IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

SEPTEMBER 2018 Vol. 18, No. 9; p. 97-108

INSIDE

Does Use of Biospecimens From Children Require Reconsent When They Are Adults?

Questions both ethical and regulatory

By Gary Evans, Medical Writer

There is considerable ethical debate about the issue of reconsent at age 18 from research subjects who provided biospecimens as infants, children, or adolescents. Practices currently vary widely among institutions, with some permitting continued use of deidentified samples and others requiring all samples to be destroyed when the subject reaches age 18.

Attempting to cut this Gordian knot, a group of bioethicists recently argued that there is no need to seek reconsent for use of biological samples donated by children if permission was given originally by their parents.

> PRACTICES CURRENTLY VARY WIDELY AMONG INSTITUTIONS, WITH SOME PERMITTING CONTINUED USE OF DEIDENTIFIED SAMPLES AND OTHERS REQUIRING ALL SAMPLES TO BE DESTROYED WHEN THE SUBJECT REACHES AGE 18.

"In most cases, parental permission is needed to obtain samples from minors," the authors reported.[1] "In addition, almost all commentators and guidelines maintain that researchers need the consent of donors if they want to continue to store the samples and make them available for future studies after the donors reach the age of majority. We argue that this near-consensus view is mistaken on the grounds that the agreement of the parents at the time of obtaining samples provides sufficient permission."

ReliasMedia.com

Financial Disclosure: Author **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Editor **Jesse Saffron**, Editorial Group Manager **Terrey L. Hatcher**, Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics, and Nurse Planner **Kay Ball**, PhD, RN, CNOR, CMLSO, FAAN, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

IRB ADVISOR

IRB Advisor,
ISSN 1535-2064, is published monthly by
Relias LLC
111 Corning Road, Suite 250
Cary, NC 27518

Periodicals Postage Paid at Cary, NC, and at additional mailing offices.
GST Registration Number: R128870672.

POSTMASTER: Send address changes to:
IRB Advisor
111 Corning Road, Suite 250
Cary, NC 27518

SUBSCRIBER INFORMATION:
Customer Service: (800) 688-2421.
ReliasMediaSupport@relias.com
ReliasMedia.com

SUBSCRIPTION PRICES:
Subscription rates: U.S.A., Print: 1 year (12 issues) with free AMA Category 1 CreditsTM or Nursing Contact Hours, $419. Add $19.99 for shipping & handling. Online only, single user: 1 year with free AMA Category 1 CreditsTM or Nursing Contact Hours, $377. Outside U.S., add $30 per year, total prepaid in U.S. funds.

MULTIPLE COPIES: Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

ACCREDITATION: Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [1.5] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

This activity is intended for clinical trial research physicians and nurses. It is in effect for 36 months from the date of publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

AUTHOR: Melinda Young
MEDICAL WRITER: Gary Evans
EDITOR: Jill Drachenberg
EDITOR: Jesse Saffron
EDITORIAL GROUP MANAGER: Terrey L. Hatcher
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger

EDITORIAL QUESTIONS
Questions or comments?
Call **Jill Drachenberg**,
(404) 262-5508.

Parents have broad authority to make decisions on behalf of their children, they argued, citing examples of financial decisions to distribute future money to children and donating newborn stem cells from the umbilical cord.

"This suggests that parental permission can be sufficient and, for most studies, obviates the need for reconsent when the donors turn 18 years old," they concluded. "We believe that this position is consistent with a reasonable interpretation of current U.S. regulations protecting human subjects."

That said, every effort should be made to inform parents during the original consent that their children's biospecimens may be used for future research, says lead author **Benjamin Berkman**, JD, MPH, head of the ethics of genetics and emerging technologies at the National Institutes of Health Department of Bioethics.

"It should be made very clear to parents that they are not just providing consent or permission on behalf of their children right then, but they are making a decision that is going to bind children into adulthood," he tells *IRB Advisor*. "They are making these kinds of decisions for the kids all the time, but in the research context it is different. I think it should definitely be clarified to parents that they are making a decision that has some lasting implications for their kids."

This could include at some point explaining to children who were enrolled in research that their biospecimens may be used in the future, he says.

Reconsent at the age of 18 should not be required unless the future studies require interaction with research subjects who now are adults. In addition, reconsent should not be required unless the subsequent research poses greater than minimal risk, Berkman and colleagues argue. What would constitute risk that goes beyond minimal?

"This is a big debate in the literature," he says. "I am generally of the view that once samples are collected — even if there is going to be genetic analysis done — that it is almost certainly [minimal risk]."

