IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

INSIDE

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Newest Oncology Studies Raise Ethical, Other Questions for IRBs

IRBs must stay on top of study design changes, experts say

By Melinda Young, Author

Clinical research — especially involving oncology trials — is evolving with the introduction of new therapies and therapeutic mechanisms. These raise new and sometimes challenging questions for IRBs reviewing the study protocols.

For instance, some Phase I studies no longer look solely at safety. The new model for some Phase I studies also evaluates efficacy for first-in-human trials, says **Lindsay McNair**, MD, MPH, MSB, WIRB-Copernicus Group chief medical officer in Princeton, NJ.

"It's changing the paradigm, and studies are not just phase one, two, three anymore," she explains. "It's changing the whole process of how we think about drug development."

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Another change is in the characteristics of people recruited for these early-stage cancer trials. The traditional participant was someone who had cancer and who had exhausted their options for available therapies.

"Now, we have therapies that are so promising they're not tested in people who have exhausted all other therapies, and they might be first-line therapy," McNair says. "When do we think we have enough evidence about an investigational product to be comfortable having somebody forgo or delay an approved therapy to take an investigational therapy?"

This is a question each IRB confronting such a study proposal will need to answer — and it's not an easy one from an ethical standpoint.

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"There's just a wider variety of early-stage oncology studies happening now, and IRBs have to examine long-held assumptions and [let go of] 'this is the way we have always done it,'" McNair adds.

The clinical trial industry is shifting toward studies that advance personalized medicine. They have new study designs like the basket protocol, in which people with the same genetic mutation in their tumor — regardless of where the tumor is in their body — are placed in the same study arm, she explains.

The study could include people with breast cancer, colon cancer, and prostate cancer. "It's called a basket protocol because everyone with the same mutation goes in one basket," McNair says.

"It's not a treatment based on the location of cancer in the body, anymore," she adds.

When presented with these new era protocols to review, IRB members might have a number of questions to consider, including:

- When is there enough scientific evidence to be comfortable going forward with a therapeutic purpose in a Phase I trial?
- When is it appropriate for a cancer patient, who has not received any oncology treatment, to receive an investigational therapy instead of a standard chemotherapy regimen?
- How do IRBs assess risks for patients receiving their first "treatment" in the form of an investigational drug trial?
- How do they assess the weight of science to determine potential benefits of these new study designs?

IRBs that review protocols with new study designs need to make certain they have relevant expertise on their board.

"IRBs need to have people on the board who are comfortable doing that review and comfortable understanding what standard of care is," she says. "They need someone who can help determine the risks of doing something different than standard of care."

WCG has dedicated oncology panels, as well as specialist consultants who can provide assistance when protocols involve rare situations or unusual cancers. WCG also has an advisory board of experts.

"We meet with them, along with IRB chairs, a couple of times a year to talk about what is at the forefront of cancer research," McNair says.

"We talk about what's in discovery now and how research designs are changing," she adds. "We find out what's happening at other institutions, so we can make sure our boards are as prepared as possible for the new research coming through. We've had this board in place for more than three years."

Another issue IRBs might note involves informed consent with studies using new therapies and mechanisms.

"How do we ensure that someone's decision to participate in research is informed when we know that the animal models may not be predictive of risks in humans?" McNair asks. "We don't know very much about long-term risks because some of the mechanisms are so new that we don't know what might happen in 10 to 15 years from now."

Cancer treatments and cures have evolved, and IRBs should think of long-term effects, she notes.

The problem is that answers to study participants' questions about these new cancer trials mostly are unknown. "How do we make sure when people are thinking about participating in a study that they understand how much is unknown,

before they make their decision?" she says.

With previous Phase I oncology studies with patients who had exhausted all other options, the chance of their responding to the study drug was pretty low. For people in the first group of a new drug's trial, the study drug dose they'd receive was too low to have therapeutic value, as the goal was to test the drug's safety, McNair explains.

Informed consent could explain this to people before they choose to participate in the study. The saying in the research community was that no one gets better in a Phase I study, and there is no potential personal benefit to participants.

