IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

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INSIDE

NIH Ethics Panel Vetoes Zika Human Infection Trials

Cites risk to subjects, possible transmission

While there are reports of various Zika vaccine trials proceeding, one the most promising methods to quickly and accurately measure vaccine efficacy has come to a full stop.

"Human challenge trials," or "controlled human infection models," involve exposing research subjects to a pathogen, typically in some attenuated state under rigorous controls and oversight, to test a vaccine candidate.

With regard to Zika virus, a bioethics committee convened by the National Institute of Allergy and Infectious Diseases (NIAID) has concluded at present the risks of this approach outweigh the benefits. Among other reasons, the panel cited the risk to research subjects, possible transmission to others, and the availability of safer vaccine trial approaches.

Though a way forward is described in the panel's recent report to NIAID, for now a red flag has been raised and human infection trials for Zika vaccines are being reconsidered. A researcher who helped develop a controlled human infection model for dengue virus — which is closely related to Zika — questioned the panel's decision, saying it thwarts the fastest method to develop safe, effective vaccines.

> "THERE ARE SPECIFIC QUESTIONS WITH ZIKA THAT A CONTROLLED HUMAN RESEARCH MODEL COULD REALLY ANSWER."

"There are specific questions with Zika that a controlled human research model could really answer," says **Anna P. Durbin**, MD, a professor and researcher in the Johns Hopkins University Vaccine Initiative. "I am not sure the committee had adequate information in making their recommendation. I think they overstepped. There is a pathway

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forward in the recommendations, but unfortunately it is a very narrow pathway and it does limit the value of the controlled human infection model." *(For more information, see related story, page 52.)*

Durbin may pursue one example offered by the panel that could sufficiently mitigate the risk of human controlled research risks: a Zika human research model that only enrolled women who use effective, long-acting contraception. That would mitigate both the risks of subsequent birth defects and concerns about the prolonged presence of Zika in semen, which has resulted in sexual transmission of the virus.

"[The panel] did say you may be able to move forward with women only, on very reliable birth control, and that is something we are considering," Durbin says. "We would would like to develop a controlled human infection model in parallel as we first begin to evaluate our candidate Zika vaccines. If we have breakthrough viremia in those people that were vaccinated, then we may need to re-evaluate our strategy and shouldn't necessarily take that vaccine candidate forward, even though we saw good immunogenicity." *(See related story, page 52.)*

This is not an inconsequential decision. The CDC announced at a recent press conference that about 10% of pregnant women with confirmed Zika in the U.S. in 2016 had a baby with one of the well-described horrific birth defects. Zika infection — particularly in the first trimester — can lead to fetal microcephaly and other serious congenital brain abnormalities, limb defects, and vision and hearing problems.

NIAID convened a committee to evaluate the ethical issues of Zika vaccine efficacy trials though the controlled human infection model. The panel was charged with determining whether a Zika virus human challenge trial could be ethically justified, and if so, under what conditions. A writing committee comprised of bioethicists, researchers, and federal agency officials recently issued the panel's report.[1]

"Given the potentially devastating effects of Zika infection during pregnancy, the insidious nature of the disease, and the promise of what can be learned from human challenge trials, the writing committee concluded that a Zika virus human challenge trial could be ethically justified if certain conditions were met," the panel concluded. "However, at this point in time, based on what was heard at the consultation meeting and on our review of the latest scientific and ethics research, the writing committee has determined that these conditions preclude the conduct of a Zika virus human challenge trial."

Unusual Suspects

In an analysis of risks of a Zika virus challenge study, the panel cited several unresolved issues about the epidemiology of virus, which was first found in a monkey in the eponymous Zika Forest in Uganda in 1947. According to the CDC, Zika is the first mosquito-borne virus that can cause birth defects. It also is the first mosquito-borne virus that can be sexually transmitted. In findings that somewhat validate the committee's concerns, Zika has surprised public health officials on both counts.

There also have been some

secondary transmission incidents that are concerning. These include infection via needlestick to a lab worker, a case of female-to-male sexual transmission, and the strange case of a 73-year-old patient in the U.S. who apparently transmitted Zika to a visiting acquaintance — possibly through tears — before dying with an incredibly high level of circulating virus in the blood.[2] The secondary case developed symptomatic Zika infection, but subsequently recovered. It is possible that hormonal treatment for prostate cancer somehow accelerated viral replication in the index case, investigators concluded. In addition, some people infected with Zika have developed a rare paralytic syndrome called Guillain-Barré.

