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Adverse event reporting often creates confusion, conflicts over when and how

IRBs have wide range of policies about AEs

IRBs often are inundated with hundreds of adverse event (AE) reports that are not always useful to their mission of protecting human subjects. However, some IRBs are hesitant to make policies that would limit these reports because of a fear of missing important information. Others find the federal regulations about reporting AEs to be ambiguous and somewhat confusing.

"The federal regulations are very general," says **Kathleen Gifford**, RN, a research compliance coordinator with Penn State Milton S. Hershey Medical Center, Penn State College of Medicine in Hershey, PA.

"Serious or unexpected adverse events will be reviewed by the IRB, but then you must define serious and unexpected," she says.

The U.S. Food and Drug Administration (FDA) regulations do not require sponsors to send AEs involving drugs to IRBs, and IRBs don't have to accept AE reports of drugs, says **Jeffrey A. Cooper**, MD, a research expert and physician in Washington, DC. However, the regulations do require reporting of unanticipated adverse device effects, and federal regulations do oblige IRBs to review unanticipated problems that involve risks to human subjects, he adds.

"IRBs are being inundated with AEs because the sponsors are sending all their AE reports to investigators and asking them to pass those on to IRBs," Cooper explains. "My sense is that many of those AEs are clearly unrelated or the AEs are expected."

For example, a common complication involving patients infected with HIV is toxoplasmosis, an infection that takes advantage of an immunosuppressed body. Sometimes during HIV clinical trials, patients will develop the infection, he says.

So every time an HIV patient got toxoplasmosis, a serious AE report would be filed. "When I was working with an IRB, we saw a lot of serious complications of AIDS that were expected complications being reported as adverse events," Cooper reports.

"I think IRBs are struggling with what to do with these reports," he says, adding that according to federal regulations, the anticipated AEs, such as toxoplasmosis, do not need to be reported.

"IRBs should have procedures in place to get reports of unanticipated problems of risk to subjects or others. My message is to get people to look at AE reports as this issue of unanticipated problems of risk," Cooper says. "IRBs would meet 24 hours a day, seven days a week, if they reviewed every AE they got."

While some larger IRBs and research institutions have decided to review only AEs that occur within their own institution, others will review AEs reported during outside studies that use the same or closely related protocols, Gifford says.

"We let the principal investigator [PI] determine whether it's closely related, and we've opted to look at all serious and unexpected AEs that are closely related," she adds. "If it's listed on the consent form, it's expected, and if not, then it's unexpected."

However, the institution doesn't waste staff and IRB time on all of the unexpected AEs reported by outside studies. "We're not looking, for example, at cold symptoms in a patient just because they're not listed on the consent form," Gifford says. "That's unless the cold symptoms happen routinely, and we have a category of trends of AEs that are not truly serious but happen so consistently that you start to get suspicious about them."

The research compliance office at Hershey Medical Center assists three separate IRBs and about 1,200 active protocols. The staff include three research compliance coordinators, an administrative assistant, and five staff assistants who are well trained in IRB administration.

Some IRBs and institutions have policies that take the decision of what is a reportable AE away from the PI and require that IRBs review all AEs.

For example, the Edward Hines Jr. VA Hospital in Hines, IL, research service requires that all adverse events be reported, says **Della Herzog**, RN, human studies subcommittee coordinator.

"Our IRB wanted to make the judgment of whether or not an AE is related," she explains. "We do expect the investigator to give his assessment, but there are times when we change the assessment and require him to call it a related situation."

For example, there have been incidents when PIs did not consider a series of AEs to be related to the study, but because there was a trend of serious AEs, the study was closed, Herzog says.

"Now it's a rare occasion when that happens," Herzog adds. "So whether this continues to be worth the additional workload is up in the air."

Herzog says she spends a day and a half each month preparing AEs, and this includes assistance from secretarial staff who enter the information in the computer database.

At Hershey Medical Center, about eight hours a week is spent on handling adverse events, Gifford says.

The IRB's AE workload is high partly because many reported AEs come from outside studies. IRBs must determine whether to review only AEs that occur at the IRB's institution or whether the board also will review all AEs that occurred at other institutions during identical or closely related protocols.

"Some of those related protocols are so slightly related that you wonder why in the world you're looking at those AEs at all," Gifford says.