Now, it's difficult to give people an idea of what to expect. There might be little hope of response to a new drug, or it could be a life-extending therapy.

"Now we have these therapies and different kinds of study designs, and we see responses that are better than what's available with some of the approved standard therapies," McNair says. "For example, the response rate in some melanoma studies was better than what was available with approved treatment."

For example, Merck's pembrolizumab (KEYTRUDA) received an FDA breakthrough therapy designation for advanced melanoma. The overall response rate in a Phase 1b trial, of 2mg/kg dose among 89 patients, was 24%, according to a 2014 media release from Merck. The drug was available to patients before Phase II and III trials began.

The success of novel studies like these can be confusing to people, and it's up to IRBs to ensure the informed consent process provides some clarity about the purpose of research and what to expect.

"We have a long way to go in terms of the general public understanding — and, sometimes, our researchers understanding — that clinical research is designed to develop generalizable data to move forward to new therapies," McNair says. "It's not designed to find optimal treatment for individuals in a study." ■

Finding the Best Role for Community Members: A Look at Two Strategies

A few questions answered

IRB questions sometimes arise about the role and responsibility of community members/nonscientists on review boards. Should their — and other nonaffiliated members' — contributions be limited? Do they have enough training to be primary or secondary reviewers?

These questions were raised in a recent online IRB Forum post in which an IRB director asked if other IRBs had community members review protocols as primary reviewers on their own or paired with someone else. Responses were varied, and *IRB Advisor* asked a couple of IRB leaders to explain how they handle responsibilities for community/unaffiliated members of the board. The following are their strategies:

- **Evaluate nonaffiliated IRB members by their particular CVs.** "We have nonaffiliated IRB members with different backgrounds and expertise," says **Kevin R. Johnson**, PhD, CIP, IRB manager at Novant Health in Winston-Salem, NC.

For example, the IRB's nonaffiliated members include a pathologist, a CPA, and a member who is bilingual in Spanish and English. When the IRB reviews studies with informed consent forms in English and in Spanish, the bilingual nonaffiliated board member is asked to review them to see if the translations differ in tone or accuracy with regard to medical terminology.

The pathologist board member sometimes performs first reviews, so there is no policy limiting first reviews to affiliated IRB members. Also, nonaffiliated members often contribute observations about studies from a community-oriented perspective, as well as drawing on their medical, scientific, and clinical trial expertise, Johnson says.

"Every person on the IRB lives in the area and can represent the general community," he adds.

Community members of the IRB are longstanding members and are well-trained on human subjects research regulations. All IRB members are trained through videos from the Office for Human Research Protections (OHRP) and CITI, he says.

Occasionally, the IRB will have members take ad-hoc training, such as a brief review related to handling pediatric research when a

rare pediatric study is submitted for review.

"It's similar for genetic research," Johnson says. "We have the brief reviews at our meetings. I send out a blurb about it, and if there are any articles or documents, I'll send those out ahead of time with the meeting agenda."

Johnson gives board members one-and-a-half weeks' notice, and the presentations are held at the end of the meeting.

When Johnson was with a previous IRB, community/unaffiliated members lacked scientific expertise, so their input usually centered around the language of informed consent documents and the general quality of a study, he recalls.

"But I've never felt that community members were undervalued," he says. "It always felt like they brought a good, fresh look to the review."

• Capitalize on the fresh perspective community members bring to IRB. "The spirit behind the requirement is that you have a community member who brings to the table the perspective, thoughts, and interests of the general public," says **Megan Roth**, PhD, director of research and sponsored programs, and chair of Abilene Christian University IRB in Abilene, TX.

People who work in an academic and research setting develop certain ways of understanding research ethics. Having a nonacademic, nonscientist IRB member brings a different perspective, one that might mirror the thoughts of the average person who will be a research volunteer, she explains.

"Academics are necessary on IRBs, but they have certain biases that have an impact when they review a study," she notes.