Panel Recommendations

In light of such concerns, the Zika bioethics panel made the following points and recommendations:

• There is substantial uncertainty about the risks to potential volunteers in a Zika virus human challenge study. Although the known risks of a Zika human challenge trial appear comparable to the risks of Phase I research with healthy volunteers, without greater knowledge about outcomes from Zika exposure these risks would require high social benefit to be justified.

• The committee was particularly concerned about possible risks to third parties, i.e., that Zika virus might be transmitted from study volunteers to others, such as fetuses and members of the community. Because these third parties generally cannot know about, protect themselves from, or consent to risks, the risks are only reasonable if they can be reduced to near-zero. However, the mechanisms of transmission of Zika virus and how long individuals with Zika can infect others are not fully understood. Before proceeding with a Zika virus challenge study, researchers should therefore demonstrate that the risks to third parties are not likely to be realized.

• Whether a Zika virus human challenge trial has sufficient social value to proceed depends on the reasons for conducting it and whether there are alternative ways to obtain the information. The most compelling rationale for conducting a Zika human challenge trial, given the risks and uncertainty, would be if field trials were prohibitively difficult to conduct in light of a waning epidemic. This rationale is not currently met, but could come to pass in the future.

• A Zika virus human challenge trial only should enroll individuals with capacity to provide their voluntary informed consent. Such a trial should also take steps to minimize the risks to fetuses to as close to zero as possible.

• Researchers and sponsors of a Zika human challenge trial should use a robust informed consent process. For example, researchers and sponsors could require multiple voluntary steps for individuals to take to enroll, adequate time for discussion, and evaluation of and feedback given to enhance participant understanding about critical issues.

• Volunteers should be paid fairly for their time and inconvenience, but they should demonstrate understanding of the risks and uncertainties involved and be evaluated with objective evidence of their eligibility and compliance wherever possible.

• The right to withdraw should be respected in challenge trials by halting the collection of data for volunteers who want to withdraw even if they will have to remain confined to protect themselves or others.

• In the event a Zika [human challenge] trial proceeds, study sponsors should ensure that sites are adequately insured to cover the costs of care and compensation for research-related injury, to both study participants and third parties, and that insurance policies that are purchased have adequate processes in place to efficiently and fairly evaluate and resolve claims.

• Community engagement with the geographic community surrounding the site(s) of a Zika human challenge trial should be conducted in advance of the research to show respect for the community and its values, obtain community buy-in to the goals of the research, and proceed with transparency.

Committee Concerns

IRB Advisor asked the following questions of **Seema K. Shah**, JD, Zika committee chair and an associate professor at the Treuman Katz Center for Pediatric Bioethics at the University of Washington and Seattle Children's Research Institute.

IRB Advisor: Just to clarify, given the current state of the science, does the committee recommend against conducting human trials that involve intentionally infecting subjects with Zika virus?

Shah: The committee concluded that a Zika virus human challenge study should not be conducted at this time, based on what we heard about the state of the science, the risks to volunteers and community members, the reasons for doing this

type of research, and the alternatives. The committee was concerned that the full spectrum of disease caused by Zika virus is not yet characterized. However, the committee was impressed by how much has been learned about Zika virus in the past two years.

IRB Advisor: Similarly, the committee was particularly concerned that Zika virus might be transmitted from study volunteers to others, such as fetuses and members of the community.

Shah: The committee was concerned about the possibility of transmission to others outside of the study, and recommended that a Zika virus human challenge study should not proceed until researchers can show that risks to others are unlikely to be realized. Research to learn more about how Zika virus is transmitted and how long individuals with Zika virus are infectious is of high priority.

IRB Advisor: There are some safeguards mentioned in the report, such as "long-lasting reversible contraception." Could research proceed if these type of safeguards are in place?

Shah: The committee concluded that research could proceed if there was a strong enough rationale to justify the risks and uncertainty, and a number of safeguards were in place. We saw two compelling rationales for doing a Zika virus human challenge study: One, if field trials become impossible to conduct, or two, if human challenge trials could accelerate development of a vaccine that could prevent congenital Zika infection. We did not hear evidence that the conditions we laid out are currently met, but we think they could be met in the future.

