CLINICAL TRIALS
ADMINISTRATOR
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IN THIS ISSUE

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Electronic grammar check doesn't ensure consent process effectiveness

Experts offer suggestions for improving informed consent process

The informed consent process has become much more complicated and burdened with legalistic language in recent years, and there is little research available to show what the impact is on subjects' understanding of their role in studies, experts say.

Some of the studies about informed consent are three and four decades old, and they were conducted with hypothetical subjects rather than people who were enrolled in clinical trials, notes **Nancy Kass**, ScD, a professor of bioethics and public health at the Bloomberg School of Public Health and Johns Hopkins Bioethics Institute at Johns Hopkins University in Baltimore. Kass spoke about writing effective consent documents at the 2005 annual HRPP conference on ethics and trust across boundaries, sponsored by Public Responsibility in Medicine and Research (PRIM&R) and Applied Research Ethics National Association (ARENA), held Dec. 3-6, 2005, in Boston.

While it's good news that investigators no longer question the need for informed consent, as might have been the case decades ago, the down side is that their informed consent process typically is guided by regulations, Kass says. "What the regulations tell them to do is disclose to participants a lot of information about the trial," Kass says. "The regulations don't tell them to find out if participants understand what was said," she adds. "We've interviewed research investigators who said, 'I wish we spent more time figuring out what people understand.'"

When asked how many investigators do some sort of research into what subjects understand, only 16% said they did, Kass says. "This is despite the fact that the vast majority of researchers think we should to more than we do," she notes.

One clever strategy for assessing a subject's understanding is to eliminate the most used and obvious question of "Do you have any questions?" and replace it with specific questions about the informed consent information discussed, Kass suggests.

"It's common for researchers to give people a lot of information and then ask, 'Do you have any questions?' and participants say, 'No, I don't,' and that's it," Kass says.

A better approach would be to ask questions, such as these:

- Would you please tell me what you think is the purpose of this study?
- Would you please tell me what is the benefit to you personally for joining the study?
- What do you think would happen if you decided to drop out of the study?

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Editorial Questions

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"This way you will find out what people understand and what they don't understand, and you can correct their misunderstandings," Kass says.

Clinical trial sites and IRBs also could put more effort into making informed consent forms readable, and this means going beyond the word processing program's readability scores, another expert suggests.

"It's easy to look at an automated Microsoft Word readability score, but it's easy to fool that system," says **Michael Paasche-Orlow**, MD, MPH, assistant professor of medicine in the section of general internal medicine, department of medicine, Boston University School of Medicine. Paasche-Orlow also spoke about the consent process at the recent PRIM&R conference.

The MS Word readability tool is based on the Flesch Reading Ease score and Flesch-Kincaid Grade Level index, which score documents according to sentence structure and complexity of language.

The Flesch-Kincaid system was developed to adapt Navy training manuals many years ago, Paasche-Orlow notes. "Their equation has nothing to do with the frequency of words," he says.

Also, the way MS Word uses the system it won't pronounce any document to be above a 12th-grade reading level, Paasche-Orlow says. This becomes important when an informed consent is checked on a paragraph-by-paragraph basis, because while the document as a whole might have an eighth grade reading level, individual paragraphs could be listed at a 12th grade reading level, he says.

"It's hard to say what is the appropriate standard and what is the reading level target," he says. "The most common target in the U.S. is an eighth grade reading level, but that's not based on any empirical evaluation of what the need is."

Also, while an eighth grade reading level might be the appropriate target for some protocols, it might be too high of a reading level for others, Paasche-Orlow says.

"I've seen a few IRBs that set targets as low as fifth grade reading level, but the federal standards don't specify readability levels, they only say the document should be readable by the average subject," he says.

The best approach to assessing an informed consent document's readability level is to have lay people read it and note the problem areas, he advises. "I recommend that everybody have their form be read by a non-scientist and maybe even

somebody who is legitimately in the target audience for their study," Paasche-Orlow says. "They should even have their children read it if they have grade school children who might be able to read it for them."

