IRB ADVISOR

*Your Practical Guide To Institutional Review Board Management*

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IN THIS ISSUE



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# Creative thinking needed when IRBs educate community partners

*Face-to-face training proves benefit*

IRBs working with community partners on non-medical studies need fresh tools, such as resourcefulness and imagination, when engaging in training and education.

Popular existing models fall short, some experts say.

"We've known for some time there have been problems with the training we provide to our community collaborators," says **Ryan Spellecy**, PhD, an associate professor of bioethics and medical humanities and psychiatry and behavioral medicine at the Center for Bioethics and Medical Humanities, Institute for Health and Society, Medical College of Wisconsin in Milwaukee.

"These collaborators typically are people at community organizations, which could be outreach programs or community groups like the YMCA or veterans groups that are engaged in community research and want to be partners in research endeavors," says Spellecy, who also is an IRB chair.

Many research organizations use online training programs because they're affordable and convenient, but they might not work as well for community partners' specific needs, Spellecy says.

Community partners can have difficulty with such programs because they may not be as computer-savvy as investigators, and those programs may not capture some of the salient issues in community-based research, he explains.

Because online human research protection education programs' methods and content do not fit every need, some creativity was needed to find a solution for community partners, says **Stephanie Solomon**, PhD, an assistant professor at Saint Louis University.

Solomon helped launch a new training program that is geared toward the reality of community partners' needs and knowledge.

The community partners training program recently was piloted and results are being published in a series of papers, including a recent one in the journal *Clinical and Translational Science*. The pilot proj-

ect showed significant, positive changes in mean knowledge scores from the pre-test to post-test.[1]

"While working at the University of Michigan as a post-doc in research ethics and community engagement, I worked with community engagement liaisons who worked with community partners," Solomon says. "We embarked on creating this training that would be applicable and recognizable by local IRBs and offers something that makes sense to the reality of community ethics."

For instance, the vocabulary in an IRB biomedical research world could be interpreted differently in the context of community-based research. "Vulnerability," "inducement," and "conflicts of interest" are examples of words that could be seen differently, depending on the research context.

"With conflicts of interest in a community setting, it could relate to community organizations that provide services to people who also are in their research," Solomon explains. "Or they could be recruiting a research participant who asks the organization to do something in the study that violates the protocol, but is part of the organization's service."

Other examples of conflict of interest include a community or religious leader who is a powerful community persuader and might convince people to participate in a study whether or not they are comfortable doing so, she says. *(See story on tips for training community partners, page 63.)*

## Next challenges

The community partner training is done both electronically and with one-day sessions.

An academic leader and community partner lead training, Spellecy says.

"We had videos and written materials and covered a number of units over the course of a day," he adds.

"We also received permission from the human research protection office that this course would count as responsible conduct training, so community partners didn't have to do the CITI course on top of it, and that was a benefit," Spellecy says.

Qualitative feedback from participants and facilitators suggests the hands-on nature of the training sessions worked well, Solomon says.

"We worked hard to take adult learning theory into account," she says. "People needed practical, hands-on training."

Community partner training should be flexible and adaptable to work for all organizations, she notes.

"We designed the training with two things in mind: Each site had to do some things the same for measurement purposes, but we left room for some information to be varied, depending on the context," Solomon says. "This type of training requires more leadership skills."

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**Editorial Questions**

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The goal is to have the audience apply the concepts that are taught in their own individual context.

"It seemed people really responded to that," Solomon says.

One of the next challenges will be to turn this pilot training program into a model that could be used by other organizations partnering with community groups.

It requires an institutional-level commitment to work long-term, he adds.

"We are not alone in recognizing that there is a difference in face-to-face, responsible research training," Spellecy says. "Certain categories of grants have been revised, and they say that eight hours of face-to-face training are needed; it's no longer sufficient to rely on an online model."

So the community partner training would help meet this type of requirement. Its program is tailored to the kind of research the community partner does, he adds.