For example, although field trials are being conducted now, the epidemic may burn out or become more unpredictable over time, making a human challenge study the only way to move vaccine research forward. Additionally, although we did not hear this evidence at our consultation, regulatory agencies and other key stakeholders might clearly indicate that a Zika virus human challenge study would be an acceptable and important way to speed up the licensure of a Zika virus vaccine.

IRB Advisor: So there are conditions that would meet the committee's concerns and open a way for this type of vaccine trial?

Shah: With a compelling reason to favor a Zika virus human challenge trial over alternative research designs, we were also open to the possibility that a carefully designed Zika virus human challenge trial could move forward. A Zika virus human challenge trial might be ethically justifiable based on applying the latest scientific information to minimize risks, the small numbers of participants who would be enrolled in a Zika virus human challenge trial, and the use of creative approaches to minimize the risks to others so they are near-zero. In our report, we provided a road map for researchers with concrete ethical issues to address and strategies for protecting volunteers and third parties. We did not review any specific protocols and determine whether these conditions were met. Ultimately, the leadership at NIAID will judge whether protocols they receive can meet the ethical conditions for moving forward. ■

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Researcher: Human Infection Trials for Zika Could Be Safely Performed

Imperative to begin testing vaccines while virus circulates

It sounds counterintuitive, but one of the main arguments for getting a Zika virus vaccine into human trials is that as susceptible people become immune through prior infection, it will be harder to test vaccine efficacy in a large population.

Though there is less immediate need for a vaccine if the Zika virus fades back, the problem is that no vaccine will be available if it returns later to infect susceptible populations. This very point was made during the massive Ebola epidemic outbreak in West Africa, where no vaccine was available because it was not developed during past outbreaks of the hemorrhagic virus.

One caveat that bears mentioning at this juncture: The CDC is urging vigilance and warning that Zika will return as the weather warms and *Aedes egypti* mosquitoes that carry the virus emerge across a large swath of the nation.

An ethics panel recently advised federal public health officials against using controlled human infection trials to test Zika vaccines, but said the model may be justified if the virus begins to wane. A researcher who developed a controlled human infection model for dengue virus — which is closely related to Zika — questioned the panel's decision to red-light the approach, warning that this may end up being a missed opportunity.

IRB Advisor asked **Anna P. Durbin**, MD, a professor and researcher in the Johns Hopkins University Vaccine Initiative, to discuss this point and explain how Zika vaccine controlled human infection trials could proceed safely.

IRB Advisor: Are you concerned that Zika virus will diminish to the point that wouldn't be able to test a vaccine in a large population?

Durbin: I am absolutely concerned about that. If you look at the data right now, this is the peak season for Zika in South America, but they are seeing very few cases. In Puerto Rico and the Caribbean we may see some more cases this summer, but I'm not convinced there will be enough Zika circulating by the time a vaccine is ready to go into Phase III trials for efficacy studies. It may become very sporadic like chikungunya virus or West Nile, and it will be difficult to predict where it is circulating. You want to have a vaccine ready to go in case it comes back. It needs a susceptible population, and as it went through Brazil and South America, those countries have fewer and fewer susceptible people. So then you have to wait until there are new birth cohorts that are susceptible.

IRB Advisor: The Zika vaccine ethics panel report cited the risk of transmission from study participants to their contacts. What assurances to you have that this would not occur?

Durbin: When you look at the data, third-party transmission or sexual transmission is not common. More than 40,000 travel-associated cases of Zika have resulted in some 40 cases of sexual transmission, which is less than 1%. The big problem is that we don't have very good data on shedding of actual virus that we can replicate. Everything is done by PCR, which doesn't tell you whether that virus is infectious — it only tells you that pieces of that virus were recovered.

> "THE REASON WE THINK CONTROLLED HUMAN INFECTION TRIALS ARE VALUABLE IS YOU CAN HAVE A VERY EARLY LOOK AT WHETHER OR NOT YOUR VACCINE MAY BE PROTECTIVE."

IRB Advisor: What are the advantages to using human infection vaccine challenges?