However, the moral implications of some research could raise the perception of risk; for example, if biospecimens were used in cloning research or in experiments with gametes that could be used to produce human embryos, he notes.

"You can imagine the kind of research where people might have a moral objection," he said. "Those are the kinds of things that would be beyond minimal risk, but in terms of actual welfare harm to people it is, at least to my mind, pretty hard to imagine cases where there would be more than minimal risk."

Counterview

A counterview[2] on the subject argues that the revised Common Rule and OHRP guidance do not necessarily support the contention that reconsent is not needed. It is something of a gray area, but Berkman and colleagues concede in their paper that they have taken "a controversial view about pediatric reconsent that may seem counterintuitive in a field where autonomy is sacrosanct."

There is an ethical testing in this process, as Berkman and colleagues conclude that "the broad support for an obligation to obtain new consent at the age of majority is understandable, but ripe for a challenge. Intuitively, it seems odd

that a one-time sample donor remains a subject indefinitely."

In the opposing view, another group of bioethicists underscore that there are important ethical reasons to obtain consent when specimen subjects reach 18. However, they balance this against the demands of efficiently and economically conducting research that benefits children.

"Given current guidance from the relevant regulatory bodies, it remains necessary to obtain consent for the continued use of identified pediatric samples when participants reach the age of majority unless the institutional review board grants a waiver of consent," the authors stated. "However, we argue that waivers of consent should more frequently be granted by institutional review boards and used for this purpose."

If the donor children are still involved in the research as they reach adulthood, "there is really no excuse for not getting consent," says lead author **Kyle Brothers**, MD, PhD, an associate professor of pediatrics at the University of Louisville in Kentucky, where he also is affiliated with the Institute for Bioethics, Health Policy, and Law.

That would be an obvious case when it is "practicable" to obtain consent when child specimen donors become 18, he adds.

In contrast, a biorepository may store thousands of specimens from children whose parents originally gave consent, but there may be little information to contact the donors even to get reconsent.

"Some of these biorepositories are quite large," he says. "You don't necessarily have updated contact information, so it may not be practicable to get consent. However, the IRB is allowed to create a waiver of consent."

An IRB waiver of consent in these cases cannot be made if the research poses greater than minimal risk to the subjects.

"I think both papers agree it should be possible to continue using these samples without getting permission of the child," Brothers says. "The difference is we are saying that you have to get waiver of consent from the IRB if you want to store identified samples. Or you need to deidentify the samples, and essentially that moves your research [out] of the human research category."

Both of those are good options under current guidelines to use biospecimens if obtaining reconsent from research subjects is going to be problematic, he says.

"We are essentially saying, if you can [get reconsent], you should — that's really a good thing to do," he says.

Brothers and colleagues conducted a study of a consortium of biorepositories to assess practices on this issue.

"An IRB at one of the sites required them to destroy the samples when the children reached age 18," he says. "They were not even allowed go back and try and get their consent. Some IRBs allowed them to keep using the samples even if they were identified. Some of them required them to go back and try to contact the people and get their permission. If they did not get permission, then they had to either destroy the samples or deidentify them."

Although this issue may still fall into a gray area if the Common Rule is finalized as currently drafted, it is clear that IRBs have the aforementioned options and these should become more standardized, he adds.

"The IRBs that are very restrictive and force people to destroy samples are really going beyond what is required by the regulations," Brothers says. "They are primarily doing that because they are worried about doing something that is not allowed by OHRP. We are trying to make it really clear that you are allowed to do this" through IRB waiver or deidentification of specimens.

"They made some good points," Berkman adds. "I think our papers are sort of complementary in a way. They're making, I think, a fairly reasonable legal argument interpreting the regulations as they stand and as they will stand. That is required under the guidance. We were looking at the broader ethical problem. Setting aside what the regulations say, we are saying that, just ethically, we don't think that obtaining reconsent is normatively required."

Asked whether IRBs that decide to follow this argument in practice could be open to liability, Berkman reiterated that his position is addressed to the ethical questions more than the legal ones.

"That's not the fight we want to have," he says. "I never want to say there are no liability issues, but I think that research subjects would have an uphill battle to be able to win negligence suits. They would have to show duty breached, causation, and damages. Given the minimal risk of most of these research activities, I think they would have a whole lot of difficulty showing that harm was due to a failure to get reconsent at 18." ■

REFERENCES

1. Berkman BE, Howard D, Wendler D. Reconsidering the Need for Reconsent at 18. *Pediatrics* 2018; 142(2):e20171202.
2. Brothers KB, Wilfond BS. Research Consent at the Age of Majority: Preferable but not Obligatory. *Pediatrics* 2018; 142(2):e20173038.