While automatic readability tools will show investigators where they have gone wrong in writing an informed consent document, they won't show what is working well and what is not working as well as it could be, Paasche-Orlow says.

Even if investigators do not have non-scientists read through the consent form, they could improve it by concentrating on the areas that are most likely to confuse research subjects.

"Specific concepts in many trials that are harder than others to understand include issues of randomization, therapy misconception, compensation for injury, and things that are easily confused," Paasche-Orlow says.

Research into the informed consent process provides clues about what research participants are most likely to understand and what they are most likely to misunderstand, Kass says.

"For example, they will generally know how often they have to come to clinic and which medications they need to take and how many times a day they have to take them," Kass explains. "What they seem to have the hardest time understanding, first of all, is that the research may not help them clinically."

Research subjects often assume that if their doctor referred them to a trial then it's because there is helpful medicine given in the trial, Kass says. "And while sometimes that is absolutely true, at other times it may be the trial is testing medicine that may not be helpful, or it may be testing against a placebo," Kass adds.

Clinical trial subjects also have trouble understanding randomization, Kass notes. "Even if they are told very explicitly in a consent process that half the people will get one thing and half get another, and this is decided by flipping a coin, when one interviews patients in a research study, they often have elaborate explanations for why they believe they got the drug," Kass says.

Subjects sometimes say, "My doctor liked me," and they'll explain how they received the drug instead of the placebo, even if they were told the trial was randomized, Kass adds. "Subjects have a common belief that the study will help them personally, and sometimes that's a misconception, and sometimes that's accurate," Kass says.

While patients typically understand that they don't have to join a study, they have more difficulty understanding that they can drop out of it once they've enrolled, Kass says. "It's more likely they understand they have a choice about enrollment than they understand they have a choice to drop out," she says.

These misunderstandings could be eliminated if investigators would encourage more discussion during the informed consent process and rely less on the consent form, Kass says. "I think they should sit down with someone and say, 'I would like to talk with you about a research study you might be interested in joining,'" Kass says. "Then they would talk with them about the study and not necessarily look at the consent form."

The investigator or clinical trial coordinator's language would be informal and possibly include these comments:

- This is what the study's about;
- Here's what you'd be required to do;
- Here are good things and bad things about being in the study.

The person providing informed consent would emphasize the more difficult parts, instead of treating each section as if it was of equal importance, Kass says. "And at the end of the discussion if it looks like the participant wants to join, they would say, 'If there are no more questions then I need you to sign this piece of paper that documents that we had this discussion,'" Kass says. "And the person might bring the document home to think about it, depending on what kind of research is involved." ■

Tips on improving the consent document

These strategies will enhance readability

It's not necessary to conduct a major research project each time a new informed consent form is written, but it's only sensible to obtain the readability perspective from someone who is not familiar with the protocol vocabulary, an expert suggests.

It's easy for investigators who are enmeshed in their own fields to become blind to the multiple uses of various words, says **Michael Paasche-Orlow**, MD, MPH, an assistant professor of medicine in the section of general internal medicine, department of medicine, Boston University School of Medicine.

"When you get into an investigational mindset, you can forget the pedestrian uses of those same words," Paasche-Orlow says. "But you can gain insight into this when you ask people who are not in your field to read it."

Also, there are sentence structures that are not common with the public, but which are common in the scientific community, he says. "A good example is that at the sixth grade reading level, no one is writing with semi-colons," Paasche-Orlow says. So when an investigator notes semi-colons in the informed consent document, that should be a signal that the form contains complex sentence structures and probably is not as readable as desired, he adds.

"You could easily simplify sentences that have semi-colons or subjunctive clauses," Paasche-Orlow says. "There's almost no purpose to these, but you find them all the time."

Paasche-Orlow offers these other strategies for simplifying the informed consent document:

• **Make good use of a layperson reader.**

A layperson reader could highlight for investigators where text is written in too complicated a fashion, while the electronic readability tools will let text slide even if it's written with arcane argot, Paasche-Orlow says.