Durbin: The reason we think controlled human infection trials are valuable is you can have a very early look at whether or not your vaccine may be protective. With Zika, I think we have a higher bar than we have had with any other vaccine. Because we know from the epidemiological studies that have been done that infection at any time during pregnancy carries a risk. We know that asymptomatic women have given birth to babies with microcephaly or Zika congenital syndrome. You don't have to be symptomatic with Zika in order to transmit the virus to the fetus. So that makes us think that even small amounts of virus could be transmitted to the fetus and result in congenital Zika syndrome.

IRB Advisor: So that increases the difficulty of developing a vaccine?

Durbin: As a vaccine developer, that tells us that we need a very high bar of protection. We need to try to prevent any Zika virus from infection to the mother. When we look at most vaccines, we are looking to not necessarily prevent infection because that is a very high bar, but you want to see aggregation of disease. People may become infected but they don't get sick. We don't think that is going to be enough with Zika. You may have to actually prevent infection, and you cannot study that in traditional efficacy studies because you won't pick up asymptomatic infections in Phase II or Phase III trials.

IRB Advisor: But you may be able to overcome these issues with a human infection protocol?

Durbin: You can use a controlled human infection model, where you vaccinate people [with a Zika candidate vaccine] and then at some time point later — whether it is a month or six months, 12 months — you administer a known amount [of virus] by subcutaneous injection. We know exactly how much they received. We administer it like we would any drug, drawing it up in a

syringe and then injecting it under the skin. Then we would follow [research subjects] very closely in inpatient settings for about two weeks. We would sample blood and probably urine, saliva, semen, and vaginal secretions for women to see if we can recover any virus. If we recover virus, we would sample using both PCR and old-fashioned virology tissue culture to see if that virus is replicating or not. If it is and you recover virus, then you know that your vaccine did not induce sterilizing immunity. Then you would have to decide whether it is worth using that vaccine.

IRB Advisor: Would you use some kind of attenuated or weakened Zika strain to induce the controlled human infection?

Durbin: When we think about what would be a good Zika immune challenge, the first thing we want is an isolate from someone who had uncomplicated Zika — so either a very mild illness or no discernable illness. And then we would start with administering a very low dose. So for the dengue model we found that 100% of research subjects had replicating virus, but the virus is at a low titer. It is 2.5 logs, about 300-400 virus particles [per ml]. Whereas when people are sick with dengue that have 10,000, 100,000, 1 million virus particles per ml. So we're 100- to 1,000-fold below the level that would make people sick.

IRB Advisor: So if you challenge vaccine immunity with low titers of Zika, that would be unlikely to transmit from the recipients to others?

Durbin: That is exactly our intent. We don't want transmission and we reduce the risk of that by giving a dose that low levels of viremia in the recipients and that's what we have been able to do with the dengue controlled human infection model. It doesn't replicate to high enough titers to be transmitted by mosquitoes. ■

IRB Has Variety of Self-Assessment, Staff Assessment Tools

Responses help with continual improvement

An Indiana research compliance program found that IRB staff and board assessments help keep the program on track and running well.

"The primary benefit of assessments is to help us identify problems we were not aware of and to confirm things we think we're doing well to keep on doing them that way," says **John R. Baumann**, PhD, associate vice president for research compliance at Indiana University in Indianapolis. The institution has seven IRBs with approximately 160 IRB members, including six chairs.

The following is an example of the assessment's use in identifying issues: IRB staff and member assessments of one IRB chair indicated a problem.

"We had a feeling the person wasn't performing that well as a chair," Baumann says, adding that the assessment feedback confirmed there was a problem.

"That person is no longer a chair," Baumann notes.

Assessments also can point out systemic problems. For instance, the research compliance office responded to an apparent IRB office crisis by surveying researchers anonymously about their experiences with the IRB.

"A few years ago, the office was in a real crisis; staff were demoralized, researchers were unhappy with us," Baumann recalls. "The IRB's turnaround and throughput were bad, so quantitatively and qualitatively, our measures were not very good."

The first survey had a good response rate and made it clear that the IRB had to make changes. "Our rate of satisfied or very satisfied was 40% to 60%, depending on the question asked," Baumann says.

After the IRB made changes and corrected what researchers said was not working well, follow-up investigator surveys improved dramatically.