Tackling AAHRPP Accreditation Requires Time, Focus, Documentation

By Melinda Young, Author

Research institutions seeking first-time accreditation or reaccreditation can always expect challenges. These hurdles are a little higher now as rules and regulations will change in 2019 under the new Common Rule.

But the basic process of preparing for accreditation remains the same, and any IRB can fast-track its preparation with organization and willingness to adapt.

"IRBs are used to doing things the way they were," says **Michael Mahoney**, director of research operations and services, human research protection program (HRPP) administrator, at the University of Florida in Gainesville.

When IRBs seek accreditation, they have to adapt to doing things differently, he adds.

For instance, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC, has high expectations for research institutions, Mahoney says.

Successfully obtaining AAHRPP accreditation depends on having strong institutional leadership and having all staff engaged in the process, he says.

"We held ourselves to high standards and we wanted to get it done on the first pass, so everyone knew they had to be engaged on it," he explains. "We were shooting for full accreditation, our No. 1 goal, and we accomplished that."

The University of Florida's HRPP underwent a fast-track accreditation preparation process, spending a total of 18 months from its AAHRPP application to its approval in March 2018.

"Most institutions take two to three years to get accredited," says **Gailine McCaslin**, MS, HRPP coordinator at the University of Florida.

"At the University of Florida, we had a more aggressive timeline, partially tied to funding we had received — and, more importantly, it also was something our vice president for research mandated," McCaslin says.

McCaslin and Mahoney describe how the program achieved accreditation fairly quickly, following these strategies:

1. Hire someone to handle the accreditation preparation workload.

The first step was hiring a dedicated professional with experience in the accreditation process.

"We knew we needed a full-time employee to serve as project manager in coordinating all the gap analyses, policy changes, and coordinating changes, and we were very fortunate that Gailine was fabulous," Mahoney says.

"Prior to my role here, I had worked in the college of pharmacy and was familiar with the accreditation process," McCaslin says. "I was not intricately familiar with the IRB, but that served me in terms of giving the process a new set of eyes."

Just having McCaslin dedicated to the accreditation role was a big commitment for the institution.

"Most institutions use some in-house manpower, designated staff in other IRB positions, and they tack on the AAHRPP accreditation responsibilities," McCaslin notes.

Since the institution wanted a fast track to accreditation, it made sense to dedicate a full-time position to this job.

However, due to limited resources, some IRBs might still choose to put accreditation duties on another employee's plate as half or three-quarters of their duties, she notes.

2. Review policies and procedures.

McCaslin spent several months reviewing all of the HRPP's policies, procedures, and practices, and speaking with stakeholders.

"Then we looked at AAHRPP standards and regulatory guidance and mapped everything together," she says.

AAHRPP's Evaluation Instrument for Accreditation helped: "It allowed us to complete a thorough assessment, and we benefited quite a bit," McCaslin says. "Then we saw where our gaps were in terms of areas we needed to work on."

"Using AAHRPP standards, including required policies and procedures, I identified a series of potential gaps," she adds. "Even if one IRB met a standard, but another didn't, I listed that as a gap because all three of the IRBs had to be on the same page."

As policies were reviewed and revised, newly created investigator guideline documents were developed. They were in a question-and-answer format that makes it easy for investigators and others to understand regulatory requirements.

For example, one guideline involved enrolling and overenrolling study subjects. It asks the question, "When does the IRB consider a study subject to be enrolled?" and answers it with three bullet points:

An enrolled subject is someone:

• who has signed an informed consent form, or

• whose data you have collected, or

• whose medical record you have reviewed (in the cases where consent is not required). Every record you look at is an enrolled subject. *(See samples of revised IRB policies, below.)*

3. Compare HRPP's policies and processes with those of other institutions.

"I sent out cold emails, made connections at the AAHRPP conference, and leaned on those connections," McCaslin says. "I started looking at people's HRPP pages and looked at their policies and how they addressed gaps like the ones we had." Some IRBs use toolkits and make other helpful information available online.

"After presenting that information to our various boards, we tailored our policies and procedures [P&Ps] to fit our current practices," she says. *(See story on aligning P&Ps of multiple boards, page 102.)*

4. Fix gaps.

Gaps were closed wherever possible. For instance, there was one gap involving the lack of specific AAHRPP-required language in sponsored study agreements/contracts.