The community IRB member could explain what the average person in the community would think about a particular study and explain their concerns. While the community member might not become a primary reviewer of a study, it's not because it's prohibited, Roth says.

When Roth first became the director of research and sponsored programs, she wanted to find a community IRB member who would be enthusiastic about participation on the board. The previous community member was not attending meetings regularly or providing feedback, she says. "This was not acceptable; it was not fulfilling the purpose of this role."

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As a small institution, Abilene Christian University has only one IRB and a spot for one community board member. A change was necessary. "When it was time to start a new year, I didn't renew with the previous community member," Roth says. "We had a discussion on the board about the value of having a student perspective."

The IRB's idea was to find a mature graduate student who was not a part of the institution and who could bring to the IRB the perspective of a student, as well as that of a community member.

"I reached out to a colleague at another institution and asked for someone who could fit that description," Roth says. "I found someone who was very eager to participate."

The new community member is an older student who has professional work experience. "She also has a student's perspective and a community perspective, and I find that she's particularly eager to participate and tries not to miss meetings," she says.

Roth conducts orientation and training meetings for all new IRB members, and she has additional training meetings for the entire IRB at the start of each year.

"We try to catch anything that's changed or issues that have come up, and we refresh people's memories on things," Roth says.

New IRB members also can meet with Roth to talk about their role and to ask questions.

"This establishes a good rapport, so they feel comfortable reaching out to me as things go along," she says.

A community member can participate in reviews to the level with which he or she is comfortable. Input is not limited just because the member is a nonscientist, Roth says.

"It depends on the community member's skill level and competency," she says. "Usually, senior IRB members mentor a newer member."

Community members often have a great deal of insight and maturity to offer an IRB review, Roth adds.

IRB training includes online modules and a couple of hours of in-person orientation, conducted by Roth.

All new members are given an IRB member handbook to read, as well as human research protection regulations.

"In my orientation, I break it

down to a little less legal language and hit the highlights, walking people through those," Roth says. "We talk about consent, what needs to be in the informed consent document, and what research can be waived. We walk through vulnerable populations and expectations, and we touch on the spirit of the Common Rule."

Roth explains privacy rules and HIPAA, the institution's research review process, the different types of IRB applications, and timelines for submission.

For returning IRB members, there are refresher courses that look at what's changed and new issues. ■

Community Research Training Helps Subjects Become Investigators

IRBs might consider new dynamics

A new social-behavioral research model IRBs might encounter is one in which researchers include people who also could be participants, or their guardians, for the same studies.

Here's an example: a middle-aged woman has a special needs child. She collaborates with a team of pediatricians, music therapists, neurologists, and epidemiologists to pursue a small business innovative research (SBIR) grant to create a music intervention mobile application for autistic children.

The intervention, which is aimed at reducing agitation and increasing speech, will be part of a study.

"One of the tenets of community-based participatory research [CBPR] is that no one knows better what the issues are in a community than community members," says **Goldie Komaie**, PhD, supervisor of public health research at Washington University School of Medicine in St. Louis.

The university has a community research fellows training program that provides 15 weeks of training, based on master of public health curriculum. It enhances the capacity for CBPR, Komaie says.

The training program has a broad spectrum of topics offered, including research ethics, human subjects training and certification, and how to conduct CBPR.

"The purpose is to train community members to become good consumers of research," Komaie says.

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Those taking the course will be able to pick up a journal article and understand how to use the information to benefit their own communities, she adds.

"Another program goal is to understand how to use research as a tool to improve health outcomes in their communities and to help them understand how to work with academic researchers," Komaie says.

The program involves 15 sessions. Each week, a different faculty member leads the class. Some instructors are from the university, and others are from local community-based organizations. More than 100 fellows have graduated from the program, receiving a human subjects protection certificate. They can participate in academic research projects and serve on community advisory boards, she says.

"Some have college degrees, master's degrees, but it's been a long time since they've been to school, so this program is a refresher for some," Komaie says. "For others, it's new information."