"We made a lot of changes, and it went above 90% who said they were satisfied or very satisfied," he says.

The organization originally began to create assessments as part of an AAHRPP accreditation standard that required that IRB members and staff be periodically evaluated and given feedback.

This is accomplished via a variety of mechanisms, including member self-assessment, assessment of IRB members by IRB staff, of IRB staff by IRB members, and researchers assessing the IRB process.

The staff's survey of IRB members was designed to provide insight into the working relationship between IRB

staff and individual board members, Baumann notes.

"The first time we had the staff evaluating IRB members was in 2013," says **Shawn Axe**, CIP, director of the human research protection program in the office of research compliance at Indiana University.

Axe and Baumann explain how the assessments work:

• Staff assessment of IRB members and IRB members' assessment of staff. "We evaluate each IRB member based on how often they worked with the member on five or more areas," Axe says. "We ask how well they understand the federal regulations and how well they apply them."

The assessment also looks at how robust their documentation is and how accessible the member is.

The staff's evaluation of IRB members is scored from one — extremely unsatisfied — to 5 — extremely satisfied. IRB employees are advised to not score members unless they are familiar with them.

The following are the scoring items:

- ability to apply federal regulations, ethical principles, and IU IRB policies and procedures to research;

- completion of reviewer requirements: completed reviewer checklists, clear provisions (changes requested by the IRB reviewer to the IRB application), and presentation to IRB;

- accessibility: willingness to review minutes, willingness to consult with staff/investigators, willingness/timeliness of review expedited or high-priority submissions, and willingness to serve as an alternate or attend off-cycle meetings; and

- working relationship with staff: positive interactions, supportive of staff requests, and responsive to communication.

Based on the survey IRB members complete about the staff, the IRB office has learned that its most effective educational format is the 10-15 minute presentation by staff at the start of board meetings, Axe says.

"We have general regulatory or ethical topics and a PowerPoint presentation, usually with an opportunity for questions and answers," Axe says. "This month, the topic was on promptly reportable events, focused on unanticipated problems and noncompliance."

> "THE PRIMARY BENEFIT OF ASSESSMENTS IS TO HELP US IDENTIFY PROBLEMS WE WERE NOT AWARE OF AND TO CONFIRM THINGS WE THINK WE'RE DOING WELL TO KEEP ON DOING THEM THAT WAY."

Other topics have included regulatory updates, vulnerable populations, informed consent, recruitment, and regulatory/ethical compliance.

The assessments are anonymous and include room for comments. "That's how we found out the concern over one chair was pervasive," Axe notes.

• Researcher surveys about IRB experience. Researcher surveys are held twice a year over a four-week period. Survey invitations go out to each principal investigator of a study that is approved during those time periods.

"We ask a series of seven questions and we're clear that we're asking about their experience with a particular approval," Baumann says. "Then we have additional questions about the time to approval, the new electronic system, or things like that."

The researcher survey simply asks investigators to answer each of six questions, based on ratings from extremely unsatisfied to neutral to extremely satisfied. A seventh question is open-ended: "What can we do to improve these responses?"

Each question begins with "How satisfied are you with..:

- Your working relationship with the IU Human Subjects Office staff?

- The staffs' pre-review/screening of materials for review?

- Your IRB Chair?

- Your IRB Vice Chair?

- The qualifications and performance of the board?

- How the IRB meetings are run?"

The narrow nature of the questions has made the ratings more useful, Baumann notes.

"It's pretty much spot-on," he says. "We don't find very many petty comments or personal comments other than what is directly related to performance."

The counterpart assessments sometimes reveal an expectation or communication problem.

For example, one board member's assessment of IRB staff noted that staff's pre-review missed issues in protocol submissions that the board member felt should have been found prior to the IRB meeting, Axe recalls.

But the problem was not as it appeared. The staff had done their jobs as they were instructed. They conducted the pre-review for the

purpose of identifying regulatory omissions in protocols. The issues the board member raised were related to grammatical errors.

"Staff are not the grammar police and nor should they be," Axe says. "These are not the things that hold up approval."

So instead of changing how staff handled the pre-reviews, Axe spoke with board members about how to adjust their expectations of what the pre-review is intended to accomplish.