McCaslin shared this information with contract office leadership and key IRB administrators. It included nuts-and-bolts details about the identified gap.

"I provided the skeleton in terms of AAHRPP requirements, and the key stakeholders added muscle with revised P&Ps," she says. "The gap was procedural and related to the ways we negotiate contracts and the language we include in contracts, which needed to be AAHRPP-specific."

One of the more significant gaps involved how IRBs documented the handling of protocols that had extra requirements from specific funding agencies. These policies needed to be documented, and the line of documentation was not often clear.

"So while sitting down with applicable IRB administrators, they'd walk me through the practice, and I'd follow up with Michael and the IRB chairs to discuss the best ways to document our practices in order to be in line with AAHRPP's standards," she says. "We needed a little bit more."

The result was the IRBs needed to change how they reviewed studies with additional funding agency requirements, she explains.

Newly Accredited Program Has Made Policies and Procedures Easier to Follow

When the human research protection program (HRPP) at the University of Florida in Gainesville decided to undergo accreditation with the Association for the Accreditation of Human Research Protection Programs (AAHRPP), officials revised policies and procedures, making them consistent across IRBs and easy to follow.

Here are a few examples of information included in one of the newly created investigator guideline documents, which are in question format:

Q: What does the IRB look for when offering subject compensation?

Answer: Compensation cannot be coercive or unduly influence subjects. The IRB will review proposed subject compensation on a protocol-by-protocol basis, including the type of compensation and amount, schedule, and proration of payments to assure that the proposed compensation is not so significant that prospective subjects may consider participation in research that they may otherwise not participate in if it were not for the compensation.

Q: What should potential participants be told when they are excluded from participation?

Answer: Unless there is a specific reason for informing potential subjects about the basis of exclusion, the default recommendation is to merely tell them that based on their responses, they don't qualify for inclusion in the study, and thank them for their time.

Q: What should be done if you need more study subjects than you are currently approved for?

Answer: Submit a revision and justify why additional subjects are needed. If your study is a greater-than-minimal-risk study, such a revision must be reviewed and approved by the full board since you are exposing additional subjects to the risks in your study. ■

IRBs were still doing a great job in review of such studies, but they had not been documenting their processes. "It was about documentation. That was the theme of the process changes: Clear documentation was key," she says.

5. Conduct program evaluation plan of action.

"We set up work groups and had weekly meetings," McCaslin says. "I worked with IRB staff and chairs and various other components of the HRPP. From July through October, we completed a thorough program evaluation and consulted with in-the-works groups to review identified gaps."

They focused on policy and practice revisions, based on the gap analysis.

"The director of research operations and services, Michael Mahoney, provided periodic updates to key stakeholders and institutional leadership on the accreditation process, addressing any issues or concerns that needed to be tackled, and elicit feedback," McCaslin says.

Additionally, the main point emphasized to IRB chairs and administrators was that the organization needed one set of P&P documents for all IRBs, and policies and practices needed to match. If a policy was written down, then the practice had to match it.

"We would be essentially setting ourselves up for failure if we have all of these great, newly created and/or revised policies and procedures, but couldn't realistically put those policies into practice," she says. "We had to make sure that while aligning ourselves with AAHRPP's accreditation standards, in written documentation, that our internal business practices also reflected those standards." ■

Consistency Is a Challenge, but Necessary With Multiple Institutional IRBs

It can raise morale among researchers

Research institutions that undergo accreditation preparation quickly learn that having separate policies and procedures (P&Ps) for each IRB is a problem.

Accrediting organizations want documentation, compliance with regulations, and consistency between an IRB's policies and its actual practices. Having several different P&Ps for the same processes increases the likelihood of survey findings and problems.

Accreditation is an opportunity to improve an organization's operations, says **Michael Mahoney**, director of research operations and services, human research protection program (HRPP) administrator at the University of Florida in Gainesville. Mahoney previously was an IRB coordinator for one of the IRBs that had undergone accreditation.

"When the University of Florida made the decision it wanted to pursue accreditation, I had a thorough understanding of what that meant," Mahoney says. "Even though one IRB mostly met the standards, we had two other IRBs, and we didn't have synchronized policies across all of the IRBs."

That was one of the biggest problems the institution faced as it sought accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

The reason one IRB was further along in meeting accreditation standards was because it had been an IRB of record for an accredited Veterans Administration organization and had changed its policies a decade earlier to meet accreditation standards, says **Gailine McCaslin**, MS, HRPP coordinator at the University of Florida.