An informed consent document could be loaded with words that don't mean anything to subjects, but because they have fewer than three syllables, they do well on the readability tool, he notes.

"The readability system doesn't know how rare words are," Paasche-Orlow says.

For example, a simple word like "diet" can have very different meanings to different people, Paasche-Orlow says.

"When doctors say the word 'diet' they're talking about all the food a person is eating, all of the caloric intake," he explains. "But when patients see the word 'diet,' they think you're talking about weight loss."

• **Improve the font and text size.**

"Not only is the typical informed consent document very long with information overload, but some people are printing materials in a font that is too small," Paasche-Orlow says. "Unless they're going to check people's vision, there's almost no reason to have font that's less than 14 points."

People with 20/60 vision can read 14 point font, but if it's printed any smaller than that it might make it difficult for some target populations to read, he says.

"This may be more of an issue with an older patient population, and they may not even admit to you that they can't see it," Paasche-Orlow says.

Also, when type face is enlarged, it increases reading speed for marginal readers, Paasche-Orlow notes.

"Another strategy is to have the whole text in the same type face," he says. "There's no reason to go from Arial to Times to Garamond."

Informed consent forms sometimes will have different type faces to draw attention to particular sections of text, but this just makes it harder to read for marginal readers, Paasche-Orlow says.

As far as which type face to select, Courier gets good grades and so does Times New Roman, Paasche-Orlow notes.

"Most of the fonts people are using are okay, but bold is more effective than italics," he says. "I've seen people have difficulty with italics."

• **Be more creative with headings.**

Headings could be printed in bold-face or in a larger font, but the most important thing is to make the headings engaging, Paasche-Orlow says.

"So instead of having a heading that is bland and not personal, some people go with questions as headings," Paasche-Orlow says.

For example, headings could include these questions:

— What will happen in this study?

— What will I be asked to do?

"Questions like those are more interactive, and we want these documents to be a conduit, the platform through which the research assistant and potential subject get into an interaction in the process," Paasche-Orlow says. "The best thing is if these forms promote an interactive learning process."

These types of engaging headlines show the subject that the consent form is there for them to talk about and not just another disclaimer form like the ones they sign at the gym without actually reading, he says.

"There are disclaimers all over society, and if they have to engage in it as a legalistic ritual then they're likely not going to understand what they're signing on to," Paasche-Orlow says.

• **Think about the research assistant's role.**

Investigators should think of informed consent documents as patient education tools, and they should understand that their research assistants also are heavily influenced by the forms, Paasche-Orlow notes.

"So if the form is arranged in such a way that research assistants are prompted to interact and

teach subjects, then it's possible to get past any misunderstandings that might happen," he says.

"I recommend the research assistant has his own version of the form that prompts him to ask questions," Paasche-Orlow says. "These prompts could be at the end of the text box."

For example, prompts might include the following:

• Let's go over the information we just talked about;

• Tell me in your own words what the idea of this study is;

• Repeat back to me the idea of what we were just talking about, just so I know that you understand it.

"Get the potential subject to reflect on this information and not to just do this at the end," Paasche-Orlow says. "This should be done multiple times throughout the course of the trial."

Whoever is engaging in the informed consent process should be cued for teaching and confirming understanding, Paasche-Orlow adds. ■

Bioethics committee weighs in on continued drug use

Flow chart helps PIs steer ethical course

Whether investigators are conducting pharmaceutical research domestically or overseas, there always is a question about what will happen to subjects when the study ends. There are a variety of ethical questions regarding whether it's better to continue to provide access to a study drug or whether it's best to let the access end with the trial.

Eli Lilly & Co. in Indianapolis has tackled this question through guidance developed by a bioethics committee that has been in place since the late 1990s, says **Mark Lange**, JD, an associate general counsel for global regulatory and a member of the bioethics committee.

"We have fairly senior people who serve on the committee, and it focuses on ethical questions in the clinical research phase," Lange says. "One role we play is to look at topics within the industry that we think we need internal guidance on."

So one of the topics analyzed by the bioethics committee was the issue of what is an ethical obligation of a pharmaceutical company for patients who participate in clinical trials when the study ends, Lange explains.

