, with three sections pertaining to a contingency plan.

When OHRP and FDA first issued the draft guidance, the IRB was preparing for accreditation. Ennever and the IRB brought the draft guidance to the institutional officials responsible for the Federalwide Assurances (FWAs) to see whether they should act on it.

"We said, 'It's draft guidance and not final guidance,'" Ennever recalls. "And they said, 'Yeah, but it makes sense.'"

The institution went ahead with creating its own contingency plan (http://bit.ly/2xwAbS3), which includes these items:

• **Disruptions and recovery:** The first information in a contingency plan would identify the time frame of the disruption and who is responsible, Ennever says.

Many IRBs are located in areas where a natural disaster could cause a short-term disruption in service. And every IRB could be targeted by cybercriminals who disrupt operations.

When disruptions occur, the goal is to return to normal operations within a week, the Boston Medical Center IRB's contingency plan states.

"The one-week goal is appropriate for most HRPP operations (IRB review, education, and compliance)," the plan says.

"An important question is, 'Who makes the decision?'" Ennever says. "At our institution, it's the IRB director who will make the decision about how serious the disruption is and what measures are needed."

• **Backup and recovery of the electronic system:** A key component of the contingency plan is the availability of HRPP records, the Boston Medical Center IRB's contingency plan states.

"For IRB functions, the electronic system is used as the system of record, and no records that are essential to IRB oversight are maintained only in paper or only in other forms such as email correspondence," according to the plan.

Boston University's server backs up IRB data daily, with a secondary backup made through a third-party vendor.

Before creating the contingency plan, the only backup was on servers within the institution — and these were located in the same floodplain, Ennever notes.

"So we found that Boston University has a professional backup where critical files are backed up, put on tape, and sent on a truck to the Philadelphia area," she explains.

THE FIRST INFORMATION IN A CONTINGENCY PLAN WOULD IDENTIFY THE TIME FRAME OF THE DISRUPTION AND WHO IS RESPONSIBLE.

"We found that we could just add our electronic system to that daily backup."

Two things made this an affordable option. First, the IRB's files did not add significantly to the data that the data recovery company already was handling. Secondly, the IRB decided that it could wait a week for its data recovery, she says.

"The quicker you need to restore an electronic system, the higher the cost," Ennever says. "We said we didn't need to get data back for a week, and the cost was so low the university didn't even charge us for it."

• **Personnel disruptions:** From the IRB's perspective, this is the part of the contingency plan that could be the most challenging. In the event of a major disaster, such as flooding or a storm that causes evacuations and property damage, some of the IRB staff might not be able to return to work for days or weeks.

"There could be an electricity problem or a really bad flu season," Ennever says.

Other causes could be multiple resignations, interruptions in internet service for work, and epidemic diseases, the contingency plan notes.

"In the specific instance where the disruption results from the inability of IRB staff and members to travel to the IRB office location, as long as electricity and internet access are available, they may use the electronic system from home and participate in convened meetings via teleconference," the contingency plan states.

When the disruption is more severe or results in IRB closure, such as what happened with Coast IRB, then a contingency plan would be to have the IRB's protocols transferred to an independent IRB.

In most cases, the independent IRB could provide staffing help during a limited disruption, Ennever says.

"We have relationships with independent IRBs and they can provide backup," she explains. "They have said they could provide staff to review protocols according to our policies and procedures."

The idea is to have the independent IRB serve as a staffing backup without transferring oversight.

"The independent IRB essentially would be a consultant, providing personnel who would act as our temporary employees," Ennever says.

The IRB director would make the call of whether a disruption is temporary and short-term, or possibly long-term and necessitating a transfer of some studies, she adds.

"The IRB director would decide when the disruption is over whether to bring studies back or leave them where they've been transferred," Ennever says. ■

FDA Explains IRB Written Procedures Policy

Written procedures may vary

New federal guidance on IRB written procedures leave "meaningful content" open to interpretation. The final joint guidance, titled "Institutional Review Board (IRB) Written Procedures: Guidance for Institutions and IRBs," was issued in May 2018 by the Department of Health and Human Services Office for Human Research Protections (OHRP) and the FDA. *(The guidance is available at: http://bit.ly/2LNuJ0r.) IRB Advisor* asked the agencies to provide more information on what they are looking for from IRBs.