"Since that time, the P&Ps were never changed or revisited, so we were in alignment with accreditation policies in some ways, but not in others," she says.

So when the University of Florida decided to seek AAHRPP accreditation, each IRB would need to update and adjust its P&Ps, but also align these with each other.

The University of Florida has three foundational IRBs, one of which is on a distant campus, and also uses an independent IRB. They often work in silos, so the accreditation process was a rare opportunity for the IRBs to talk with each other, McCaslin says.

"It didn't happen before," she says. "We had different sets of policies and procedures and types of research reviewed; staff had different internal practices that might not have always been shared."

Even best practices weren't always communicated.

When Mahoney first met with the three IRB chairs, top-level administrative IRB staff members, and a quality assurance team, and introduced McCaslin, they began the policy revision process.

"We needed to make sure when we drafted a new or revised policy that it would work for all of the boards," McCaslin says.

McCaslin provided stakeholders with a spreadsheet report that had been vetted first by Mahoney.

"He's extremely familiar with the boards and had served as the assistant director of IRBs, and he knew the key players and their practices," McCaslin explains. "He also knew the gravity of changing policies and the reasons for certain gaps and things like that."

Mahoney acted as facilitator, explaining when gaps would be more of a challenge to address, providing reasonable resolutions, and identified when the IRBs would have to change procedures.

"There were times when people would drag their feet or have differences in opinions, and when we ran into resistance, I'd be a diplomat and make sure we found common ground on issues related to compliance," Mahoney says.

IRB chairs were accustomed to having autonomy, so it was challenging for them to work in unison with the other boards to follow the same policies and processes, Mahoney adds.

"We have a biomed IRB, a sociobehavioral IRB, and a biomed that serves an indigent population, and they all have different justification for why they do things the way they do," he explains. "But it was too cumbersome to have three different P&Ps. We need a single way to deal with these issues."

During the accreditation process, the IRBs began to share information. All of the boards also moved toward full electronic submission systems, and that helped with getting all of them on the same page, McCaslin says.

Another strategy was to send each IRB regular emails and electronic reports about their progress in aligning their policies and procedures. McCaslin scheduled meetings with IRBs to discuss the changes and progress.

Sometimes, IRB chairs disagreed about the items on the gap analysis list. One chair thought some of the gaps were just differences in how the IRB liked to do things. But each procedure now had two standards to meet: regulatory rules and accreditation rules.

IRB CHAIRS WERE ACCUSTOMED TO HAVING AUTONOMY, SO IT WAS CHALLENGING FOR THEM TO WORK IN UNISON WITH THE OTHER BOARDS TO FOLLOW THE SAME POLICIES AND PROCESSES.

"We're trying to uphold ourselves to higher standards for AAHRPP accreditation, and we need to be on the same page," McCaslin says. "I would give them the highlights, a 30,000-foot overview of AAHRPP standards, and Michael would help translate that into practice."

Aligning the various boards was a challenge, she notes.

"We had one meeting, which blew everyone's minds because there are so many standards to follow," McCaslin says. "We presented a long Excel spreadsheet, which outlined where we met standards, where we sort of met standards, and where we had a gap."

Mahoney helped IRB chairs find a middle ground when there were disagreements among them about how a policy should be worded. It was sometimes difficult to reach a consensus.

"You need a constructive argument for whatever the middle ground is," he says. "In some cases, I had to play the tiebreaker."

Despite disagreements, the meetings were never contentious, he says. "From the beginning, we set expectations that we needed to do changes for accreditation, and everyone understood it wasn't an option, but we'd grow in the same direction."

The process worked. Policies and procedures were made more consistent. This improved things operationally and was a morale booster, Mahoney says.

"Researchers could use any one of our IRBs and instead of learning different ways of doing things, they now had a single mechanism for all IRBs on campus," he explains. "It improves compliance and simplifies human research protection."

Prior to the change, investigators would complain about their meeting requirements for one IRB only to have to start over again with another IRB. "They'd say, 'I learned what I learned to protect subjects over here at IRB 1, so now why go through different training courses for IRB 2?" Mahoney says. "It's a valid point."

The changes resulted in rebranding for the institution's HRPP, McCaslin says.

"We created an HRPP website to provide the full rollout of UF HRPP and to create buzz," she says. "We started laying the foundation of a message that it's not just the

IRB that makes up the HRPP, but various other stakeholders, such as institutional leadership, compliance offices, sponsored programs, researchers and research staff, and any other entities that played a role in human subject research."