Perform Self-assessments

• **IRB self-assessments.** "We've had self-assessment by IRB members and confirmation by chairs since we've been accredited," Baumann says. "Every IRB member is required to complete a self-assessment."

The self-assessments include staff-added performance data.

The IRB chair meets with Baumann or Axe and reviews the board member's self-assessment and the IRB staff's assessment of that member to confirm the member is performing as expected, Baumann says.

Self-assessments are identifiable, and assessments also include a confidential set of questions that are not identifiable about the IRB chair, vice chair, and staff. "We have everyone reflecting and assessing everybody," Baumann says.

The self-assessment form, like the other assessments, asks for ratings from extremely satisfied to extremely unsatisfied.

Members are asked to describe "How satisfied are you with the following:

- Your knowledge of the federal regulations and ethical principles in research;
- Your ability to apply the federal regulations and ethical principles in research;
- Your knowledge of the IU IRB policies and processes;
- Your ability to apply the IU IRB policies and processes;
- Your attendance at IRB meetings;
- Your availability for conducting expedited reviews; and
- Your participation in IRB meetings."

There also are several open-ended questions, including:

- What can we do to help you improve as an IRB member?
- What additional educational resources may we provide?
- Any additional comments?

The staff pull data about each IRB member's meeting attendance, CITI completion, total new study reviews for the full and expedited boards, and other information.

Most assessments are positive, and they're given positive feedback via email. "We might email to say, 'Everything looks good! Here's your appointment letter for the next round,'" Baumann says.

When IRB chairs and Axe meet with IRB members or staff about their assessments, it's usually because there were red flags that have to be addressed face-to-face.

"It's always done with respect to confidentiality," Baumann says. "It's all designed around, 'How can we make you a better IRB member?'" ■

BEST PRACTICES *SPOTLIGHT*

Creating an Optimal Research Training and Mentoring Program

A nine-year IRB chair veteran and a medical school's associate dean identified gaps in their institution's human research protection education. They noticed that online training was fine for general information, but came up short when investigators were struggling with specific protocol issues.

Their solution was the Clinical Research Training and Mentoring Program (CRTMP), a peer-to-peer, hands-on, protocol-specific mentoring and training program.

Often, investigators cannot relate what they learn online to their specific needs, says **Robert Edelman**, MD, clinical professor of medicine and pediatrics at the University of Maryland School of Medicine in Baltimore. Edelman also is the director of the CRTMP at UMB and an associate director for regulatory affairs and bioethics at the Center for Vaccine Development in Baltimore.

"You can go to a half-dozen classes and not solve the problem of a particular protocol," Edelman says. "Each protocol is unique in its own right, and there has never been

a protocol we have looked at that's exactly like another — there's always some wrinkle to it that makes it different."

Time Savings, Increased Satisfaction

The CRTMP has proven successful. A study of its implementation showed that 179 of 2,340 protocols were assisted by CRTMP. The program reduced the number of protocols that were returned for revisions by the IRB. For non-assisted protocols, the mean number of returns were 1.6 per protocol. For protocols assisted through CRTMP, the mean for returns was 0.7. For protocols that received the program's assistance while they still were in draft form, the mean protocol returns was only 0.4.[1]

This saved the IRB an estimated 1,291 hours of work, which equates to 161 person days saved over 4.5 years, or 36 person days per year.[1]

Also, an anonymous CRTMP survey showed 100% satisfaction for IRB chairs, vice chairs, and staff.[1]

About 95% of the protocols seen in the program were successfully approved. The remaining 5% were withdrawn by the investigator after they were told their research was not going to be scientifically valid or ethical because of a lack of volunteers, nursing staff, or other issues, Edelman says.

"That's an enormous time savings for everybody," he notes. "Those few protocols can take an enormous amount of time of the IRB and panel reviewers, going back and forth until they realize the study cannot be done."

Research requests for help through the CRTMP come primarily from the school of medicine, though there also are requests from the schools of dentistry, social work, pharmacy, nursing, law, and regular graduate school. "Sometimes faculty in the school of law do healthcare research that requires questionnaires and interviewing people," Edelman says.

Here's how the program works:

1. Advertise through presentations. The program was described in presentations at 27 departmental meetings at six UMB professional schools. Other referrals came from the IRB and UMB faculty networking.[1]

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Edelman tells faculty and staff at presentations that the university feels the protocol mentoring program is so important that they are willing to invest his time and other staff's time to support it.