REFERENCE

1. Solomon S, Bullock S, Calhoun K, et al. Piloting a nationally disseminated, interactive human subjects protection program for community partners: unexpected lessons learned from the field. *Clin Transl Sci.* 2014; April: Epub ahead of print. ■

# Tips for community partner education

*Avoid the one-size-fits-all approach*

When it comes to training community partners on human research protection ethics, IRBs would do well to create educational content that best suits the needs of those partners, an IRB chair suggests.

Research ethics training that is presented in an interactive and engaging format will benefit the IRB as well as the people receiving the training, says **Ryan Spellecy**, PhD, an associate professor of bioethics and medical humanities and psychiatry and behavioral medicine at the Medical College of Wisconsin in Milwaukee.

Human research protection training is not one-size-fits-all, notes **Stephanie Solomon**, PhD, an assistant professor at Saint Louis University.

Solomon and Patricia Piechowski, MPA, MSW, MA, were instrumental in creating a flexible model for training community partners in research ethics and protection. The training program was developed by a team at the Michigan Institute for Clinical and Health Research, and the University of Michigan unit supported by a clinical translational science award (CTSA). It was implemented as a pilot test at nine sites for the study.[1]

"We did this at our own institution to fill a need," Solomon says.

Their goals for the training program were to increase awareness and competency in community partners' conduct of ethical human subjects research.[1]

"I work a lot at the national level with community engagement and ethics," she adds. "Different institutions are coming out with training in this area."

Spellecy and Solomon offer these tips on how to educate community partners and address the research issues and concerns most relevant to them:

• **Address the blurry line between a community organization's services and a research study.** "Things that start out being a practice or intervention can turn into a research study at some point," Solomon says. "The blurry line between service and interventions and research is very hard and actually very gray."

Education facilitators can help community partners understand the differences by offering stories that illustrate both an organization's service and its involvement in research.

A story example might involve a community-based organization like a women's community health clinic that provides sexual education, Solomon says.

In one scenario, the story's protagonist is a social worker who encourages clients of the health clinic to take a free course on how to prevent the spread of sexually transmitted diseases (STDs), she explains.

The second scenario has a social worker who questions whether the clinic's free sex education course is increasing people's knowledge of STDs. The social worker wants to ask people about their experience in a group setting to see whether the education actually is working, she adds.

In a group setting, a facilitator could ask community partners to describe the difference between the two scenarios and how the second one could be research or quality improvement, Solomon says.

• **Use the group setting to collaborate and enrich discussions.** Education geared toward com-

munity partners in a group setting has the advantage of encouraging discussions and networking, Spellecy says.

"We found that getting different community groups together in the same room was beneficial for networking," he explains. "Some collaborate and talk about common issues."

For instance, one community partner might bring up a problem his organization had with the IRB during a research project, and another person will say, "Yes, we had that too, but this is how we addressed it," Spellecy says.

When the facilitator is with the IRB, this also is helpful.

"Having me there as an IRB chair was beneficial because it put a face on the IRB and we could talk about things they cared about," Spellecy says.

For some community partners, the IRB is an impersonal regulatory entity that makes research more challenging. Seeing an actual IRB chair or member at these educational sessions helps to demystify the IRB process, he adds.

• **Design process to include flexibility.** For the pilot test, each participating location chose a facilitator who had knowledge of good research practices and a health ethics education. Facilitators were offered online training materials as well as face-to-face sessions and training sessions via webinar. The training sessions were designed to be responsive to local community needs. Investigators took existing research protection education and adapted for community partners after consulting with local IRBs and community partners.[1]

As the educational sessions were launched, facilitators quickly found that there needed to be flexibility throughout the process, Spellecy notes.

"You have all these different groups at the table and need to have a rich discussion and have interaction," he says. "But we also need to be more flexible in the shape of training as it went on."

For example, one module might generate a great deal of discussion. So the facilitator could choose to spend more than the allotted time on that module and cut a different module a little short to make up the time, he says.

"That's what happens in face-to-face discussion," he says.

## REFERENCE

1. Solomon S, Bullock S, Calhoun K, et al. Piloting a nationally disseminated, interactive human subjects protection program for community partners: unexpected lessons learned from the field. *Clin Transl Sci.* 2014; April: Epub ahead of print. ■

BEST PRACTICES SPOTLIGHT

# Every improvement helps IRB inefficiencies

*Here's how to meet AAHRPP standard*

Accredited human research protection programs (HRPPs) are required to meet a seemingly simple standard that requires a quality improvement program to be focused on efficiency and compliance.