As the revised P&Ps were approved, new tools were created, and the AAHRPP application was being completed, McCaslin kept a list of what still needed to be done.

"You have a puzzle piece, and you know what the puzzle has to look like, and one by one, you put in each piece," she says.

"Gailine compiled all documents that met the accreditation standard and coordinated the drafting of various policies, guidance, and guideline documents that would fill those gaps previously identified," Mahoney says. "We knew the payoff would be in the long-term, so there were no problems in getting people to participate in the meetings and provide feedback on the changes." ■

FDA Gene Therapy Draft Calls for Long-term Follow of Subjects

Weighing the risks and benefits of emerging science

The FDA recently issued multiple draft guideline documents on the fast-emerging field of gene therapy, including guidance on specific diseases like hemophilia and the need to follow some research subjects long-term to assess delayed adverse events.

Much of the FDA gene therapy guidance addresses stakeholders in the research and development industry. However, IRBs will be involved in establishing the risk-benefit of gene therapy and ensuring research subjects are followed for adverse effects that may appear years later.

"IRBs assess whether the risks are reasonable in anticipation of the intended benefits to the subjects and the importance of the knowledge to society," says **Currien MacDonald**, MD, CIP, IRB chair at the WIRB-Copernicus Group (WCG). "There are a lot implications for study design and monitoring of subjects for safety, both routinely and for unexpected adverse event reporting."

Three different FDA guidance documents address human gene therapy for hemophilia,[1] retinal disorders,[2] and rare diseases.[3] The long-term follow-up guidance[4] addresses the risks of gene therapy in general, as adverse consequences may arise that are not initially apparent. These FDA guidance documents and two others are available for comment through Oct. 10, 2018.

"The main implication I see from this is the attention and detail that the FDA has obviously put into the oversight of these products," MacDonald said. "I expect to see an increase in the amount of information and specifics for gene transfer studies that will come out of this. From the other side, the IRB's role hasn't changed. This guidance makes it clear that there is an increase in the knowledge base required to be current and compliant, and adequately protect the rights and welfare of human subjects."

While opening a path for a dynamic research platform, the FDA is to some extent trying to stay abreast of the rapid advancement in gene therapy science.

"The guidance is about as current as the FDA can be in keeping up with a rapidly advancing field," he says. "We are definitely seeing some of these issues and sponsors starting to struggle with them. The FDA is very timely in putting out this guidance."

Risk and Reward

In announcing a total of six draft guidelines now open to comment, FDA Commissioner Scott Gottlieb, MD, emphasized that gene therapy research carries an implicit risk.

"We still have much to learn about how these products work, how to administer them safely, and whether they will continue to work properly in the body without causing adverse side effects over long periods of time," he said in a statement.

Indeed, the follow-up guidance is necessary because gene therapy is not without a variety of risks inherent in, for example, inserting a virus in cells to target certain diseases. Thus, gene transfer into human research subjects must be approved by institutional biosafety committees (IBCs).

"For example, if you are producing a virus that is intended to transmit a therapeutic gene, you need to make sure that nothing else in there is infectious — nothing other than the product that you want to transfer," says **Daniel Kavanagh**, PhD, senior

scientific advisor, gene therapy at WIRB-Copernicus Group. "That is part of the federal guidance and that is also part of the domain of IBC review."

The draft guidelines contain a lot of information about best practices that could be generally applied to drug development and clinical trials, he says. The IBC will "look at risks to the study participants, the clinical staff, and the general public related to the recombinant nature of gene therapy products," he adds.

In that regard, IBCs can be a source of information for IRBs trying to better understand FDA guidance that goes into "nitty-gritty detail about how the products should be manufactured and tested," Kavanagh says.

"The typical roster of an IBC includes molecular biologists and microbiologists — people who came up through their careers handling these kinds of products," he says. "So a well-constituted IBC can be a really valuable addition to the IRB in terms of the specialized knowledge. Beyond that, the IBC checks that the waste handling is appropriate, the injections are done safely, and that the material is handled correctly."

Gene therapies are being studied in many areas, including genetic disorders, autoimmune diseases, heart disease, cancer, and HIV/AIDS, Gottlieb noted. The three disease conditions for which FDA guidance was issued — hemophilia, retinal disorders, and rare diseases — account for a lot of current gene therapy research, Kavanagh says.