The following is FDA's response from **Theresa Eisenman**, press officer at FDA:

IRB Advisor: In the new guidance, OHRP and FDA state that IRBs develop written procedures that restate 45 CFR 46 regulations, and this does not contain sufficient detail about the IRBs' operations. How might IRBs develop "meaningful content for written procedures," and do you have any examples of more thorough written procedures from any IRBs?

FDA: Developing meaningful content for written procedures involves a comprehensive and critical assessment of the IRB's responsibilities, functions, and operations, and the institution's organizational structure.

Written procedures should be sufficiently detailed to help IRB members and institutional administrative staff understand how to carry out their duties in a consistent and effective way that ensures that the rights and welfare of subjects are protected and that the IRB operates in compliance with the regulations.

FDA and OHRP recognize that written procedures may vary among institutions and IRBs because of differences in the way organizations are structured, the type of research studies reviewed by the IRB, institutional policy or administrative practices, the number of IRBs at the institution, affiliation with an institution, and local and state laws and regulations. This variability in organizational structure allows for a broad range in content to meet the regulatory requirements for written procedures.

WRITTEN PROCEDURES SHOULD BE SUFFICIENTLY DETAILED TO HELP IRB MEMBERS AND INSTITUTIONAL ADMINISTRATIVE STAFF UNDERSTAND HOW TO CARRY OUT THEIR DUTIES IN A CONSISTENT AND EFFECTIVE WAY.

Institutions/IRBs may decide to make their written procedures available to ensure that others (e.g., investigators, sponsors) are aware of their requirements, and to facilitate compliance. Some institutions/IRBs post their written procedures on a website to provide broad access. Such examples may be helpful to institutions/IRBs.

IRB Advisor: What are some links to the guidance documents that could serve as useful resources to IRB staff?

FDA: Footnote 2 in the guidance refers readers to three websites for other guidance documents that may serve as useful resources to institutions and IRBs.

Both FDA websites listed in the guidance include links to other guidance documents that may be useful resources to institutions and IRBs. For example, FDA's webpage of Selected FDA GCP/Clinical Trial Guidance Documents at: https://bit.ly/2JZx86W includes a section titled "Institutional Review Boards (IRBs) and Informed Consent."

IRB Advisor: Would use of the Written Procedures Checklist, which is provided in the guidance, suffice to satisfy regulatory requirements during an institutional survey? If not, what else might be needed?

FDA: FDA and OHRP created a Written Procedures Checklist to assist institutions and IRBs in preparing and maintaining detailed written procedures. The checklist is designed to prompt a thorough evaluation of written procedures that helps to ensure the protection of human research subjects. The checklist incorporates the HHS and FDA regulatory requirements for written procedures for the IRB and recommendations about operational details to include to support each of these requirements. It includes some additional topics the institution/

IRB may consider when developing comprehensive procedures.

We remind institutions and IRBs that the checklist is intended to facilitate an improved understanding of regulatory requirements for written procedures for the IRB, to provide recommendations on the operational details to include in support of these regulatory requirements, and to provide some additional topics the institution/IRB may consider when developing comprehensive procedures. The checklist is intended to be a tool to assist in determining what information should be covered in written procedures rather than a tool for assessing compliance.

Our guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes FDA's and OHRP's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

IRB Advisor: How might this guidance change what IRBs/HRPPs do in their daily work?

FDA: FDA and HHS regulations allow flexibility in both format and content of written procedures, which gives IRBs the ability to establish procedures best suited to their own operations, including how much detail to include. The checklist is intended to facilitate an improved understanding of regulatory requirements, provide recommendations on the operational details to include in support of these regulatory requirements, and to provide some additional topics the institution/IRB may consider when developing comprehensive procedures. Institutions and IRBs should use the flexibility afforded by the regulations to adopt written procedures that are suitable for their organizations.

IRB Advisor: Why was this guidance needed?