Once trained, the fellows can work on pilot CBPR projects, forming groups of two to four people, paired with academic mentors. "These are submitted to the IRB, and we add community members as research team members," she says.

CBPR benefits from having community members on the research team, she notes.

"They know the topics and some of the problems better than anyone

else," Komaie says. "When academic researchers come up with project ideas, I think community members can give feedback and input on why it would work."

A community-based research project is stronger when both academic and community groups are brought together. Community members can help trained researchers answer questions about what might work in recruitment and which aspects of a study might raise ethical concerns among the target population.

Sometimes, the fellows start their own pilot projects. For instance, in 2015, the Grassroots Community Foundation wanted to fund a pilot project about women and girls, so a group of four fellows applied for, and received, a $1,000 grant for a project to study mental health among unemployed African-American mothers. The group recruited and enrolled participants, working closely with academic mentors. They designed a brief intervention that included having participants watch a video on coping skills and how to recognize stress, and they conducted a post-survey, as well as follow-up telephone interviews with the participants, Komaie says.

Community-based participatory research is a priority because its framework is a great way to build trust with underserved populations, she adds. ■

The Single IRB: One Board to Rule Them All

NIH enthusiastic about sIRB oversight for multisite trials

The National Institutes of Health recently delayed the effective date of its requirement to designate a single IRB (sIRB) in research involving multiple boards, but NIH officials have lost none of their enthusiasm for the idea.

The effective date of the NIH policy on the use of a single IRB for multisite research has been extended from Sept. 25, 2017, to Jan. 25, 2018.[1] A point of clarification on the dates and deadlines: Though the Common Rule does not officially require sIRB review of multisite research until Jan. 20, 2020, the NIH has issued a policy[2] "establishing the expectation sIRB review will be used for all NIH-funded multisite studies, unless there is a requirement for local IRB review under federal, state, or tribal law or regulation" by the aforementioned January 2018 deadline, according to a recently published commentary[3] by two top NIH administrators.

They present the historical problem of multiple IRB review as a story of redundancy and irksome delay.

"It seemed straightforward on its surface: a minimal-risk study to look at financial incentives for evidence-based treatment of hypertension. In the end, however, it took 27 months and 115 submissions to get through the 17 institutional review boards involved in reviewing this multisite study,"[4] wrote **Carrie D. Wolinetz**, PhD, lead author of the commentary, and acting chief of staff and associate director for science policy at the NIH.

Other egregious examples are cited, suggesting prolonged delays over minor revisions as "clinical trials [are] delayed months as dozens of IRBs bicker over the details of consent."

There may have been some prior perception that multiple IRBs added appropriate precautions and enhanced patient protection, but the NIH view now seems to be that this entanglement of the review process may actually increase risk by diffusing responsibility and delaying innovation.

Though the measure appears to enjoy general support, some have questioned the wisdom of making it mandatory. However, the NIH concluded that "strong encouragement" would not affect change in an entrenched system.

NIH Q&A

IRB Advisor asked Wolinetz to speak to this and other related issues in a recent interview.

IRB Advisor: Just to clarify, the shift to a single IRB for multiple sites will eventually be mandatory — this is not a recommendation. Can you elaborate a little on the commentary's point that leaving this as a voluntary policy would not have solved the problems described?

Wolinetz: The pre-2018 Common Rule encouraged the use of single IRBs when their use would result in greater efficiency of review. Furthermore, the FDA has previously issued guidance promoting single IRB review. While the use of sIRBs has grown in recent years, it has not been adopted in widespread fashion, despite the increasing number of multisite studies. In order to assist in accelerating a change in culture and

promote harmonized practices, HHS determined that it would be useful to include a requirement for single IRB review in the revised Common Rule.

IRB Advisor: Your commentary cites numerous examples of overlapping and contradictory oversight by multiple IRBs, leading to prolonged and unnecessary delays in research. Can you comment a little on how such a system arose historically?