"The knowledge that this is available to investigators does good things to investigators at the highest level," Edelman says.

2. Identify principal investigators (PIs) who will benefit. The CRTMP works with principal investigators, department/division chairs, and the IRB and human research protection staff to identify PIs and their protocols that would benefit from the mentoring.[1]

"You should have a feeling for the needs of the investigator," Edelman suggests. "You have to empathize with their needs."

Many investigators are busy, distracted, and involved in research to the point that if they receive an IRB deferral or modification, they feel rejected, he notes.

"So I go in there and reassure them that I really like the research, and it has to be done properly," Edelman says.

He tells PIs that he's giving them his time at no cost to the study and that the mentoring program is supported by the president of the university.

3. Customize one-on-one instruction. Edelman spends an average of six hours with each investigator in the mentoring program. The other mentor is a professor of pediatrics, who also is very experienced in human research protection.

"We read over the protocol and go into the science of it, if necessary, and we review the regulatory requirements," he says.

"We have a slideshow we bring with us and answer the questions their protocol demands from reading off the slide principles," Edelman adds. "I tell investigators, 'I am not the IRB. I'm just a representative.'"

Edelman also explains that he cannot guarantee that everything he tells them will be approved by the IRB.

"They understand that, but they also realize that we have an enormous amount of experience," he says.

"I tell them I've spent years doing IRB work and decades of work in clinical research — both international and domestic," Edelman says. "So they respect my background."

The goal is to work for the research participant's welfare, addressing study volunteers' rights, confidentiality, and the ethical quality of the study, he notes.

"The investigators need to have a certain mindset of caring for the patient," Edelman says. "Fortunately, most of the time, they're very much in tune with their volunteers."

4. Help the PI strengthen the study's design. The goal is to rescue protocols that need help so they can contribute to science and the world of medicine, Edelman says.

An example of a protocol's issue is one about kidney failure. The study needed to answer questions about obtaining informed consent, collecting blood, and use of a research blood bank.

Edelman meets with the investigator and staff for an hour or two to focus on the protocol. He answers their questions and reviews their changes.

"Sometimes I give them suggestions on how to improve it, but I always provide constructive criticism, saying, 'I'm now on your team — I'm not the IRB. You can take my advice or leave it as you wish,'" he says.

Although the CRTMP program mentors researchers from a variety of scientific areas, Edelman is able to help them answer scientific questions after doing a little research.

He says it's his job to make them answer the hypothesis. "The regulatory requirements are the same, wherever they come from," Edelman notes.

If an investigator has a question Edelman cannot answer, then Edelman will call an administrator to help him solve the issue.

5. Stay with the PI until protocol is approved or withdrawn. "When a PI gets the protocol approved, it is a major sign that we're on the right track," Edelman says. "I think the program not only improves the morale of investigators, but it improves the morale of our HRPP staff."

From the staff's perspective, the mentoring program saves them time and helps fill in gaps in their own expertise. ■

REFERENCE

1. Edelman R, Campbell J, Doherty J, et al. Clinical Research Training and Mentoring Program (CRTMP) – A peer to peer approach – 2012-2016. Poster presented at PRIM&R's 2016 Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA. Poster: 5.

Conduct a QA/QI Research Program Risk Assessment

Assess the office that conducts assessments

Human research protection programs (HRPPs) are required to assess their quality, efficiency, and effectiveness if they're seeking accreditation. HRPPs can do this through ongoing quality assurance/quality improvement (QA/QI) programs. But sometimes the quality improvement program also needs to be assessed for quality.

This was what one research institution decided. "Our assistant vice president asked that every program in research integrity and compliance — all 13 of us — conduct formal risk assessments," says **Julie Moore**, JD, MS, PA, associate director of research integrity and compliance at the University of South Florida in Tampa.

"Each of the programs did a soup-to-nuts risk assessment, writing formal reports describing the processes they went to and their determinations about their levels of risk," Moore says.

They also described processes that needed to be changed.

"I found the risk assessment process to be very valuable and thought it might be something other people could utilize in their programs — whether they are IRBs or QA/QI programs," says Moore, who published a poster on the risk assessment project at PRIM&R's 2016 Advancing Ethical Research Conference, held Nov. 13-16, 2016, in Anaheim, CA.