FDA: FDA and OHRP frequently receive questions about the scope and content of written procedures and issued this guidance to address those concerns. To enhance human subject protection and reduce regulatory burden, we have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This guidance document was developed as a part of these efforts.

In addition, on Dec. 13, 2016, the 21st Century Cures Act was signed into law. The Cures Act requires the secretary of HHS to harmonize differences between the HHS human subject regulations and FDA's human subject regulations.

FDA and OHRP believe that it is most helpful to the regulated community to issue a joint guidance document that describes the agencies' approach to preparing and maintaining written procedures. ■

IRBs and IBCs: Critical Partners in Gene Research

Common Rule changes could create disconnect

In addition to IRB oversight, the National Institutes of Health (NIH) requires that research using "recombinant or synthetic nucleic acid molecules" for gene transfer into human research subjects be approved by institutional biosafety committees (IBCs).

A primary concern is the transfer of genetic material via a virus, for example, that can then replicate in a living cell. Thus, the need for biosafety to protect workers and the public as researchers seek ways to use gene therapy to fight disease.

"Over time, many institutions have chosen to assign their IBCs the responsibility of reviewing a variety of experimentation that involves biological materials (e.g., infectious agents) and other potentially hazardous agents (e.g., carcinogens)," the NIH states. "This additional responsibility is assigned entirely at the discretion of the institution."[1]

An institution must follow the NIH guidelines if it receives any funding from the NIH for research. Institutions at the local level must ensure that the IBC has adequate expertise and training. In addition, the IBC must file an annual report with the NIH clearly indicating the chair and the human gene transfer expert.

While clear communication and synergy between IRBs and IBCs is needed for timely and safe review of research, the two panels look at gene research through separate lenses.

While the primary role of the IRB is to protect research subjects from safety and ethical compromise, the primary role of the IBC in clinical trials is to protect study staff and the general public from risk associated with gene transfer agents, explains **Currien MacDonald**, MD, CIP, IRB

chair at WIRB-Copernicus Group. *IRB Advisor* asked MacDonald about the overlapping missions of these two important review groups.

IRB Advisor: Can you comment on what some of these risks are and, specifically, how an IBC can mitigate them?

MacDonald: The majority of concerns that an IBC is looking at are the potential unintentional spread of the gene transfer agent. For example, viruses infect cells, which is not a good thing in most cases. But scientists can transfer genes into that virus to only infect cancer cells. So it is infecting a cell, and making more virus that contains a gene to turn a disease into a cure. That also makes that agent that they are working with infectious, so it could spread. And just like in every other medical intervention, there could be risk from that spread, and risks from even the intended and intentional outcome of the gene transfer agent.

We never want to expose people to risks. To prevent them, the IBC is looking very closely at gene transfer agents, their ability to infect, and what measures there are to limit the chances of that happening. They are very attentive to all of the details, including to the level of going to the site and inspecting the equipment that protects the clinic staff from exposures, such as the cabinet where the agent is readied. The IBC looks at all of those details, both for the clinical staff and the general public. They look at the procedures and make sure that the waste from the agent is disposed of properly and does not go somewhere else.

IRB Advisor: With the expanding array of procedures, are the odds of these kinds of risk increasing?

MacDonald: No, current agents and several that are approved are not really infectious in any way. So, the gene transfer review is really focused on what the intended outcome is from the agent itself, and it's much less a concern of the agent spreading. The field is still growing, and it is now getting into some of the [research] going into cells and producing those kinds of effects. But the fear about the spread of the agents has largely been without any evidence of it happening.

"THE GENE TRANSFER REVIEW IS REALLY FOCUSED ON WHAT THE INTENDED OUTCOME IS FROM THE AGENT ITSELF, AND IT'S MUCH LESS A CONCERN OF THE AGENT SPREADING."

IRB Advisor: Are there instances where IBCs and IRBs can be at cross-purposes due to their different respective goals of protecting staff and public vs. research subjects?