These are two different requirements, and the issue for most IRBs is determining how to do both simultaneously, says **John R. Baumann**, PhD, executive director of the HRPP, office of vice president for research at Indiana University in Indianapolis.

"Sometimes there's a strain between those two things, as you can imagine," Baumann says.

Indiana University has found a successful balance between efficiency and compliance while meeting the accreditation standards set by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

The research institution has seven IRBs and approximately 5,000 active studies, so a lot of paperwork, emails and forms go through the IRB office, Baumann notes.

"In being consistent with AAHRPP standards, our quality improvement activities revolve around questions of efficiency and questions of quality," Baumann says. "Metrics indicate it has made a noticeable difference, resulting in a shorter submission to review time."

The IRB's review time is below AAHRPP's mean review time, he adds.

Here are a few tips on how to meet this QI standard:

**1. Identify processes that can be made more efficient without sacrificing quality.**

"Look at what you can do differently without sacrificing quality," Baumann suggests.

A good starting point is shortening the time between when a submission is received and when it's complete. One factor is finding missing information in submissions, he says.

Questions to ask include:

• What kind of outreach and guidance can we

do to eliminate those problems?

• What's missing and how can we get the message out to decrease the number of submissions that are incomplete?

"At this stage of the game, so much of what we're dealing with is to improve the completeness and quality of what comes in," Baumann says. "And we want to reduce the back-and-forth between our office and the researcher because that takes time."

Another initiative is to move submissions to review and approval more quickly, Baumann says.

"The way we're trying to do that is by reducing the back-and-forth between our office and the research team to get it ready to be reviewed," Baumann says.

When the IRB office used the standard of making the submission perfect before sending it to the IRB reviewer, they found it caused a significant time delay because they would send questions to investigators who would seek sponsor approval, and then finally return the answers to the IRB office, he explains.

"Then we'd send it to the reviewer, who in a high percentage of cases wants other questions answered, and then we'd have to repeat the whole process," he says.

The solution was simple: "Instead of asking the researcher to make changes before we send the submission to the reviewer, we send our critique to the IRB reviewer," Baumann says. "The IRB accepts, revises, or adds on to our review, and so there is only one review that goes back to the sponsor."

Then the IRB office notifies the researcher that certain items need to be changed. The researcher makes the changes, sends the revised submission to the IRB, and that usually is the end of the back-and-forth process.

**2. Analyze protocol deviations and noncompliance.**

"We're initiating a process for reviewing collectively all protocol deviations and noncompliance that comes into the office," Baumann says.

"All too often we treat deviations and noncompliance as individual cases," he adds. "We treat them very seriously, but have not up until now learned as much as we could of the review of them."

Questions to ask include the following:

• Where are the protocol deviations coming from?

• What are the deviations and what can we do to help researchers avoid them?

• Are there particular patterns to the noncompliance?

• Do the IRB's education and guidance need to be beefed up?

Sometimes the problem is that an investigator is being too specific in the protocol, Baumann notes.

"The appointment occurs 24 hours later than scheduled," he says. "Does it matter whether it's a Tuesday or Wednesday when the participant comes in?"

This is easily resolved by just writing the protocol with more flexible language, as long as it's consistent with best interests of the subject's well-being and the purpose of the research, he adds.

**3. Address provisional approvals.**

Provisionally approved studies are ones that have met all of the criteria for approval, but the IRB wants some changes.

"We're launching an investigation to see what those changes are and whether there is any way we can catch them before they go to review," Baumann says. "The IRB office will hopefully catch them."

The goal is to reduce the number of studies that are provisionally approved.

Questions to ask include the following:

• What did we do right for those studies that are fully approved at the IRB meeting?

• What did we miss on the provisionally approved studies?

• What happened with studies that were not approved or were tabled?

Often, studies that are tabled have questions of science, which is not something the IRB office can address, Baumann notes.

"We had one tabled today because the reviewers did not like the statistical method they were using to answer the question," he says.

"This is not something the staff can generally catch," he adds.