Moore researched risk assessments for QA/QI and found very little guidance. She and staff made a list of everything the office does and categorized items into bigger buckets of activity.

"We take a look at each category of activity that we do and look at related processes and procedures," she explains. "Then we try to determine where there might be risk that we haven't addressed well."

For example, in the QA/QI program, activities can be divided into site audits and internal monitoring, as they relate to the IRB and HRPP. There are full routine audits and informed consent-only audits. IRB audits can be for cause or routine. They also can be audits of site records and electronic IRB system audits.

"We can go into our electronic IRB system and make sure all the approval letters contain the correct determination," Moore says.

"For-cause audits of studies are selected either by the board, chair, or IRB administrator, and the process for conducting those is straightforward," Moore says. "We looked at the most common findings for those audits and we tried to assess the sort of areas of risk on that end of it and how we could do a better job of educating study teams."

Assessing the Assessors

Other changes could include revising HRPP policy to address areas of noncompliance.

"We also looked at all IRB record audits in previous years and identified the most common findings," Moore says.

It might be a little confusing to think of conducting a risk assessment of a program — like QA/QI — that, by its nature, conducts risk assessments. But Moore and colleagues thought of the risk assessment of the QA/QI program in terms of an overall look at the program's activities.

"Our intention was to do a detailed risk assessment of every program in research integrity and compliance," Moore says. "But in the process of doing that, many of our program managers realized the formal process of conducting a research process is applicable to everyday activities done by each of our programs."

Each of the 13 divisions had six months to perform their risk assessments. The end result — the risk assessment reports — were six to 10 pages.

"We have found them to be very helpful, for example, in justifying additional support that's needed for one of our programs," Moore says. "The risk assessment has served a dual purpose in that way: It's not only forced us to look critically at our processes, but it's also highlighted gaps."

The risk assessment itself provides necessary evidence to support asking for more resources. "We can go up to senior leadership to say, 'We did this gap analysis and have this area where there is a gap, and we need additional resources to close that loophole.'"

The risk assessment has been turned into a narrative report template. It starts with the executive summary, which is where the program staff can describe the program's activities in broad terms, Moore explains.

There is space to list the risk assessment's findings. Each is assigned a risk and impact score, with activities rated from low to medium to high risk.

"There's an executive summary in that graph, followed by a narrative of risk assessment," Moore says. "We break down each area and talk about the activities conducted in that area and the standard operating procedures we follow."

They can provide justification for the impact scores and recommendations for addressing any areas of risk, highlighted in each area.

The most positive outcome of the risk assessment was the office's ability to hire a full-time employee who is dedicated to monitoring the IRB, Moore says.

The goal now is to use the risk assessment annually, she says. ■

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.

COMING IN FUTURE MONTHS

- Ethical challenges of precision medicine
- Strategies to increase IRB education attendance
- Best practices in creating a central IRB
- How to divide up local IRB review and IRB of record review

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. Scan the QR code to the right or log on to AHCMedia.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.

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CME/CE QUESTIONS

1. **A Zika vaccine bioethics panel gave which of the following examples of measures that may allow a controlled human infection trial to proceed?**

   A. Only enroll subjects that have had previous Zika infection
   B. Only enroll women using effective contraception
   C. Only enroll women who are permanently infertile
   D. All of the above

2. **The Zika panel stated that researchers and sponsors of a Zika virus human challenge trial should use an informed consent process that includes:**

   A. multiple voluntary steps for individuals to take to enroll
   B. adequate time for discussion and evaluation
   C. feedback to enhance participant understanding
   D. all of the above

3. **Which of the following are scoring items for an IRB staff's assessment of individual IRB members?**

   A. Ability to apply federal regulations, ethical principles, and Indiana University IRB policies and procedures to research
   B. Principal investigator study experience, ability to listen carefully at IRB meetings without asking too many questions
   C. Age, culture, gender, religion
   D. None of the above

4. **What are the benefits of a mentoring program for principal investigators submitting protocols to the IRB?**

   A. Board members can get to know each investigator more personally.
   B. PIs can learn better grammatical and editing techniques for their protocols.
   C. Fewer protocols are returned to the IRB; staff save many hours of work.
   D. All of the above