MacDonald: It's really not common at all for that to happen. The missions are parallel, so cross-purposes are exceedingly rare. The one that [is possible] is the IBC wanting to stop use of the agent while it improves their environmental protections for staff, while the IRB may be concerned that a subject receives a treatment that is controlling a disease. I've never seen that happen, but the resolution to that is the same as the resolution for common issues; for example, a disagreement about the way something is worded in a consent form. All that needs to happen is a discussion to make sure their two perspectives align. In most cases, they can very quickly come to a mutually agreeable solution.

IRB Advisor: The revised Common Rule emphasizes single IRB rule of multisite studies, but you note that is not currently allowed for IBCs. Do you see a possible growing disconnect between IRBs and IBCs if the rule is finalized as-is?

MacDonald: That is a very real concern. There is some contention that to the extent that the local IRB and the local IBC currently communicate well, that is mitigated by the fact that local IRBs never communicate with one another. As we just discussed, the reasons for local IBC review — for example, being able to know the site well enough, knowing what masks they wear, who removes the medical waste, quality sorts of things — kind of make sense, while the concern for multisite IRBs does not really make sense. The protocol or consent form being different between sites leads to so much duplication of effort and delay, it really is a burden and a waste. So, any local IBC that worked with a local IRB could be at a disadvantage if they then lose that relationship they had when a central IRB review is mandated.

But not necessarily. If they already have in place procedures and infrastructure to have timely and clear communications, then there is no reason they couldn't adapt that to work with an IRB that is open to that kind of communication. Of course, each of those would have to have the components to ensure that the communication was done well.

For example, if the local IRB just defers to the local IBC all the time, then a central IRB is going to be much less likely to be open to that

kind of mandated communication. The local IBC would then have to come up with a new communication style or strategy to ensure their communication is being received well.

IRB Advisor: Expediency and speed are understandably overshadowed by safety in these discussions, but why is it important to have better logistics between these two types of committees?

MacDonald: Expediency of review is important. A lot of people say cutting through red tape might sacrifice safety, but I see them as hand in glove. For example, if there is a concern from one of the two committees that is not well communicated, then you can have a delay in a study that could have some benefit to subjects.

For example, if one committee says, "Stop the study — something terrible has happened," then the other committee can say, "If we do this, we can maintain the benefits to the subjects." There may not be anything available like that [intervention] in the community and this research is very valuable [to continue] while mitigating the risk. It's kind of like the baby with the bathwater. Communication and timely review of the process can [ensure] the safety of the subjects and the overall research benefit to the community. ■

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IRBs Can Learn to Make the Most of Central IRB Partnerships

Get ahead of the Common Rule

The IRB at Inova Health System of Falls Church, VA, began working with a central IRB 15 years ago — long before the new Common Rule encouraged IRBs to designate an IRB of record for multisite studies.

Since then, the IRB developed a well-organized process for its partnerships with independent IRBs. The partnership is visualized as a triangular flowchart with the institution and human research protection program (HRPP) at the top, linked directly to both the principal investigator's study team on the left and the central IRB on the right.[1]

In 2016, 15% of the Inova IRB's protocols were reviewed by a central IRB. A year later, that proportion of central IRB reviews had more than doubled to 31%.[1]

This trend is expected to continue, and IRBs nationwide will increasingly rely on an IRB of record for reviews. The new Common Rule requires U.S.-based institutions that are involved in cooperative research to use a single IRB. This requirement has been delayed. *(For more information, visit: https://bit.ly/2JrtJRf.)*

In the meantime, IRBs can learn best practices in forming relationships with central IRBs.

"I think it's very important to have a relationship with an IRB of record and to have a dedicated person reach out to them," says **Kathy Ababio**, BS, CHES, IRB manager for Inova Health System. "Having this relationship has helped us facilitate the process easier."

Communication is key to a successful partnership, says **Annika Shuali**, IRB coordinator for Inova Health System.

"Communication between our office and investigators helps everyone know what is expected," she says. "Communication between us and the IRB of record helps everyone get on board with the changes that need to be made."

Ababio and Shuali suggest the following best practice strategies for developing an optimal relationship with an IRB of record:

• Assign liaisons to work with the central IRB. Liaisons can be IRB coordinators who are responsible for communication and maintaining workflow between the institution's IRB and the central IRB. Inova has had liaisons since its first contract with a central IRB.