"We will look at what we can put in place that we didn't catch beforehand or see what kind of training is needed for the IRB," Baumann says.

**4. Form IRB collaborative review agreements.**

"We are increasingly open to sharing, deferring, or accepting deferred IRB reviews," Baumann says.

Researchers sometimes have three IRBs looking at the exact same study. So Indiana University is forming agreements with other institutions to develop collaborative reviews.

"We've established many collaborations with many accredited organizations with IRB review," he says.

Questions to ask include:

- When can we make such an agreement?
- Which institution should be the IRB of record?
- Which institution has the risk or lead investigator?

"We make a decision based on which institution is home to the lead investigator and the location of the risks," Baumann says.

All of these quality improvement changes are fairly simple and move an IRB out of the parochial ideal that each IRB has to review everything, Baumann adds. ■

## Streamline forms with better communication

*Keep all elements; focus on a few*

As IRBs focus more on efficiency and streamlining, the chief concern involves maintaining the necessary elements while discarding or simplifying everything else. This delicate balance is especially true for streamlining informed consent documents.

"The greatest efficiency gain is having a phone call upfront," says **James MacFarlane**, CIP, director of board services for Schulman Associates IRB Inc. of Cincinnati.

One quick call to discuss expectations will improve communication and provide a quick explanation for any issues or nuances that might arise, he notes.

The IC problem could be something as simple as a locked document code needed to get the electronic IC document to open.

"It saves time upfront to know we're locked out of the consent document that was submitted," MacFarlane says. "But it's really about engagement and a collaborative spirit."

For instance, an IRB might discuss with investigators their expectations regarding process, communication, and content.

"Those are the big three: understanding our mutual expectations for how we'll communicate, how we'll interact throughout the process, and what we expect of the final content," MacFarlane says.

When this type of communication is lacking, the result is having unfinished and problematic informed consent documents, he says.

"One issue that we see most often, and this goes back to miscommunication between the submitting party and the IRB, is an informed consent submitted in a draft stage, and the IRB is not aware it's a draft and begins to work on that draft," MacFarlane explains. "Then the submitting party submits a different version for the IRB to review."

These kinds of time-wasters occur when communication is lacking.

"So it's easier and streamlines the process if the submitting party's rationale comes with the document as submitted, clearly communicating, 'We want to revise XYZ, and here's why the revision is important,'" he says.

Another issue that arises and causes inefficiency is the latest trend of sponsors embedding HIPAA privacy authorizations inside IC documents, MacFarlane says.

"IRB regulations don't require IRBs to review HIPAA, but they do require us to review HIPAA if it's inside the informed consent," MacFarlane explains. "What is important to know, and this goes back to understanding expectations of both sides, is the HIPAA document may require legal review, which is a separate review from the IRB review."

So anytime an informed consent form arrives with HIPAA embedded in it, there is greater inefficiency in the IC review process, MacFarlane says.

Schulman IRB also improves its review efficiency through the use of living templates with industry sponsors, clinical research organizations, academic medical centers, and other submitting organizations, he notes.

"To streamline the overall consent process, we need mutual collaboration and engagement from all parties," he says. "That comes through in clearly communicated expectations and documentation of content."

Collaborations like Schulman IRB's occur when the IRB and sponsors work together on creating templates before the IRB begins to review the sponsor's protocols. The templates also iron out any potential misguided expectations.

Streamlined IC forms must include all of the elements of informed consent, but not all of the elements deserve top billing.

"Of course, the elements are all equal and we have to use all of them," MacFarlane says. "That being said, the element that at times requires the most attention is probably the risk section of the IC form."

Risk speaks to element 1, involving research, its purpose, duration, and risk, and element 2 — foreseeable risks to subjects.

"Risk is the section of the informed consent document that is most often heavily laden with language that may be unfriendly to a lay person,

a lot of medical terms and jargon," MacFarlane says.

"So one of the things we can do to streamline the risk section is create tools for internal use, such as checklists that include the basic elements of consent and citations to the regulations," he adds. "We also have internal lists of suggested language to go along with the elements."

The checklist tool can help compare the IC and protocol side-by-side to make sure risks present in the protocol are present in the consent.