These dilemmas may be more readily solved if the IRB clearly defines for investigators reportable AEs.

For instance, the Catholic Medical Center in Manchester, NH, requires all unexpected adverse events that had not been previously observed or included in the informed consent process to be reported, says **Donna L. Bennett**, RN, MS, CIM, vice president of research and programs development.

"They may be minor in which no severity is anticipated, but they were unexpected," she explains.

Severe AEs are defined as those that result in

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death, a life-threatening situation, hospitalization, prolonged hospitalization, persistent or significant disability, a substantial disruption of one's ability to conduct a normal life function, a birth defect, and cancer. Serious AEs also can be a result of an overdose or protocol error, Bennett says.

The hospital's IRB has a three-page IRB report in which investigators discuss details of the protocol and AE. **(See story on IRB policies and reports that clearly define AEs, below right.)**

While the Catholic Medical Center's IRB can depend on its investigators to review AE reporting policies and procedures, there also are AEs being reported from outside studies, and these can take considerable time to review, Bennett notes.

"Many of the industry sponsors are requiring IRBs to review AEs occurring in the same drug, but maybe in a different study," she says. "For example, there may be a cholesterol-lowering drug that may be involved in five different studies, all from the same pharmaceutical sponsor."

When an adverse event occurs at a study being conducted in France, for instance, the sponsor may want to make sure all IRBs and investigators are aware the drug has had the adverse event, Bennett explains.

"We had one protocol where the investigator submitted a letter and a list of 40 adverse events from a different study," Bennett says. "The sponsor wanted the IRB to know these results occurred but did not provide the IRB with the criteria of the research study nor the number of participants involved."

This type of report sometimes can raise more questions than it answers, so even if the IRB wants the information, the report may not be useful, IRB coordinators say.

The problem is that drug safety monitoring boards (DSMBs) have a wide variation in reporting and monitoring practices, and this is part of the reason that some IRBs, such as the one at Hines VA Hospital, require all AEs to be reported, Herzog says.

"We're still not satisfied with the reporting coming back from some DSMBs — we frequently have to say we need more information," she says. "Certainly as DSMBs become more attune to reviewing adverse events and as we get better information back from DSMBs, the IRB will be more satisfied and start reviewing fewer AEs."

IRBs need the DSMB reports to provide perspective with more detailed listings of the types and frequencies of the AEs being reported, Herzog notes.

"A lot of them just say they reviewed the AEs and no recommendations were made. We're not satisfied with that answer," she adds. "So we have maintained our policy to review all of them."

Herzog is hopeful that DSMB reports will improve as they begin to follow new policies developed by the National Institutes of Health (NIH) and the FDA.

"There are more specific criteria now described by the FDA and NIH of what they expect out of DSMBs, so that will help us a great deal once DSMBs start providing us with that information," she says. "It might help reduce some of the workload." ■

AE protocol helps clarify what should be reported

Reporting rules spelled out for PIs

While each IRB has its own policies and procedures for reporting adverse events (AEs), there are some strategies that appear to make it easier for investigators to decide what should be reported and simultaneously keep a check on the AE workload for IRB members.

At the same time, IRBs should keep in mind that not all AEs involve a physical or medical problem; therefore, their policies also should address AEs related to psychological, financial, and social harms.

"Some people are focusing on AE drug events and are missing other issues that involve unanticipated problems, which should be handled in the same way," says **Jeffrey A. Cooper**, MD, of Washington, DC.

For example, a protocol may involve genetic research that, in the course of study, discovers a problem with a particular subject's paternity, he says.

"If investigators disclose that information it might cause problems when a person finds out that the person who he thought was his father is not his biological father," Cooper says. "This situation involves unanticipated risk, although there are no drugs, biologics, or devices involved."

An investigator may fail to file an AE report on

such an incident, so it's the IRB's job to have some sort of process established to deal with these types of unexpected adverse events, he states.

Likewise, there may be an AE that results in potential, if not actual physical harm. For instance, there could be a study in which an investigator is monitoring a subject's drug levels only to discover that the lab has made a mistake in its analyses and the last 20 drug levels were incorrect, Cooper says.

"This needs to be reported to the IRB as an unanticipated event, a failure of monitoring procedure and not an adverse drug event," he adds.

"Think about risk — psychologically, economically, and socially," Cooper says. "IRBs should consider what additional steps should be put in place to minimize those risks and to inform participants."