The committee developed a risk-benefit analysis that takes into account what is known about the drug and the patient's response to it, but which also recognizes that the drug's use is part of research and not treatment, Lange says.

"So we don't know definitively that it's safe and efficacious," Lange notes.

The risk-benefit analysis is reflected in a flow chart that considers these questions regarding the study drug:

— severity of disease: Does study involve treatment of a serious or life-threatening disease? If no, then it is not recommended to provide continuing access to the study drug;

— market availability of Lilly drug: Is Lilly product on market in country of study and can it be lawfully prescribed for the disease? If yes, then it is not recommended to provide continuing access to the study drug;

— phase of development of Lilly drug: In what phase of development is the drug? If it's a phase I study, then it is not recommended to provide continuing access to the study drug;

— individual patient response to Lilly drug and other therapy options: In a phase II study, has the individual patient received the Lilly drug in the study and shown benefit? If not, then continuing access is not recommended. In a phase III study, has the individual patient received the Lilly drug in the study and shown benefit? If yes, then the Lilly drug is offered to the patient, based on best clinical judgment of study investigator and as part of a roll-over/extension study until the Lilly drug is commercially available in study country or development of drug/indication is discontinued;

— length of time and method of supply of Lilly drug: Have all available therapies marketed in study country failed to benefit the individual patient? If no, then it is not recommended to continue access to study drug; if yes, then continued access is offered.

The decision tree is for the drug study team to consider when writing the protocol, Lange says.

"You're working with a company and saying, 'What should I do? What should I say in the protocol?' and the algorithm gives you a guide for thinking it through," Lange says. "We leave the decision up to the individual drug development team, but the decision tree gives them guidance."

The bioethics committee also has made it clear that the protocol will spell out for investigators and IRBs what will be done with regard to

continuing access of the study drug, and it will discuss the rationale for the decision, Lange says.

"You always say in the protocol for the IRB's benefit what you're going to do, even if you're not going to do anything, and put in the rationale for why you are doing it," Lange adds.

Lange explains how the bioethics committee developed the guidance about continuing access to study drug at the end of a clinical trial:

• **Global ethical standards set the stage:** The bioethics committee considered Article 30 of the Declaration of Helsinki, which states, "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study."

Also, a 2004 clarification includes this language: "…reaffirms its position that it is necessary during the study planning process to identify post-trial access…" and "post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review."

Committee members discussed what is meant by the terms "access" and "best proven therapy," Lange says.

For instance, does access mean that the person is provided the drug for free, or does it simply mean that the drug is provided before it has been approved by regulatory agencies and is available on the marketplace, Lange says.

The bioethics committee decided that access referred to regulatory access and not financial access because how could anyone make a decision about financial affordability for each patient, he says.

"How do you decide whether they are wealthy enough or not to afford this drug, and when does your obligation continue?" Lange says. "Is it a lifetime obligation? Where do you draw the line?"

Also, if continuing access meant lifetime access, then it would become fiscally challenging for pharmaceutical companies, particularly with large studies and post-market research, Lange says. So the decision tree ends the continuing access to the drug when the drug is readily available on the market and patients could be prescribed it by physicians, he says.

• **Severity of illness is a major consideration:** "The more serious the illness, the more likely we should consider providing the drug to the patient, even if it hasn't been approved," Lange says.

"Conversely, for a less serious illness we'll shy away from continuing to provide the drug because you're still taking some risk with that patient population," Lange adds.

One issue that arises with subjects who have severe illness is whether providing continuing access to a study drug is too great of an incentive for joining a clinical trial, and whether subjects should be told up front that they will be offered continuing access to the drug at the trial's completion, Lange says.

"Are you withholding the whole picture, or are you making too much incentive?" Lange asks. "We're still working through that one."

• **The study phase matters:** Oncology trials are not included in the algorithm because they are unique, but with other types of studies, the decision tree recommends that continuing access to a drug not be provided for phase I studies, Lange says.