"The checklist helps us remember what to look for, and it helps us navigate through the protocol as we compare it side-by-side with the consent," MacFarlane says. ■

# Plan ahead for imaging IFs, experts say

*Consider informed consent, expertise issues*

Advancements in imaging technology mean a greater chance of detecting incidental findings in imaging research subjects. As IRBs turn their attentions to figuring out how to handle and manage IFs, some may not know where to begin or how to get their plans to the implementation stage.

"[IRBs] are very aware of the issue, but are not sure how to approach it," says **Judith Carrithers**, assistant dean for Human Research Protection and director, Human Research Protection Program at Johns Hopkins University School of Medicine in Baltimore. "Many IRBs do have plans in places, and others are working on plans but are not quite ready to implement them."

The Johns Hopkins Medicine IRBs, the Wake Forest School of Medicine IRB, and the Dornsife Cognitive Neuroscience Imaging Center all shared their strategies for creating IF management plans with *IRB Advisor*.

To further assist IRBs that may be facing uncertainty, the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) released the *IRB Primer: Incidental and Secondary Findings* in April. The primer was created to assist IRBs in understanding and implementing the commission's recommendations for ethically managing IFs. Among the recommendations in the primer are suggestions for informed consent, researcher expertise, participant preferences, and researcher responsibilities. *(The primer can be found at http://bioethics.gov/sites/default/files/IRB%20Primer%20-%20Incidental%20and%20Secondary%20Findings.pdf.)*

## Responsibilities of researchers

The *IRB Primer* suggests that researchers' IF management plans include what the responsibilities of the research team are if an IF is discovered.

The Johns Hopkins Medicine (JHM) IRBs require that investigators plan for incidental findings when conducting imaging research. The IRB's electronic application process includes 10 questions that investigators must answer to help develop the plan. *(For more details, see box on page 68.)*

"The IRB reviews the protocol and how they will manage the findings, and if they think the investigator has to rethink how to handle the findings, the IRB work with them to revise their plan," Carrithers says.

## Informed consent, participant preference

Researchers should communicate the plan for IFs to study subjects in the informed consent, including how, when, and if IFs will be reported to them, in order for subjects to decide whether they are comfortable with proceeding, the *IRB Primer* suggests. The investigators may also choose to allow subjects to opt out of receiving findings. It also recommends that investigators decide how a subject's opt-out preference could affect study participation, and advises that IRBs should be prepared to answer questions if a researcher approaches them about disclosing a life-saving IF to a subject who opted out.

"In some very limited cases, investigators offer subjects the opportunity to follow up with them if they wish to know about non-serious and non-actionable findings, rather than simply reporting them to the subject," says **Joseph Andrews**, PhD, director of the Human Research Protection Program and IRB at Wake Forest School of Medicine in Winston-Salem, NC. "The reason is that in cases where the effect on a subject's health is negligible and no prevention or treatment is available, subjects may prefer not to be told about findings because their inability to lessen or stop the non-serious health issue could be a source of frustration. Thus, no subject is denied access to the information if they want it, but those who would rather not be told of this type of finding

have the opportunity to decline the information."

At Wake Forest, the consent form sample states plainly that unexpected results will be shared with the subject and, with permission, the subject's physician. It also states that the images will be saved in the radiology study library and copies available upon request.

"Typically, if there are scans or some sort of diagnostic that is being performed for research purposes, the board will ask how the findings will be handled," Andrews says. "We want to make sure that the plan is set in an appropriate way. We look at the particular protocol, and if there are diagnostic or genetic procedures going on for research purposes, we will have the investigator speak to that in the consent form."

So far, Andrews has not seen situations in which an investigator has not reported relevant incidental findings to research subjects. "The only circumstance I can think of when relevant incidental findings would not be made available to a subject is if the samples or data were de-identified. In such a case, subjects are told in the consent form that the samples will be de-identified and once that occurs there will be no way to withdraw the samples or to receive individually specific research results," he says. "The circumstances we see where identifiable subjects are not provided research test results are when the tests themselves are investigational, and therefore it is not clear if these direct findings are valid and reliable as predictive tools."