Shuali is one of the liaisons for the Inova IRB. "I have a broad role and also work as an IRB coordinator for some local studies at Inova," she says.

Inova has two liaisons who review submissions that go into the electronic submission system. They maintain consistency in their work through use of a one-page checklist with 12 submission tasks, including these examples:

- department impact forms indicating notification to other affected departments like pharmacy, nursing unit, radiology, as applicable;

- sponsor of study is listed and matches name listed on protocol and consent;

- research training completed and up to date for all investigators and research staff;

- financial disclosure forms are submitted for investigators and coordinators. Conflict of interest reviewed and referred to committee, as applicable;

- consent form(s) or waiver requested and documented appropriately;

- consent form includes site-specific requirements, including subject injury language matching contract.

• Screen studies for external IRB. "When a study is submitted in the electronic system, we have a pre-review checklist that determines whether it is allowed to go to an external IRB," Ababio says. "That would be a study that does not have a vulnerable population, with a few rare exceptions."

Also, sponsored studies that are required to be reviewed by a central IRB would be accommodated, she adds.

"We are well aware of the change that's coming with the Common Rule, so we will be updating our policies," Ababio says.

• Streamline processes. Since starting its first central IRB relationship in 2003, the institution has made changes and updated as needed, Ababio notes.

"In 2016, we saw a need to make more drastic changes to increase our turnaround time in our metrics," she explains. "We found redundancies in our review and IRB of record."

After conducting a root cause analysis, they learned that the pre-review checklist included redundant tasks, she adds.

"We were looking for certain items to be met before we gave a cover letter to the IRB of record, and those same things were being done by the IRB of record," Ababio says. "So there could be delays."

To streamline the process, they stopped performing the same tasks as the IRB of record.

> "WE'VE LOOKED AT OUR PROCESS AND STREAMLINED IT SO WE COULD HAVE IMPROVED METRICS WITH A TURNAROUND TIME AND REDUCTION IN ERRORS IN THE POST-APPROVAL PROCESS."

"We streamlined the process and allowed studies to go to the IRB of record within 48 hours," Ababio says. "The study team will send the cover letter, which we changed to an acknowledgement letter."

The IRB conducts a quick post-approval look at the informed consent to confirm that all Inova-specific language is intact and other requirements are met.

• Agree on informed consent language. Investigators use sponsor templates as the main part of the consent form and include information about informed consent for research purposes and the investigator's specific contact information, as well as contact information for Inova IRB, Shuali says.

"If people have questions they want to ask us about research studies and injury compensation, they can contact us," she says.

Inova developed an informed consent template specific to its central IRBs, which approved this language as part of the contract process, Ababio says.

"We gave them the exact template for the informed consent," she explains. "We have wording that is very specific for each section, and they approved the language before ratifying our contract and they were OK using this language."

Study teams insert the approved language into the sponsor's consent form when they submit the consent document to the IRB of record.

"They may negotiate with the sponsor to make sure they understand this is language that needs to be required, and most sponsors are fine with it," Ababio says.

• Check for consent errors. The IRB reviews the informed consent form post-approval by the IRB of record, Ababio says.

"We see if our language was used as required by the contract, and if there's a problem we have someone on the study team rectify the problem," she says. "That process has reduced the number of errors from what we found prior to reviewing it post-approval."

For example, the IRB once found that the IRB of record had reverted to the informed consent that had the sponsor's language. "We reminded them that this language must be present, and they'd go back and fix it," Ababio says.

Collecting errors data also helped one central IRB make quality improvements.

"The IRB was interested in knowing how many errors were made because they pride themselves

on following the contract," she says. "We checked and told them the errors we had found, and since then they've been very cognizant to ensure they follow the contract and template language."

As a result, the number of errors has decreased tremendously, Ababio says. The reduction in errors was one of the positive changes to the program.

"We've looked at our process and streamlined it so we could have improved metrics with a turnaround time and reduction in errors in the post-approval process," Ababio says. ■

REFERENCE

1. Kim C, Pulsipher E. Cultivating a successful partnership between institutions and central IRBs. Poster presented at PRIM&R's 2016 Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA. Poster: 39.