"We don't know if we'd have enough information to provide that drug at a phase I study," Lange says. "At a phase II or III study, we're seeing the patient's response to it, so if there are no other drugs on the market, then we can provide them the drug." The decision is tiered by the study's phase, the individual subject's response, and whether there are alternative treatments available, Lange says. ■

Fill often overlooked site education gap

Focus on training research coordinators

Research institutions and clinical trial sites often pay close attention to investigator training, particularly to what's required through regulations and institutional policies. But an important educational opportunity often is overlooked, and that involves the training of research coordinators.

"Research coordinators are often the first line of contact with subjects," says **Monika Markowitz**, MSN, RN, MA, director of the Office of Education and Compliance Oversight in the Office of the Vice President for Research at Virginia Commonwealth University in Richmond. Markowitz spoke about education for research coordinators at the 2005 annual HRPP conference on ethics and trust across boundaries, sponsored by Public Responsibility in

Medicine and Research (PRIM&R) and Applied Research Ethics National Association (ARENA), held Dec. 3-6, 2005, in Boston.

"It's not that research coordinators are not acknowledged, but much of the regulatory language and institutional language is aimed toward the investigator," Markowitz says. "Even though the investigator is in charge and responsible for conduct of the research, often he or she doesn't conduct all of the research."

Virginia Commonwealth University began to provide specific education for research coordinators in the fall of 2004, Markowitz notes.

The educational program now includes monthly programs about topics of interest to research coordinators, including lectures on the IRB process.

Here is how the education program was developed:

• **Hold a 'meet and greet:'** The institution invited experienced research coordinators to attend a casual educational session in which they would meet some of the chief research people they contact through their work.

"We met with some key research coordinators who are very experienced and have worked in research for a long time," Markowitz says.

The seasoned research coordinators were asked to describe their roles, their departments, and to say whether they would be interested in serving as mentors, she explains.

"Also, at this meet and greet function, we had representatives from many of the areas with whom research coordinators need to interact, including from sponsored programs, from the HIPAA privacy board, and from investigational pharmacy, radiology, pathology, and the IRB," Markowitz says. "The face-to-face contact was very important."

More than 40 research coordinators attended the afternoon meeting.

"The feedback we received was they were glad to meet many of the people they had spoken with over the phone or had e-mailed, and they were glad to meet other research coordinators," Markowitz says.

• **Provide monthly educational sessions:** Each month the institution has a research coordinator host a fourth Friday lunch and learn in which different topics are presented as research coordinators take a lunch break.

"The ideas for the sessions come from the research coordinators themselves," Markowitz says. "We have a steering committee consisting of experienced research coordinators, and some of the ideas come from the committee."

The one-hour program typically has between 10 and 30 attendees, and the monthly programs have included these topics:

— the IRB process at Virginia Commonwealth University;

— informed consent conundrums about the language and misrepresentation of important language that often is put into an informed consent;

— using the investigational drug pharmacy;

— the responsible conduct of research;

— the sponsor contract.

Speakers have included research coordinators who have worked on complicated and interesting studies and who discussed their roles with this type of research, Markowitz says.

"They are experts in what they do, and I think it's empowering and a great use of a wonderful resource to have them share some of the progress and trials and tribulations they experience," Markowitz says.

There are no quizzes, and the educational sessions are entirely voluntary, she adds.

• **Provide networking opportunities:** Another aspect of the research coordinator education focus has been to provide informal opportunities for research coordinators to network with each other, Markowitz says.

The research department regularly updates a list of research coordinators and their contact information, including departments, e-mail addresses, and telephone numbers, she says.

"So they can contact each other if need be, or they can meet each other within these lunch and learn programs," Markowitz explains.

Since research coordinators have a variety of job titles and often change jobs and departments, maintaining such a contact list can be a little time consuming, she notes.

"Research coordinators often come into a health science setting with different job titles, and those titles rarely are 'research coordinator,'" Markowitz says. "They can be nurses and have other titles, so finding out who they are and who the new people are can be challenging," Markowitz says. "What we've been trying to do is find people through word-of-mouth and by looking at IRB protocols and getting names off of those."