The JHM IRB consent forms must inform subjects of possible IFs with IRB-approved language. A sample consent form explains incidental findings and tells the subject that a qualified expert will read the study image as if it were a part of routine medical care. The form indicates that the investigators will contact the subject by phone or mail if an IF is detected, or go to the person's home if it is an emergency. The sample form also indicates that a member of the study team will contact the subject's physician if he or she wishes, or will make a physician referral. It explains that the discovery of an IF may cause the subject anxiety, and explains potential costs and implications for health insurance. The template indicates that subjects do not have the option to decline IF information. "I don't think declining has ever come up as an issue," Carrithers says.

## Expertise

Not all researchers will have the expertise to read and interpret research images from a clinical standpoint. In these cases, researchers may rely on outside experts or facilities to read images for incidental findings.

"We've seen where researchers are very transparent saying that the scan is for research only and not diagnostic and will not be read by a physician — in that case nothing will be reported because it's not reliable," Andrews says. "Some investigators do high-resolution imaging that could be used for that.

## Ten questions for JHM investigators

*Questions form basis for IF plans*

Johns Hopkins Medical Center's electronic IRB application process prompts investigators to answer 10 questions on managing incidental findings when conducting imaging research. This gives investigators a foundation on which to build an IF management plan for the study. The IRB's questions include:

- Type of imaging procedure.
- Will the research imaging be of clinical quality?
- Will the images be read at Hopkins?
- Description of plan for external reading center, including credentialing, time frame of reading, and method of IF notification.
- Method of contacting participant (at least two methods must be maintained).
- Will the participant's personal physician be notified?
- Has the participant given permission for his or her physician to be notified?
- Describe the process for documenting incidental findings and follow-up action in the medical record.
- Will Hopkins serve as the reading center for scans produced elsewhere?
- Describe the plan for notifying the local research group of incidental findings. ■

We also determine who will read it and the time frame in which it will be read."

At imaging research facility Dana & David Dornsife Cognitive Neuroscience Imaging Center (DNI), part of the University of Southern California in Los Angeles, investigators do not seek or inform subjects of incidental findings.

All brain imaging scans at DNI are performed for research purposes only, and no staff are allowed to interpret scans as normal or abnormal, the consent form states. Rather, all scans on normal patients are sent to an outside neuroradiologist for review. The neuroradiologist does not know the identity of the subjects. If an IF is detected, the radiologist will contact the center for the subject's information so that the subject and/or his or her physician can be alerted. DNI is never told what the IF is, or of any subsequent diagnosis. "The procedures we adopted guarantee that subjects are alerted of possible findings but that the DNI, not being a health providing institution, has no access to the subject's potential health issues," says **Hanna Damasio**, MD, university professor, Dana Dornsife Professor of Neuroscience and director of the Dornsife Center.

Scans from patients with pre-existing conditions are not sent to the neuroradiologist. "We cannot expect a neuroradiologist to render an opinion on a subject with pre-existing conditions, or a new finding in someone with a pre-existing condition, without having clinical information about the subject. For that reason, scans obtained in patients with known brain conditions are not sent for review. Such scans are sent to the attending physician of the subject, so that they can either review the scan or consult with a neuroradiologist informed of all pertinent facts," Damasio says.

"We thought long and deep about it before we came to the solution we developed. In our view it was the best and most ethical we could come up with," Damasio adds. ■

# Expert advice for seeking emergency use

*FDA guidance clarifies questions*

For some patients, enrolling in a clinical trial is not an option. They may meet exclusion criteria, or the nearest trial center may be geographically inaccessible, despite having a disease or condition that could benefit from investigational treatment. In such cases, the patient's physician can request expanded individual patient access from the Food and Drug Administration. In dire situations, the physician can seek emergency use.

Emergency use can be sought from the FDA when a patient is in life-threatening circumstances and no alternative treatment beyond the test drug exists. If emergency use is approved for one person or a small group, the use of the drug is still considered research.

In 2009, the FDA updated its expanded access regulations and added different categories of access. This includes individual patients (including emergency use), intermediate-size populations, and large populations under a treatment protocol or investigational new drug (IND) application.