FDA Proposes Including Children in Adult Cancer Trials

Seeking input on safety, dosing, ethical considerations

IRB members have until Aug. 3, 2018, to submit comments on FDA draft guidance that would open adult oncology clinical trials to children ages 12 to 17 years.

"The purpose of this draft guidance is to provide the pharmaceutical industry, clinical investigators, and institutional review boards with information to facilitate the inclusion of adolescent patients in relevant adult oncology clinical trials," the FDA stated.[1]

The guidelines seek comment on three principal areas:

- appropriate criteria for inclusion of children in adult trials at various stages of drug development;
- considerations for dosing, pharmacokinetic evaluations, safety monitoring;
- ethical requirements.

"Although most cancers in children and adults are distinctly different entities, there are some diseases that occur in both and span the adolescent age groups," said FDA Commissioner Scott Gottlieb, MD. "If there's no evidence that an investigational drug might have exaggerated toxicity in younger patients, then we're encouraging sponsors to enroll adolescents into disease-appropriate trials."

Speaking June 2, 2018, at the American Society of Clinical Oncology meeting in Chicago, Gottlieb said the move is part of a general trend to include more "underrepresented" research subjects.

"Since the pharmacological parameters of adults and adolescents for most agents are comparable, early access to innovative drugs is warranted where there's proof of principle and adequate dosing information to maximize potential for clinical benefit," he said.

Under ethical considerations, the FDA draft guidance states that "Under 21 CFR 50.50, IRBs reviewing adult oncology clinical trials that allow for the enrollment of adolescents must ensure that the provisions of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, and, specifically, 21 CFR 50.52, clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects, are satisfied before approving the studies."

The FDA mission to balance risk and access is not a "zero-sum" game, Gottlieb said.

"People try to paint any change we make in our regulatory policy, or to the policy requirements we impose, as a binary choice between speed and safety," he said. "That's a false dichotomy. This isn't a zero-sum game."

Oncology research is leading the "precision medicine revolution," with FDA approving 16 new cancer drugs and biologics in 2017. However, "the generalizability of traditional clinical trials to real-world patients at the point of care is increasingly hard," he said.

"We know that traditional eligibility criteria often exclude the very patients most likely to be treated once the drug is on the market: the elderly, patients with poor performance status, organ dysfunction, brain metastasis, or other comorbidities," he said. "In 2018, a cancer patient's hope for recovery shouldn't hinge on their socioeconomic status or a ZIP code lottery." ■

REFERENCE

1. FDA. Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials: Draft Guidance for Industry. *Fed Reg* June 4, 2018. Available at: https://bit.ly/2kT3xB7.

CME/CE INSTRUCTIONS

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

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CME/CE QUESTIONS

1. **To be eligible for administration under the Right to Try law, an investigational drug must be approved by the FDA for limited use in a specific patient population.**

   a. True
   b. False

2. **The final joint guidance, titled "Institutional Review Board (IRB) Written Procedures," was issued in May 2018 by the Office for Human Research Protections (OHRP) and the FDA. Which of the following statements about this document is true?**

   a. This guidance establishes legally enforceable responsibilities.
   b. This guidance describes FDA's and OHRP's current thinking on a topic and should be viewed only as recommendations.
   c. IRBs may not use an alternative approach to what is outlined in the joint guidance.
   d. All of the above

3. **Given current requirements and the proposed final version of the Common Rule, which of the following is true concerning institutional biosafety committees (IBCs)?**

   a. IBCs at multiple sites report to a central IBC.
   b. IBCs perform only local review.
   c. Someone with IBC expertise must be added to IRBs.
   d. Multiple IBCs report to a designated central IRB.

4. **Which of the following would *not* be a good item to include in a checklist of tasks suitable for review by a liaison between an institutional IRB and an IRB of record?**

   a. Sponsor of study is listed and matches name listed on protocol and consent
   b. Research training completed and up to date for all investigators and research staff
   c. Scientific and statistical review of study's methodology
   d. Financial disclosure forms are submitted for investigators and coordinators