The distribution list also is how the department informs research coordinators about education sessions and updates, she adds.

As the research coordinator educational programs evolve, the institution might develop a

certification program and live educational programs, along with sessions that could earn coordinators continuing educational units, but the important thing is to address this missing link in institutions' research education programs, Markowitz says.

"The major reason for our talk about this topic at the PRIM&R conference was to share ideas and concerns among all institutions that are struggling with how to provide education to this group on the research team that is actively involved in the conduct of research," Markowitz says. ■

Award-winning training program available to all

Five key areas covered in curriculum

Clinical trial sites and research institutions seeking improvements to their staff and IRB training programs might learn something from the best practices developed by Family Health International (FHI) of Research Triangle Park, NC. Human Improvement Institute of Bethesda, MD, presented two of its 2005 Awards for Excellence in Human Research Protection to FHI for the organization's best practices in education and training. The winning programs were the Research Ethics Training Curriculum and the Ethics Training Curriculum for Community Representatives.

The Research Ethics Training Curriculum was designed as an educational program for the people who do research, including investigators and clinical trials staff, says **Roberto Rivera**, MD, director of the Office of International Research Ethics at FHI.

"We provide basic training to every person who has direct participation in a trial, and it would include principal investigators, nurses, social workers, and others who have a function in the research by counseling people, obtaining informed consent, and by being responsible for the follow-up of subjects," Rivera says.

The training curriculum meets all requirements by NIH and OHRP for providing basic training on research ethics to everyone who conducts research, Rivera notes. "Our policies say the same as the federal regulations, and the person who does the training is a key researcher," Rivera says.

Ethics Training Excerpt

The award-winning Research Ethics Training Curriculum created by Family Health International in Research Triangle Park, NC, has five sections, including this excerpt from section three on responsible conduct of research:

Essential Elements of Informed Consent

According to The Common Rule, in order to ensure that a research participant receives the necessary information to make an informed decision, it is important to provide each participant with:

- description of the research and participant's participation, including identification of experimental procedures
- description of reasonably foreseeable risks
- description of expected benefits
- potentially advantageous alternatives to participation
- explanation of confidentiality
- explanation of compensation for injuries
- whom to contact about the research and participants' rights
- explanation that participation is voluntary

The informed consent process is basic to a well-designed, ethically based research study. How informed consent is applied to the research study demands time, creativity, and an understanding of the participant population.

Learner note: List some of the problems that may be encountered getting informed consent with your research participants. Please write down your answers. ■

The basic research ethics training covers the core areas of research ethics, including these:

- principles of research ethics;
- foundations of research ethics;
- responsible conduct of research, including informed consent **(see sample page from this section, above);**
- supervision of research;
- special issues in research.

"Once we determined the content areas, we wanted to develop something that could be used as a tool that you could use for self-training and also for group training," Rivera says.

The result is a user-friendly training tool that is available on CD-ROM and the Internet at FHI's

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Research ethics training case study examples

The web version of the Research Ethics Training Curriculum created by Family Health International includes interactive case studies. Here are two of these case studies:

Case Study 1: Respect for Persons
A local Ministry of Health has requested a prevalence/behavioral surveillance study for sexually transmitted infection (STI) among commercial sex workers. Participants in this study will be tested for three common STIs and participate in an interview. Participants will receive a card with a number linking them to their blood sample. Women who donate blood will have the option of presenting their card to get the results of the STI tests. Those with positive results for any of the three infections will be offered free treatment. In addition, all participants will receive a small gift in return for their participation.

The target population consists of brothel-based sex workers who are strictly controlled by the brothel managers. Prior to initiating the research, the researcher meets with the brothel manager to ask permission to conduct the study. During the meeting, the manager states that all of the women working in the brothel will participate in the study.