Wolinetz: In the past, most research projects were conducted at single institutions and each research institution had one or more IRBs to oversee protections for human research participants. However, as the research landscape has changed, many clinical research projects now involve conducting the same protocol at multiple institutions, each of which has its own culture and procedures. The practice of local IRB review in multisite studies has led to increased burden for researchers and delays in the initiation of research.

IRB Advisor: The NIH cancer institute uses an sIRB, and its effectiveness recently was cited at an NIH advisory panel meeting. Is this successful cancer research model an example of what the NIH is hoping to achieve with sIRB oversight?

Wolinetz: The NCI CIRB is one of several models for single IRB review. Another example is the National Center for Advancing Translational Science's SMART IRB Reliance System. *(For more information, visit: https://smartirb.org/.)* The aim of the single IRB policy is to help streamline the IRB review process and remove redundant hurdles to the initiation of such studies. The policy will allow research to proceed as effectively and expeditiously as possible. Eliminating duplicative IRB review is expected to reduce unnecessary administrative burdens and systemic inefficiencies while maintaining appropriate human subjects protections.

IRB Advisor: How would this work in practice — would participating research institutions decide on the lead IRB for a given research project? Could this then shift to other IRBs for other research, even if the same institutions are involved?

Wolinetz: In the NIH application/proposal for research funding, the applicant/offeror is expected to submit a plan describing the use of a single IRB that would be selected to serve as the IRB of record for all study sites. This is done on a project basis, so yes, it is possible that if the same institutions were involved in a different multisite clinical study, they might choose a different IRB of record for that study.

> THE NIH ISSUED A POLICY "ESTABLISHING THE EXPECTATION SIRB REVIEW WILL BE USED FOR ALL NIH-FUNDED MULTISITE STUDIES, UNLESS THERE IS A REQUIREMENT FOR LOCAL IRB REVIEW UNDER FEDERAL, STATE, OR TRIBAL LAW OR REGULATION."

IRB Advisor: Can you elaborate or provide any examples of the commentary's statement that, "We are also considering ways to supplement support to cover direct costs for the development of costing models, business processes, system changes, and efficient procedures and tools needed to facilitate sIRB review for multisite research, as well as mechanisms for widely distributing those best practices."

Wolinetz: NIH issued a Notice of Availability of Administrative Supplements for CTSA [Clinical and Translational Science Award] awardees to develop resources to facilitate single IRB review for multisite research. *(For more information, visit: http://bit.ly/2fmjdxr.)* The notice states that the awards will support "the development of costing models, business processes, system changes, and efficient procedures and tools needed to facilitate sIRB review for multisite research." NIH will continue to evaluate the need for additional support. ■

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Gene Expert: IRBs Should Prepare for Somatic Cell Trials

Clinical trials are underway for HIV, sickle cell disease

Though human genome editing research that would create inheritable changes in offspring is the subject of somewhat ominous discussions, IRBs are much more likely to see research proposals involving genetically modified somatic cells.

A recently published report[1] by the National Academy of Sciences explains that "somatic cells are all those present in the tissues of the body except for sperm and egg cells and their precursors. This means that the effects of genome editing of somatic cells are limited to treated individuals and are not inherited by their offspring. The idea of making genetic changes to somatic cells — referred to as 'gene therapy' — is not new, and genome editing for somatic applications would be similar. Gene therapy has been governed by ethical norms and subject to regulatory oversight for some time, and this experience offers guidance for establishing similar norms and oversight mechanisms for genome editing of somatic cells."

Most basic research on human cells uses somatic cells such as those of the skin, liver, lungs, and heart. By contrast, "germline research" involves reproductive cells that could alter the human genome in a way that would affect descendants. Though the field holds great promise, it raises sufficient ethical and moral questions that intentionally creating or modifying an embryo to include heritable genetic modification is banned in the U.S.

On the other hand, somatic gene editing trials are in process, with one HIV clinical trial targeting the receptors that enable the virus to infect cells.[2] Likewise, another targeted trial is aimed at correcting sickle cell mutations.[3] Both of these trials involve somatic cell editing cells ex vivo, with therapy beginning as the cells are returned to the body.