"Think about risk — psychologically, economically, and socially. IRBs should consider what additional steps should be put in place to minimize those risks and to inform participants."

A prime example of this sort of outside-the-box thinking involves how an IRB might handle an AE that sometimes occurs with participants of HIV vaccination trials, says **Kathleen Gifford**, RN, a research compliance coordinator with Penn State Milton S. Hershey Medical Center, Penn State College of Medicine in Hershey, PA.

"People are going into AIDS vaccine trials where they receive vaccinations for a period of time, and it will appear on standard HIV tests that they're HIV-positive," Gifford says. "More sophisticated blood tests tell you that they're not HIV-positive."

However, these subjects could unwittingly be tested as part of a life insurance exam and then denied coverage based on the flawed findings.

When HIV researchers and IRBs began to realize this AE could occur, they were able to react with safeguards in the protocols, Cooper says.

"We had a trial like that and had participants issued cards from the drug company that explained their participation in the trial," he explains. "The cards said they'd be HIV-positive for antibodies, and they would need to be tested for HIV in a different way. Participants were told they'd be given this card, but it would not limit their ability in the future to get life insurance and other insurances."

So what began as an unanticipated AE became anticipated and properly handled to better ensure subject safety.

Here are some other issues and strategies that IRBs need to consider when revising AE reporting policies and procedures:

• Make AE reporting guidelines and education easily accessible.

All of the Hershey Medical Center's adverse events instructions and reporting forms are available on the center's web site at www.hmc.psu.edu/hmc-irb/downloads.htm. Investigators can easily download instructions, forms, and reporting logs that define what needs to be reported, Gifford says.

The Edward Hines Jr. VA Hospital in Hines, IL, research service has a guidelines packet and a large coordinators group that has helped to communicate the AE policies to staff, says **Della Herzog**, RN, human studies subcommittee coordinator.

"Our coordinators group — and most, but not all, are nurses — has been a major way of getting our policies across," Herzog says. "But we also have all-day educational sessions, such as a good clinical practice conference that we held last December."

Whenever there are new rules or regulations, investigators and physicians also are notified through e-mail and staff meetings.

"Our chief of research has an e-mail group so any time we want [to send] an alert to doctors we give it to her, and she sends it out to all MDs, PhDs, and other investigators," Herzog says. "And we have a research web site where we have already posted all of our forms, updated consent templates, and primary investigator guidelines on research."

• Create an AE reporting form that collects enough information to provide perspective.

Catholic Medical Center, a community tertiary hospital in Manchester, NH, has an IRB that has created a three-page IRB report that details AEs and asks investigators to assess the risk-benefit ratio based on study results at the time of the report.

"We want to know the number of participants screened, the number enrolled, the number withdrawn from research and why, the number of deaths, and the total number of adverse events to date on the local and national and international level," says **Donna L. Bennett**, RN, MS, CIM, vice president of research and program development at Catholic Medical Center.

The report form asks investigators whether the

event resulted in death, a life-threatening situation, persistent or significant disability/incapacity, hospitalization or prolonged hospitalization, an overdose or protocol error, or a congenital anomaly/birth defect, or cancer.

One question asks, "What is the likelihood that this adverse event was caused by the drug/device or procedure?" Investigators may answer that it is a definite yes, probably yes, probably no, definite no, or unknown.

The report form also asks whether the AE has been reported to the sponsor or a federal agency. Additionally, the form asks the investigator whether the consent form needs to be changed as a result of the reported AE.

Ultimately, the IRB makes the determination if there is a change in the risk-benefit ratio as a result of the reported adverse or unanticipated event, necessitating a change in the informed-consent document. An outcome of this type of reporting provides the opportunity to identify educational areas to strengthen with investigators and their staff, especially when the IRB's determination is different from the investigators', Bennett says.

• Define unanticipated, serious adverse events and closely related research.

Hershey Medical Center's AE definitions are outlined on the research web site. These include the following:

— **Unexpected adverse event:** Any adverse experience that is not identified in nature, severity, or frequency in the consent form *and* is not due to a disease process.

— **Serious adverse event (SAE):** Includes any experience that is fatal or life-threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect, or any medical event which requires treatment to prevent one of the medical outcomes previously mentioned.