"Depending on how you define gene therapy, most therapeutic modalities and clinical trials are going to fall under one of those three guidances," he says. "Certainly, a large swath of the work that we do is going to be effected by this guidance."

Hemophilia gene therapies are currently developed as single-dose treatments to trigger long-term production of the missing or abnormal coagulation factor. This may reduce or eliminate the need for coagulation factor replacement, the FDA states. Gene therapy for retinal disorders includes a wide variety of conditions affecting both adult and pediatric patients. Moreover, there are some 7,000 rare diseases, defined as afflicting fewer than 200,000 people in the United States.

"Since most rare diseases are pediatric diseases or have onset of manifestations in childhood, pediatric studies are a critical part of drug development," according to the FDA guidance. "However, treatment in pediatric patients cannot proceed without addressing ethical considerations for conducting investigations in vulnerable populations."

As many of these conditions are marked by few treatment options, the risk-reward ratio of gene therapy comes down to manipulating biological material in way that it fights a disease without causing additional harm.

Potential Adverse Outcomes of Gene Therapy

Gene therapy may warrant long-term follow-up of research subjects due to the risk of delayed adverse events. The FDA cites potential risks of adverse outcomes following exposure to human gene therapy products that are summarized as follows[1]:

"Integration activity" of the gene therapy product: Raises the potential for disruption of critical host genes that could result in malignancies.

Genome editing activity: Genome editing-based products impart their biological activity through site-specific changes in the human genome, but may also have off-target affects that raise the risk of malignancies and impaired gene function.

Prolonged expression: A gene therapy product where the therapeutic gene encodes growth factors, raising the potential for unregulated cell growth and malignancies.

Latency: A gene therapy product using, for example, a herpesvirus, has the potential for reactivation from latency, raising the risk of delayed adverse events related to a symptomatic infection.

Establishment of persistent infections: Gene therapy products that are replication-competent viruses and bacteria, such as listeria-based bacterial vectors, have the potential to cause persistent infections in immunocompromised patients. ■

REFERENCE

1. FDA. Long-Term Follow-Up After Administration of Human Gene Therapy Products. Draft Guidance for Industry. July 2018. Available at: https://bit.ly/2O4C3VE.

"The risks of most gene therapy products include the possibility of unintended effects that may be permanent, along with adverse effects due to invasive procedures that may be necessary for product administration," the FDA notes. "Because of these risks, it is generally not acceptable to enroll normal, healthy volunteers into GT studies."

Informed Consent

Given such risks, informed consent in trials involving long-term follow-up must include a description of any reasonably foreseeable risks from participating in the research, the FDA advises.

"The informed consent document must describe, among other things, the purposes of the research, the expected duration of the subject's participation, and the procedures to be followed," the FDA states. "Accordingly, the informed consent document must explain the purpose and duration of [long-term] observations, the time intervals, and the locations at which you plan to request the subjects to have scheduled study visits or be contacted by other means, and details as to what those contacts will involve."

Informed consent also should convey that an autopsy may be requested to test vector persistence and other adverse effects if the subject dies during follow-up.

"Sponsors must ensure that investigators submit the informed consent documents for institutional review board approval," the FDA states.

In addition, some of the elements the FDA recommends for long-term follow-up protocols include patient visit schedules, specimen sampling plan, and the methods of monitoring tests and clinical events of interest.

"The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject administered the investigational drug or employed as a control in the investigation," the FDA states in the guidance. "These records would include a baseline history prior to exposure to the investigational product in which all diseases, conditions, and physical abnormalities are recorded." ■

REFERENCES

1. FDA. Human Gene Therapy for Hemophilia. Draft Guidance for Industry. July 2018. Available at: https://bit.ly/2n7afEz.
2. FDA. Human Gene Therapy for Retinal Disorders. Draft Guidance for Industry. July 2018. Available at: https://bit.ly/2M1f54k.
3. FDA. Human Gene Therapy for Rare Diseases. Draft Guidance for Industry. July 2018. Available at: https://bit.ly/2JiRYNe.
4. FDA. Long-Term Follow-Up After Administration of Human Gene Therapy Products. Draft Guidance for Industry. July 2018. Available at: https://bit.ly/2O4C3VE.

SACHRP on Verge of Finalizing Informed Consent Guidance

Common Rule calls for reader-friendly informed consent forms

The Secretary's Advisory Committee on Human Research Protections (SACHRP) expects later this year to finalize guidance related to the new Common Rule, including information on how IRBs and researchers can make informed consent forms more pertinent to what participants need to know.