"SOMATIC CELL GENE EDITING IS HIGHLY INNOVATIVE AND PRESENTS MANY UNKNOWNS TO PARTICIPANTS IN CLINICAL TRIALS. IRBS WILL NEED TO BE VIGILANT TO ASSURE SUBJECTS ARE ADEQUATELY PROTECTED. ONE PARTICULAR ISSUE IS GETTING ADEQUATE SCIENTIFIC EXPERTISE TO UNDERSTAND THE SCIENCE AND POTENTIAL RISKS."

"For persistent benefit, the therapeutic modification should be made in long-term repopulating cells, such as hematopoietic stem cells," a researcher notes.[4] "As other stem cell approaches are mastered, including induced pluripotent stem cells from patients, genome editing can be applied to them as well. Prospects for in vivo genome editing are less rosy due to the challenges of delivering the materials effectively to the target tissues, but there is active research in this area."

With somatic gene cell editing already underway in some trials, IRBs should prepare to deal with protocols involving noninheritable genetic changes, says **Bernard Lo**, PhD, president of the Greenwall Foundation in New York City and director emeritus of the medical ethics program at the University of California, San Francisco.

"Somatic cell gene editing is highly innovative and, thus, presents many unknowns to participants in clinical trials," he says. "IRBs will need to be vigilant to assure subjects are adequately protected. One particular issue is getting adequate scientific expertise to understand the science and potential risks."

This is done by consultation with a Recombinant DNA Advisory Committee (RAC) to assess the protocol's risks and benefits. Among the techniques currently being used that may require some consultation is gene editing that recognizes DNA sequences via CRISPR (clustered regularly interspaced short palindromic repeats).

"Although the RAC gives an in-depth review of the study, this is done earlier in the process, before the details of how adverse effects will be identified and monitored are set," Lo

says. "Thus, IRBs will need to look closely at these parts of the protocol, and will require members who are experts in both CRISPR science and in the disease being studied. Also, IRBs should reach out to patients affected by the disease and disease advocacy groups to assure they have expertise on how to explain new, complicated concepts to participants."

IRB Advisor asked Lo to further clarify this situation, particularly the aspect of the RAC not being involved through trial completion.

"The in-depth scientific and ethical review by the RAC can be very helpful to IRBs, who should read the RAC minutes carefully," he says. "However, because the RAC does not review the final protocol, the IRB will need to assure that all the scientific and ethical concerns raised by the RAC are adequately addressed in the final protocol and that any issues raised since the RAC review are addressed."

Thus, an IRB without such expertise on the current board may need to form an ad hoc panel of scientific experts to pursue evaluation of somatic gene cell research.

Informed consent to somatic cell research participants should address the possibility of "therapeutic misconception," Lo says. This effect may be compounded by enthusiastic press coverage of novel therapies.

"Somatic cell gene editing will be used to try to treat serious illnesses for which current treatments are inadequate," he says. "Potential clinical trial participants will bring great hopes to the trial. The scientific rationale seems compelling: correct the gene that is responsible for the pathophysiology of the illness. IRBs and investigators will need to assure that patients do not have serious misunderstandings that would compromise their informed consent."

Lo recommends encouraging questions by research participants, identifying and correcting misunderstandings, and perhaps testing comprehension of the key issues. In addition, the protocol must have robust adverse event reporting, looking for problems like editing at unintended sites, finding uncontrolled growth of modified cells, or unexpected immunological reactions, Lo advises.

"AS WITH ALL HIGHLY INNOVATIVE STUDIES, THERE WILL NEED TO BE A GOOD DEAL OF BACK-AND-FORTH TO ASSURE THAT THE RESEARCHERS UNDERSTAND THE IRB CONCERNS AND THAT THE IRB UNDERSTANDS HOW THE RESEARCHERS HAVE CHANGED THE PROTOCOL IN RESPONSE TO THESE CONCERNS."