The definition for serious adverse events was derived from the Office for Human Research Protections guidelines and is similar to the definition found in most sponsor-related protocols, Gifford says.

The web site also provides definitions of what closely related research in the reporting of serious adverse events means. It states that a closely related protocol is when all study procedures and drugs and the study population are almost identical to the protocol for which the SAE is being reported. A slightly related protocol, it states, is when one or two study procedures or drugs are the same as the protocol for which the SAE is being reported. The study population is usually different (e.g., different disease being treated, adult vs. children).

"There's always the fear that you might be missing something, so you're always re-evaluating your definitions to make sure you're not," Gifford says.

In Bennett's experience, the information an IRB may obtain from closely related or similar studies may be especially valuable in protecting research subjects.

The Catholic Medical Center IRB had seen published research reports about a study involving a cholesterol-lowering drug that also was being investigated in protocols submitted locally. In the outside study, it was found that some patients were placed at a higher risk of sudden acute coronary events during a wash-out period in which they were taken off the medication, Bennett says.

"So the IRB at this institution asked one investigator what affect the wash-out period had on participants," Bennett recalls.

"We questioned the sponsor about how appropriate this wash-out period was and whether we needed it and whether it would affect randomization?" she adds. "We didn't want to put our patients who were going to enroll in a study that required a wash-out period to have a risk of a myocardial infarction."

The IRB's inquiry and its pointing out the SAEs that occurred with similar research convinced the sponsor to change the protocol because it turned out that having a wash-out period really wasn't necessary, Bennett says.

"One pharmaceutical company mentioned that we were the only IRB in the country who asked that question," Bennett adds. ■

Children in research trials: Have we gone too far?

IRBs also should consider appropriate levels of risk

Throughout the '90s, the push was on to include more children in medical research.

The U.S. Food and Drug Administration (FDA) encouraged pharmaceutical companies to begin testing new drugs on children as well as adults. The National Institutes of Health (NIH) required applicants for clinical research funding to improve measures for including children in federally funded medical studies.

But with the 1999 death of 18-year-old Jesse Gelsinger during a research study at the University of Pennsylvania and subsequent disclosures of violations of accepted patient-protection protocols at many well-known institutions, medical ethicists are taking a new look at the protections afforded to human subjects of medical research.

And some ethicists and pediatric specialists also are questioning whether the drive to include children has progressed too far, too rapidly. Are we moving beyond inclusion to exploitation? How can we protect such a vulnerable population, yet at the same time ensure that new drugs and medical treatments are adequately studied before being administered to kids?

The fear that children will be exploited in clinical research is well grounded, says **Lainie Friedman Ross**, MD, PhD, assistant director of the MacLean Center for Medical Ethics and assistant professor of pediatrics at the University of Chicago.

"Historically, children were very abused. And if you want to talk about the history of children in research, for many years, there were greater protections for animals than there were for children in research," she explains.

Friedman Ross and other experts in child health and medical ethics gathered in May at the University of Maryland for a conference discussing the history of research protections for children and whether current protections are sufficient — and sufficiently enforced.

In the 19th and early 20th centuries, Friedman Ross explains, children often were the subjects of research projects that exposed them to significant risk and harm without their knowledge, she explains. Institutionalized children, particularly those in orphanages or who were wards of the state, were vulnerable to research abuse.

Following the adoption of the Nuremburg Code in the 1940s, it became commonly accepted that subjects in research projects should give informed consent — agreeing to participate only after being informed of the risks and benefits involved.

It wasn't until the late 1960s and early '70s that society began questioning whether there were some people — children and the mentally disabled — who were unable to understand the risks involved and unable to give informed consent, Friedman Ross says.

In 1978, the National Commission for Biological and Behavioral Research drafted the first national guidelines on protections for humans involved in research projects. These guidelines became known as the Common Rule because they were adopted by all federal agencies conducting or sponsoring research: the Department of Health and Human Services, the FDA, the Department of Defense, and others.

"The Common Rule starts getting written in the 1970s, but the pediatric version isn't finalized until 1983," she adds. "The regs are very specific. First, it says basically that research should be done first on animals, whenever possible, then on adults, then on older children before younger children."

Federal regulations for kids

Because children are a vulnerable population, they required special protections beyond those given to adult subjects.

The federal regulations for children focus on three areas: the level of risk involved, the potential (or lack of potential) for therapeutic benefit to the child, and the issue of consent.