"Part of what the FDA did in 2009 was make expanded access more available to treating physicians rather than just academic centers," says **Mark Schreiner**, MD, chair of the Committees for the Protection of Human Subjects at Children's Hospital of Philadelphia (CHOP). "Smaller centers may not have an active trial — patients could be eligible, but it's not open at their center." In June 2013, the agency released draft guidance in the form of questions and answers to clarify investigator and IRB questions concerning guideline implementation. *(For more on the FDA's guidance, see article on page 70.)*

## Seeking an emergency IND

The following steps and criteria must be met when an investigator is seeking an emergency-use IND, according to Schreiner and **Barbara Engel**, MD, vice chair of the Committees for the Protection of Human Subjects at CHOP:

- **The patient is in a life-threatening health situation.** This means that there is a high probability of death from the patient's condition, or the patient may be come irreversibly debilitated.
- **No acceptable alternative treatment exists.**
- **The probable risk to the patient from the test drug is not greater than the probable risk from the disease or condition.** The safety of the drug hasn't yet be approved by the FDA, but the probable side effects of the drug cannot be greater than the risk of leaving the condition untreated.
- **The trial sponsor must agree to ship the test drug for emergency use.** Some sponsors may require IRB approval, though many will accept a written statement that the IRB is aware of the emergency use.

• **Obtain informed consent, or waiver.** As the emergency use of the drug is still considered research, the investigator must obtain informed consent. In an emergency situation, consent can be waived if all four of the following are met:

-The patient is in a life-threatening situation.

-No acceptable alternative treatment exists.

-The patient is unable to communicate his or her consent.

-There is insufficient time to gain consent from the patient's legal representative.

The waiver of consent should be reviewed and evaluated by a physician independent of the treatment within five working days.

• **There is insufficient time to obtain IRB approval.** The investigator must contact the IRB to see if a quorum can be convened for review. If treatment must begin immediately for a life-threatening condition and the IRB cannot convene in time, the FDA will not deny the request if IRB approval is the only obstacle. In these cases, a report must be submitted to the IRB within five days of receiving verbal approval from the FDA.

• **Contact the FDA for an emergency-use IND.** "The FDA hotline is available 24/7 and can very rapidly approve these," Schreiner says. "The key is getting the sponsor approval."

There are many reasons why a sponsor company would not support an emergency use request, Schreiner says. A small company may have very limited resources and quantity of the drug, and limited funds with which to develop additional quantities. Expanded access could even delay or imperil getting final FDA approval of the drug. "These requests are for acutely ill people with high likelihood of dying and they [sponsors] have to report the effects [to the FDA]," he says. "When a company denies the request, there are individuals who are not getting treated, which is very sad. Everything that delays getting the drug approved, they deny hundreds of other people use of the drug. The shortest path to approval is the right way to go. A lot of companies will not issue treatment INDs in early phases."

If the sponsor does agree to ship the drug, the next step is determining whether the IRB has sufficient time to review. CHOP has an executive IRB that can meet on short notice, in as little as 24 or 48 hours. "We need to know when they need to treat the patient. It's up to us to decide if we have enough time to review it and convene a meeting. If you have to start treatment immediately, the investigators are encouraged to exercise the option for prior review and approval, if there is sufficient time. If there is not enough time, we send them an email at their request and say that there is proof there is insufficient time. The only regulatory requirement is that they submit a five-day report," Schreiner says.

"But if we hear about it [the request] on a Friday and treatment has to start Sunday, that's not enough time," Engel adds. "If it comes in with

## Draft guidance clarifies FDA regulations

*Clarifies emergencies, length of treatment*

In 2013, the FDA released draft guidance in the form of questions and answers to clarify its 2009 regulations on expanded access and emergency use. The nonbinding guidance gives the FDA's suggestions for interpreting and implementing its regulations, and can be read at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf. The areas include:

• **Emergency procedures.** If a patient must be treated before a written submission can be made to the FDA, the agency can give verbal approval of emergency use. The physician or sponsor must submit an expanded access IND or protocol within 15 working days of approval.