"One of our main points we want to make is that the informed consent process has gotten rather stagnant, and nobody changes it, so this is a really good opportunity to make the consent process more meaningful," says **David Forster**, JD, MA, CIP, chief compliance officer at WIRB-Copernicus Group in Princeton, NJ. Forster is the co-chair of the SACHRP subcommittee on harmonization.

"There have been years of complaints about how informed consent forms are too long and they don't help understanding," he says. "The new Common Rule has a statement that this must address what subjects want to know and have it organized in a way that's best presented for the subject."

At the July 10 meeting, SACHRP members discussed informed consent and the types of information that should be included in guidance on revising informed consent forms.

The goal of the new regulations is to make informed consent forms more subject-oriented, Forster says.

A revised consent form should have a short section of key information at the beginning that includes the main points, Forster says.

"We haven't decided on which questions are the ideal questions yet," Forster says. "We think the questions can be used to help frame the key information that's put in a consent form."

This information could be presented as a series of questions or bullet points. "We're trying to come up with a tool that best identifies the key information," he adds.

One working list of questions that SACHRP has considered, but still is revising, includes the following:

- What is the information a prospective subject needs in order to make a well-informed choice about whether to participate?
- What are the main reasons a subject will want to join this study?
- What are the main reasons a subject will not want to join this study?
- What is the research question the study is trying to answer? Why is it relevant to the subject?
- What aspects of research participation or this particular study are likely to be unfamiliar to a prospective subject, confound expectations, or require special attention?
- What information about the subject is being collected as part of this research?
- What types of activities will subjects perform for the research?
- What impact will participating in this research have on the subject outside of the research? For example, will it reduce options for standard treatments?
- How will the subjects' experience in this study differ from treatment outside of the study?
- In what ways is this research novel?

SACHRP also has considered questions submitted by other experts in human research protection.

Ensuring Consistent Compliance

The SACHRP committee members also discussed how any list of questions they might produce for guidance will soon become some IRBs' checklist. But the value of the guidance is to help research programs shift away from the risk-benefit paradigm and into how the research will change someone's life and impact them, according to a video of the meeting. *(The video can be found at: https://videocast.nih.gov.)*

IRBs and researchers will want guidance, and it's necessary to ensure consistent compliance, Forster notes.

"Without any guidance, people are going to be very inconsistent in how they interpret these new consent requirements and how they put them into practice," he says. "What we're hoping to do is get a significant step toward best practices in how to understand the new consent requirements and implement them."

SACHRP reviewed best practice examples from various universities and SACHRP subcommittee members and acquaintances.

Many IRBs already have worked on changing their informed consent forms because of the uncertainty in late 2017 about when the new Common Rule would be implemented.

"I think our IRB and a lot of others actually prepared a lot of materials because there was such uncertainty of whether the Common Rule would go into effect six months ago," Forster explains. "We created new standard operating procedures and worksheets and training for IRB members."

When SACHRP finalizes its guidance before the Common Rule is implemented on Jan. 18, 2019, the research protection world should read it and use what they can, he says.

"One of the points we really want to stress is this guidance has to get to the people who write consent forms and to the people who perform the consent process — it can't just be aimed at IRBs," Forster says. "It has to get to everyone involved in the consent process." ■

IRB ADVISOR

CME/CE INSTRUCTIONS

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

1. Read and study the activity, using the provided references for further research.
2. Log on to ReliasMedia.com, then select My Account to take a post-test.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE QUESTIONS

1. **An IRB waiver of reconsent by adults who donated biospecimens as children cannot be granted if:**

   a. the subjects are 21 years or older.
   b. the research poses greater than minimal risk.
   c. the subjects are from a vulnerable research population.
   d. if there is available therapy for the disease being studied.

2. **Which of the following would not be included in a definition of an enrolled subject?**

   a. Someone who signed an informed consent form.
   b. A person whose data you have collected.
   c. One who has signed a parental permission form.
   d. A person whose medical record you have reviewed.

3. **The FDA said the ideal human subject candidates for gene therapy research are healthy volunteers with competent immune systems.**

   a. True
   b. False

4. **The Secretary's Advisory Committee on Human Research Protections soon will provide guidance on how research institutions could align informed consent with the new Common Rule. One strategy is to present information in bullet points or in a question format. Which of the following questions might be included in a revised informed consent document?**

   a. What is the information a prospective subject needs in order to make a well-informed choice about whether to participate?
   b. What are the main reasons a subject will want to join this study?
   c. What are the main reasons a subject will not want to join this study?
   d. All of the above