"For example, they have said that you need not only the parent's permission and the child's assent, but also they are specific about whether you need one or both parents," Friedman Ross explains. "For research involving no risk or minimal risk, the consent of only one parent is required."

The regulations also are specific about the need to allow the child to opt out or dissent if he or she wants to, she adds. However, there is a section in the regulations about when an institutional review board can waive the need to get the child's assent and rely only on parental informed consent.

"There are a lot of situations where you do not have to get the child's assent, although it is supposed to be taken into consideration," Friedman Ross says.

Requiring assent of the child

Although some ethicists feel that children should always be able to opt out, there are valid situations in which the assent of the child should not be required, Friedman Ross argues.

"It's very easy to sit here and say we should listen if the kids say no," she explains. "But kids say no for good reasons that we would expect from any patient in that situation, and they say no because they just don't like being in the doctor's office or don't feel like it or whatever."

There are valid reasons why researchers might not need the child's assent in every situation, she says. But if they are not going to respect it, researchers should not ask for it.

"My biggest problem with researchers being able

to waive assent is that if you ask for the kid's assent, you should respect it," she says. "My issue is that there are a lot of situations in which I just would not ask for the child's assent. I would inform the child. But I get very nervous when you have different parts of the protocol where the kid needs to sign, and if the child says no, you're still going to do it, anyway."

In England, researchers are required to get assent from any child who is age 7 or older, notes **Paul J. Edelson**, MD, a researcher at the Center for the Study of Society and Medicine in the Columbia College of Physicians and Surgeons in New York City. He is conducting a three-year study of the history of children as research subjects.

"They have taken a nuanced approach that says while that person is still too young to judge independently whether he or she can consent, you must get the assent," he says.

Children are equally entitled to personal respect, just as adults are, Edelson notes. But the respect may be played out in a different way — seeking assent in certain situations, not in others, making policies to respect assent when it is sought, etc.

"I think it should be the first step in encouraging a longer discussion with the child and family about participation," he says.

Protection vs. inclusion

During the 1980s, with the memory of past abuses of children still strong, very little medical research included children as subjects, Friedman Ross says.

"Some people argue that because children are not competent to give informed consent themselves, they should be excluded from research," she notes.

But with the advent of the AIDS epidemic, researchers began questioning the ethics of excluding children from trials of potentially lifesaving or life-prolonging medications.

"All of a sudden, there is a realization that research can be very therapeutic," she says. "All of the drugs that were approved for AIDS didn't get approved for kids for like five or six years because of the way the studies had to be done."

In the 1990s, medical research moved from being protectionist to emphasizing access, Friedman Ross says. The FDA moved to give companies that conducted research trials in pediatric populations an extra six months of exclusivity of marketing their product. And in 1998, the NIH developed guidance for researchers that stated they must include children in research protocols or be able to state why they did not.

Programs that were unable to justify why not received less money, she adds.

"There have been enormous tidal changes in what it means to be a research subject," says Edelson. "I think the pendulum has swung to the point where you feel you may be unjustly disenfranchised somehow if you are not invited to be a subject."

In the 1990s, the emphasis shifted from people willing to participate in research because of some inducement to people demanding to participate in order to get access to care or to new medications, he adds.

With children, it is important that they are included in medical research, particularly drug trials, because treatments and medications have different effects in the pediatric population.

"What happened for a long time, because children were not seen as a significant market for many high-tech drugs, companies would do studies on adults, get the adult indications, then they were done," Edelson explains. "They received permission from the government to market the drug for a specific use. But once available, a physician has the power to use it any way he or she decides is appropriate. You had all of these drugs that were tested only in adults, but for which there was no alternative but to use them in pediatrics because there was no pediatric equivalent."

That led regulators to question the safety of using drug dosages in pediatric patients that had never been tested. That led to the FDA's passage of the Best Pharmaceuticals for Children Act that encourages drug trials for children.

"There are legitimate reasons for children's study to be encouraged and promoted, and they need to be," Edelson says. "On the other hand, there are many forces at work."

The drive for access, many now fear, is in danger of going too far.

"In certain situations, like AIDS, a [then] nontreatable, deathly illness, you might want to include children more quickly in certain research," Friedman Ross says. "But there are many reasons why we still need to be protecting kids differently."