"These concerns, and others, will need to be addressed by the IRB," he says. "As with all highly innovative studies, there will need to be a good deal of back-and-forth to assure that the researchers understand the IRB concerns and that the IRB understands how the researchers have changed the protocol in response to these concerns."

Another challenge is protecting privacy, as there may be considerable press interest in obtaining materials and clinical information IRBs or researchers share with colleagues, he notes. IRBs should be wary of conflicts of interest, with red flags triggered if institutions or investigators have financial stake in the intervention tested.

Regarding the research participants, issues of compensation and access will likely arise, including whether there are barriers to low-income patients. And while current somatic cell gene therapy is accepted for critical medical conditions, at what point could the risk be sufficiently low to treat less serious conditions, Lo asks. That raises the specter of nonmedical use, "enhancements" that could be possible with such gene research. Public input and debate are essential as the social and moral considerations go beyond the current risk/benefit equation, he emphasizes. ■

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Pregnant Pause: Time to Push 'Play' on Trials With Expectant Mothers

The shadow of 'long-tail' liability clouds progress

There are many obstacles to including pregnant women in research, and IRBs may understandably err on the side of caution when it comes to expectant mothers in clinical trials.

The risk of liability is foremost in the minds of legal counsel, who well remember the thalidomide exposures in the 1950s and 1960s, when thousands of babies in Europe were born with birth defects linked to an anti-nausea drug taken by their mothers. In a recent article calling for the inclusion of pregnant women in more clinical trials, a lawyer and bioethicist raise the provocative point that the disaster "arguably could have been mitigated had pregnant women been included in early testing of thalidomide."[1]

There also is the fear of so-called "long-tail" liability, where offspring of a mother injured in a clinical trial could seek subsequent redress for their own harms. With good reason, there is no way for an expectant mother to "informed consent" her way past this.

"If you are asking whether an informed consent process that describes risks to the fetus could in some way mitigate the potential for 'long-tail' liability, the regulations prohibit waiver of any legal rights — for example, a right to sue, so any waiver-like language is not legally permissible," explains **Anna C. Mastroianni**, JD, bioethics expert and professor of law at the University of Washington in Seattle. "Notifying a pregnant woman of the potential risks to her fetus is ethically required as part of a clinical trial under any circumstance. In my opinion, that effort alone would not assuage a lawyer's concern about long-tail liability. As we alluded in the article, considerations related to insurance and compensation will be important components of any risk management program."

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If the risk can be mitigated, needed research breakthroughs could result. Indeed, one need only look back at the success of preventing HIV transmission to the fetus with early drugs like zidovudine — or the current threat of Zika virus congenital defects — to realize the risk of excluding pregnant women from research carries perils of its own.

"I am confident there are possible policy solutions — and there will need to be more than one approach," she says. "The 21st Century Cures Act recently signed into law created a committee tasked with taking the first step toward that effort — to identify gaps in knowledge with respect to pregnant women's health."

The NIH Task Force on Research Specific to Pregnant and Lactating Women is slated to convene Aug. 21-22, 2017.

Three Strikes

The recently published review article by Mastroianni and colleagues was based on a day-long meeting with a group of legal experts. In addition to the long shadow of liability, there are several other traditional deterrents to including pregnant women in clinical trials. The group concluded that those include these three, which are paraphrased as follows:

- The FDA does not require the inclusion of pregnant women in research studies for basic drug approval, so it makes no "commercial sense" to expand the clinical trial population.
- Pregnancy is widely perceived as generating "background noise" in the overall clinical trial data, potentially complicating the safety and efficacy profile of a profitable product.
- There is no financial incentive to conduct studies with pregnant women. The market for drugs that treat pregnancy-related conditions is small, and drugs for general medical conditions that may arise or persist

during pregnancy are frequently prescribed to pregnant women anyway.

An Ethical Obligation?

In the absence of incentives, *IRB Advisor* asked Mastroianni whether IRBs and their legal counsel have an obligation to pursue paths toward more research inclusion for pregnant subjects.