• **Approval for more than one use at the same facility.** The FDA will allow more than one emergency use of the same drug at the same institution. When one emergency use is approved, the investigator is expected to go through IRB approval for subsequent uses. But if the second request is also an emergency, the FDA won't deny the request on the grounds that IRB approval cannot be granted, and typical emergency procedures apply.

• **Length of treatment.** Emergency use is good for one course of treatment for the patient. "For some chemo agents, this could be five years," says **Mark Schreiner**, MD, chair of the Committees for the Protection of Human Subjects at Children's Hospital of Philadelphia (CHOP). Under expanded access, the FDA has said it typically authorizes access for an extended duration for patients with chronic conditions. ■

enough time, it goes through the same [approval] process — they submit a brief treatment protocol to the FDA, telling why they think it's the best option and what the treatment plan will be."

When an emergency exemption from IRB approval is granted, the investigator must submit a report to the IRB of record within five working days. The reports should contain:

-drug/biologic name;

-IND number;

-reason for insufficient IRB approval time;

-patient information, including date of planned use, age/sex/diagnosis, summary drug use and risks/benefits;

-whether informed consent was obtained (and independent physician evaluation letter and exemption criteria statement if it is not);

-summary of the emergency use of the drug.

The investigator must also alert the CHOP pharmacy that the test drug is being shipped and provide a copy of the emergency IND from the FDA, the sponsor's approval, and either the IRB's approval or the notice of emergency exemption.

## Types of requests

The CHOP IRB mainly sees emergency use requests for chemotherapy drugs and, occasionally, infectious disease treatments. "In the case of a virus treatment, you have to start as soon as you get the drug, as it is really urgent," Schreiner says. "For chemo, we really try to convene an executive IRB meeting so they can continue to report to us and have some oversight."

The IRB does occasionally deny requests. "Our IRB denied one [expanded access request], but it was a single-patient treatment and it was a first in human use and there was insufficient information that the risk was managed and reasonable, and no evidence of possible benefit," Schreiner says. "It was a situation where the company refused to allow the expanded access IND. It would have been an off-label use of the drug. It was a situation of having to review proposed safety and risks and benefits."

"We can be willing to review it before the IND is issued and approve it contingent to IND approval," Engel adds.

Conversely, treatment that does not show promise in a clinical trial can be approved for use in a single patient. "Another area we've seen is a case in oncology where a clinical trial basically didn't show sufficient promise, but one patient responded positively and an IND allowed continued access," Schreiner says.

The FDA may also deny emergency use requests. Being at a certain stage of a disease or having comorbid conditions that could make use of the drug dangerous for the patient can lead to denial, or if access impedes clinical development of the drug. However, "I've never seen the FDA not approve if the sponsor has agreed to release the product," Schreiner says. ■

## CNE/CME OBJECTIVES & INSTRUCTIONS

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

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

Physicians and nurses participate in this continuing education program and earn credit for this activity by following 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 www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests 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 last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

## COMING IN FUTURE MONTHS

- How acceptable is teleconsent?
- Maintaining ethics with transformative Internet research
- Identifying hidden research participation influences
- Consent issues for biorepositories

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# CNE/CME QUESTIONS

1. A research ethics program designed for community partners uses what device to illustrate the elements of consent, says Stephanie Solomon, PhD?
   A. Illustrations
   B. Stories with examples
   C. Songs
   D. All of the above

2. According to John Baumann, PhD, which of the following is a good question to ask about the way the board treats deviations and noncompliance?
   A. Where are the protocol deviations coming from?
   B. What are the deviations and what can we do to help researchers avoid them?
   C. Are there particular patterns to the noncompliance?
   D. All of the above

3. When sponsors embed HIPAA privacy authorizations in research informed consent documents, what is the result, according to John MacFarlane, CIP?
   A. There is no change.
   B. The embedded language has to be separated and reviewed as a separate entity.
   C. An IRB is not required to review the HIPAA authorization unless it's included in the informed consent document, so this embedded language can slow down the review process and may even require a separate legal review.
   D. None of the above

4. According to Joseph Andrews, PhD, when might an imaging research subject prefer not to be told about incidental findings?
   A. The subject is afraid to hear the result.
   B. There is negligible effect on the subject's health.
   C. The subject cannot stop or lessen the health issue.
   D. Both B and C