'Me-too' trials

An area of key concern is placebo-controlled pediatric drug trials, Friedman Ross says.

For every 100 drugs that get to market in the United States, almost half are taken back off the

market due to health complications that are discovered once use of the medication is expanded, she states. For every 100 drugs that research is performed on, only one drug actually makes it to market approval.

"There is good reason to want to go slow with kids, especially with the so-called 'me-too' drugs, drugs that are essentially just like a drug on the market that has already proven effective," she says.

FDA regulations require placebo-controlled trials of all new drugs coming on the market. So children randomized into the control arm of a trial of a me-too drug will get a placebo — not the drug already on the market that has proven effective and safe treatment for the same condition, she says.

"In these situations, we know there is a drug available that is good for kids, but we are not going to give it to them. We are going to test them with a new drug, that is probably good, but some of these kids will be on placebo when we know they need medicine," she explains.

Unacceptable levels of risk?

In addition to discussing ways to improve informed consent for children involved in research, it is also important for IRBs to examine whether there are some levels of risk that are inappropriate to expose children to, whether the child assents and the parents consent or not, Friedman Ross says.

"If you are going to talk about consent, you have to talk about whether parents have the right, in a sense, to expose their children to risk for no benefit to the child," she says. "Some experts have argued that children should not participate in nontherapeutic research even if it involves no risk."

But parents place their children at risk all the time, even when there is no benefit to the child; so it is pointless to argue whether they have the right or not, Friedman Ross says.

"If I take my children to the store to buy a bottle of wine for Mommy and Daddy in the rain, I am putting them at risk of getting into a car accident or something, and that is not for their benefit," she illustrates. "Parents do things like this all of the time."

Parents obviously have an obligation not to abuse or neglect their children and obligations to help develop and protect the child, she says. But parents need a wide latitude of freedom about things that are clearly not harmful or neglectful, that may not promote an individual child's best interests, yet may be promoting the family's interest or the interests of other people.

"I am comfortable saying that parents should be able to enroll their children," she says. "Yet, I like the idea of an IRB limiting the amount of risk that they are willing to expose children to, because children do not belong to their parents."

IRBs sometimes forget they have the function of protecting subjects, not just ensuring that the subjects give informed consent to whatever level of risk the researchers are proposing, she adds.

"We focus a lot on consent," she says. "But consent is the second step. We need to focus on research that is as minimally risky as possible, especially for children. The 1990s regulations emphasized equitable access to research benefits. But don't forget that for every benefit, there are hundreds of risks." ■

On-line conference trains researchers

An independent review board stresses training

While many IRBs must plan and develop strategies for training researchers, independent IRBs have an even greater challenge since they often do not have the advantage of working with the same investigators year after year. Researchers they encounter might be entirely new to the research process or have never conducted studies that were reviewed by a hospital-based or university-based IRB, which means the independent IRB needs to provide both basic education about human subjects protection and specialized training about their policies and procedures.

"We have worked with doctors who have not received any official investigator training," says **Matt Baker**, director of operations for Coast IRB in San Clemente, CA.

Baker founded a research company that provided coordinating services for physicians in northern Utah, and it was his experience that investigator training was nonexistent.

"That was my experience with every independent IRB I worked with for five years," Baker says, adding that the IRBs would answer investigators' questions, but had no formal training or educational programs available.

So when Baker became the director of operations

for Coast IRB, an independent review board that is paid by sponsoring companies to review research by investigators who are researching a particular product, he decided that investigator training would be a top priority.

"When a company comes to us with 30 doctors who will be doing research, part of our service is to provide quarterly training for staff and investigators at those 30 sites," Baker says.

High-tech, but simple

Here's how the training program works:

• **Step 1:** Investigators visit the conference web site and sign on with a pass code they are given. At the same time, they are connected via conference call. The web conference can be held anywhere in the world, and up to 2,500 people can participate at one time.

"People don't have to travel; and it's cheap to do this because they can participate on-line, and we can run the conference any time of the day," says **Darren McDaniel**, chief executive officer and founder of Coast IRB.

The cost of the web conferences is free for investigators and is conducted by Interactive Meetings, which charges study sponsors minimal fees based on the number of sites participating and the length of the conference session. McDaniel, who is affiliated with Interactive Meetings, has coordinated the web-training sessions.