"There is a legal obligation — imposed by federal regulations — to ensure that the research undergoing review is equitable," she says. "From an ethics standpoint, this means that IRBs should at least ensure that researchers provide a reasonable justification for the exclusion of pregnant women."

That includes asking investigators how they plan to respond if a female subject becomes pregnant during a study protocol, despite contraceptive precautions. Those questions could include whether the subject will be able to continue on the study medication and will data continue to be collected, Mastroianni says.

"The responses raise ethical issues, and decisions should be grounded in science, not fear," she tells *IRB Advisor*. "Particularly when the woman is suffering from a serious condition that would otherwise go untreated. It is notable that in 2001, the regulations essentially shifted a presumption from exclusion — pregnant women may not be included in research unless 'xyz' conditions are met — to inclusion — pregnant women may be included in research if 'xyz' conditions are met."

Off-label Use Inevitable

Still, with few FDA-approved products indicated for pregnancy — due in no small part to their exclusion from clinical trials — off-label use of various medicines is inevitable. That creates risk for both mother and fetus, but the result is a classic Catch-22: Some of the same regulations and policies requiring data also restrict its collection.

"There are a number of actors throughout the research pathway that can play a role in the effort to ensure that the health of pregnant women can benefit from research — whether funders, regulators, IRBs, institutions, legal counsel, researchers, and pregnant women," Mastroianni says. "This paper was designed to highlight the legal barriers to that research. It would be helpful for lawyers who have successfully managed that risk on behalf of their clients to share their strategies with each other. We have another paper in preparation that we hope will highlight some of the key factors to successfully including pregnant women in clinical trials, including those with HIV." ■

REFERENCE

1. Mastroianni AC, Henry LM, Robinson D, et al. Research with Pregnant Women: New Insights on Legal Decision-Making." *Hastings Center Report* 2017: 47(3): 38-45.

Medical Marijuana Inc. Moves Forward With Proof of Concept Study

Cannabis company works with Israel-based CRO

Medical Marijuana Inc. announced in late July 2017, that the San Diego, CA-based company's AXIM Biotechnologies was working with an Israel-based contract research organization to begin a clinical proof of concept study (POC) with its cannabidiol and gabapentin chewing gum product to treat restless leg syndrome in patients.

There will be a randomized, double-blind, single-center, phase two trial to demonstrate the efficacy of AXIM's chewing gum product. Thirty study subjects will be enrolled in Israel.

Restless leg syndrome (RLS), also called Willis-Ekbom disease, is when nocturnal sensorimotor symptoms occur. People with RLS have lower extremity muscle spasms while they are sleeping. This can disrupt their sleep and cause pain. Anywhere from around 4% to 14% of the U.S. population has this condition.

"We believe that advancements in clinical cannabinoid research may hold keys to helping people experience symptomatic relief from challenging and debilitating neurological disorders," **Stuart Titus**, PhD, chief executive officer of Medical Marijuana, said in a news statement. ■

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CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **The oncology clinical trial industry is changing with new models that raise some ethical questions for IRBs. How are these changing?**

   a. Some oncology studies require participants to have no previous clinical trial experience or enrollment.
   b. Some Phase I studies evaluate efficacy in first-in-human trials, no longer looking solely at safety.
   c. One new oncology study model has clinical trial participants meet directly with IRB members.
   d. All of the above

2. **What is a chief asset that community IRB members can bring to IRB review discussions, experts say?**

   a. Community IRB members could edit informed consent documents and check for readability.
   b. Community members are the best primary reviewers of protocols.
   c. Community IRB members could explain what the average person in the community would think about a particular study and explain their concerns.
   d. None of the above

3. **How many IRBs were involved in a low-risk study cited by NIH authors as indicative of the problem with multiple IRB review?**

   a. 27
   b. 115
   c. 17
   d. 9

4. **Bernard Lo, PhD, said IRBs can count on the guidance of a Recombinant DNA Advisory Committee from the onset of a somatic cell gene editing trial until the research is completed.**

   a. True
   b. False

CME/CE OBJECTIVES

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

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