"We can archive these meetings, record them, and [create] a web link specifically for training sessions," he says. "So if there's a long study, and there's turnover, we can give training to the new subinvestigator and coordinators through the web link."

• **Step 2:** Participants view slides with material relevant to their particular study and also general information about research involving human subjects, policies, regulations, etc. Slides are used instead of video/audio over the web because of the bandwidth problems that may frustrate participants who have slow computer links.

"We try to keep things simple," McDaniel says. "The audio is over the telephone on the conference call because you have to have speakers on your computer to hear voices on-line."

The slides, which are similar to PowerPoint slide presentations, list a few sentences or bulleted items on each, staying on the screen a few moments before moving to the next item.

Included among the slides are brief questionnaires that ask investigators to select an answer,

Have book, will study

Web-based training is quite popular, but there is effective training available in good old-fashioned textbooks, says the publisher of *Protecting Study Volunteers in Research*, a manual written for those involved in human subject research.

"On-line delivery has its benefits — you can take at your own pace, and it's often inexpensive. But it's not very accessible or convenient if you're traveling or riding the train," says **Kenneth Getz**, MBA, president of CenterWatch, a Boston-based publisher of information on the clinical trials industry.

Those looking for a more portable way to educate themselves or staff may be interested in the recently updated *Protecting Study Volunteers*. The book's seven chapters, which covered topics such as federal regulations and roles and responsibilities of institutions and investigators conducting human subject research, has been expanded to 11 chapters.

New chapters include discussions on conflicts of interest, ethical issues in genetic research, and recruitment and retention.

The manual includes a chapter on secondary studies, tissue studies, and records reviews, and discussions of special ethical concerns in clinical research, such as the use of placebos, the roles and responsibilities of data-monitoring committees, and community-based qualitative research.

"Investigators have begun to use community-based qualitative research to explore public health problems," says Getz. There are issues unique to the approach, he points out, including the need to engage the community during all stages of the study, from design to dissemination of information.

Readers can earn 6.5 CME hours at no additional charge by completing the test included in the book or by going on-line to access chapter tests. Additionally, the book can be customized to include materials specific to institutions, or institutions may enroll participants on-line as part of a subscription service. The service allows participants to access the manual and tests via the web. For more information or to order the book, visit www.centerwatch.com. ■

usually multiple choice, which will be instantly tabulated so that the conference coordinator can give both the participants and other interested parties feedback about how well investigators understand various educational materials.

"We have the ability to ask polling questions and quiz investigators about their understanding of different items," McDaniel says.

"They click on a circle with the answer; and after they answer, I can go ahead and publish the results on-line," McDaniel says. "These data go into a report for the folks at Coast IRB to show who answered them correctly and who didn't."

• **Step 3:** Much of the information investigators need to know can be found on government and other web sites. So rather than duplicate the information on the slides, the conference coordinator will electronically move participants to a web link, such as the U.S. Food and Drug Administration (www.fda.gov), the Office for Human Research Protections (http://ohrp.osophs.dhhs.gov), or another site that has information about the Health Insurance Portability and Accountability Act and how that will affect research.

This web tour also can take participants to Coast IRB's site to show investigators how the IRB expects them to submit information and forms. Participants also can visit the sponsor's web site to review clinical practice guidelines. If investigators wanted to see an example of a particular form, such as an initial review submission form, they could be directed to a web site that publishes sample forms. "We could go to any web site in the world and bring anyone on the web tour," McDaniel says.

• **Step 4:** Once the web tour is complete, the coordinator will bring participants back to the conference web site for more slides and polls.

The conference often will include information about how the IRB reviews protocols, how to submit a safety report, how to submit advertisements, what the process is, what the final study notes should be, how to prepare financial disclosure, and how to close out a study, McDaniel says. Also, investigators are asked to learn about the study communities' attitudes toward research as well as state and local laws regarding human subjects research on their own.

"We'll take a rookie doctor and make him an investigator," Baker says. "Our motto is that when investigators are being reviewed by us, we hope we've made them better investigators by making them better informed."

Although the web conference training is not mandatory, it has been widely used. Baker estimates that up to 80% of investigators will take the course. Even investigators who do not participate often will have a coordinator from their site take the training, he adds.

"This gives us more contact with doctors, so if they have any questions or concerns, they can have better communication with us," Baker says. "We hope this kind of communication and openness will help to protect the patients better." ■

SPOTLIGHT ON COMPLIANCE

Off-label use differs from investigational use

If the intent is research, IRB review will be required

By **J. Mark Waxman**, JD
General Counsel
CareGroup Healthcare System
Boston

Drugs and devices that are prescribed must be approved by the U.S. Food and Drug Administration (FDA) for use. In this context, it is recognized that although a drug or device may be approved for a specific use, it also may be used to treat other conditions, not specified when originally approved. This use is often referred to as an off-label use.

To the FDA, the off-label use of a drug or device is part of the acceptable practice of medicine. Use of a drug in this way does not require an IND — Investigation of New Drug Application (or the comparable IDE — Investigational Device Exemption for devices), or even IRB review.

They're not the same thing

Off-label use, however, must be carefully distinguished from investigational use, which is use that is part of an attempt to create generalized knowledge or information beyond the care and treatment of a specific, individual patient. If the

intent of the prescription extends to research purposes, the research oversight processes of the institution must be employed, and IRB review will be required.

The investigational use of drugs and devices approved for marketing would also potentially require submission of an IND or IDE. If an IDE is required, then the requirements elaborated in 21 CFR Part 312 must be met. For example, §312.3(b) makes it clear that a "clinical" investigation means "any experiment" in which a drug is used except for the use of a marketed drug in the course of medical practice, and that the provisions apply to *all* clinical investigations unless specific exception exists.

Clinical trial exemptions

One of the principal exemptions relates to clinical investigations conducted through an appropriately supervised clinical trials process. This exemption requires an investigation meeting the following conditions [21 CFR §312.1(b)]:

- It is not intended to support a new indication for use or any other significant labeling change.
- It is not intended to support a significant change in advertising.
- It does not involve a route of administration or dosage level, use in a patient population, or other factor that significantly increases risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- IRB oversight and the related informed consent processes are present.
- The rules applicable to promotion and charging for investigational drugs are followed (see §312.7). For example, this means that charging for the drug under the clinical trial would not be permitted without prior FDA approval.

One question that arises from the distinction between an off-label drug use and an experimental or research use is whether disclosure of the fact that the prescribed use is off-label should be part of the informed consent process. While a discussion of the risks and benefits of various treatment alternatives are clearly part of the informed consent process, it is generally accepted that a discussion of whether a use is off-label, need not be part of the informed consent process. See e.g., *Gaston v. Hunter,* 588 p. 2d 326, 350-51 (Ariz. Ct. App. 1978); *Smith v. Yohe,* 194 A.2d 167 (Pa 1963). ■

Clarification: ProIRB, an IRB software package profiled in the May issue, was characterized as being "convenient for mid-sized IRBs." Though small- to mid-sized IRBs may find the software convenient and affordable, the software is in use by many major universities and institutions, some handling more than 1,000 open protocols. ■

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CE/CME objectives

The CE/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;
- understand the regulatory qualifications regarding human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research;
- apply the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- have an understanding of the potential for conflict of financial interests involving human subject research;
- understand reporting adverse events during research. ■

CME *questions*

For more information on the CME program, contact American Health Consultants' customer service department at (800) 688-2421.

5. Food and Drug Administration regulations require sponsors to report to IRBs what types of adverse events?
   A. Unanticipated adverse drug events
   B. Slightly-related adverse drug events
   C. Unanticipated adverse device effects
   D. All of the above

6. Which of the following is a good definition of a serious adverse event?
   A. Any adverse experience that is not identified in nature, severity, or frequency in the consent form *and* is not due to a disease process.
   B. Includes any experience that is fatal or life-threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect, or any medical event that requires treatment to prevent one of the medical outcomes listed above.
   C. Any adverse event that is both unexpected and life-threatening.
   D. None of the above

7. Some experts have questioned allowing the participation of children in what type of research?
   A. Testing of gene therapies.
   B. Behavioral health studies.
   C. Placebo-controlled trials of drugs very similar to drugs already approved and on the market.
   D. None of the above

8. Which of the following is true of investigational use:
   A. Is an attempt to create generalized knowledge beyond the care and treatment of an individual patient.
   B. Investigational use is not subject to the informed-consent process.
   C. Is the same as off-label use.
   D. Does not require IRB oversight.