Questions: (Please write down your answers, then click on the question to reveal possible answers.)
1. What steps can the research staff take to ensure that the informed consent is freely given by all participants?
(A possible answer is given as follows: First, the researcher should work to educate the brothel manager. Informing him or her that nonparticipation is acceptable to you may cause him or her to relax his or her attitude. In addition, the informed consent process should take place in a private, confidential setting. Women should be reminded repeatedly of the voluntary nature of the research.)

2. If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager? (A possible answer is: Because the manager may insist that women participate, it will be imperative that nonparticipants are anonymous. Conducting informed consent individually will be important so that peer pressure is reduced. In addition, one might consider treating all of the women as if they had enrolled. For example, giving nonparticipants thank-you gifts or fake blood sample cards will make it difficult to distinguish the participants from the nonparticipants.)

3. If you believe the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health? (A possible answer is: If the target population will not be able to consent freely, then you are obligated to change the study or choose a different target population. For example, commercial sex workers who are not brothel-based may not face pressure from a manager that would alter their decision-making process.)

Case Study 2: Beneficence and Justice
A time-series intervention trial was conducted with commercial sex workers. The goal of the trial was to assess the impact of adding the female condom to a male condom distribution system, measured in terms of a change in the proportion of sex acts protected by condoms. Condom use was estimated by interviewing study participants about their use of protection in their last 10 sex acts. These measurements were to be made at five time points: twice following exposure to male condom promotion and distribution activities, and three times following promotion and distribution of both the male and female condom. The local principal investigator, a highly respected advocate for the sex workers, explained that women were very enthusiastic about participating in the female condom trial, as it would provide them free access to this innovative method of dual protection.

The first round of condom use measurement was completed as planned. Preliminary data analysis revealed that study participants were reporting male condom use in more than 95% of sex acts. Following verification of the interviewers' techniques, a second round of interviews was completed. It yielded a similar, exceptionally high-level of male condom use. There is concern that introducing a new product will have a negative effect on the use of male condoms. In addition, there are questions about the availability and affordability of female condoms after the conclusion of the study, even if the study is successful.

Question: What is the best way to proceed?
A. Continue the study as designed. (Participants who click on this answer receive the following feedback: While this is certainly an option, continuing the study may not be in the best interest of the participants. The established high rate of male condom use and the uncertain post-study availability of the female condom make this a poor choice.)

B. Terminate the study. (Feedback: This is the best answer. The study may have scientific merit, but this is clearly not the best participant population.)

C. Suspend the study. Seek assurance that female condoms will be made available if proved successful. (Feedback: This is not the best answer. However, it would address the issue of justice. Studying female condoms in a population that will not have access to the product following the study is not a fair distribution of the risks and benefits of the research.) ■

web site: www.fhi.org. It can be located by putting "ethics training" in the web site's search engine.

Each version has PowerPoint slide copies with narrative text, and group presenters can expand the narrative text according to their own knowledge and skills.

The curriculum is designed to be presented in a four- or five-hour training session if used individually or as a self-study program, and the group training version could be covered in one eight-hour session or in two four-hour sessions.

For those who use the training on-line, it has interactive case studies. **(See sample case studies from training tool, p. 21.)**

The training tool, which FHI makes available to the public has had more than 300,000 visits, and it has been downloaded as a PDF file more than 10,000 times, Rivera says.

The tool includes 25 multiple choice questions for participants, and it has a reader's evaluation of the curriculum. Participants who submit documentation of having taken the training course could receive a signed certificate from FHI. The training is available in Spanish, French, and Portuguese on the web site. It's also available in Mandarin Chinese on a CD-ROM, and it's being translated into Swahili, Rivera says.

"One thing we had in mind for the training was to have something that would be globally accepted," Rivera says. "We wanted a program that addressed research ethics without any direct reference to particular interests or regulations."

When investigators conduct research internationally, they often hear from local collaborators, "Why do you tell me I have to do things this way? Why do you want me to do things the way the U.S. government regulations say things have to be done?" Rivera says.

"It's a prevalent attitude, so we developed it to have in mind an international audience that would find the training acceptable," Rivera says.

While the training programs at NIH and the CDC are useful for U.S. investigators who wish to make certain they follow federal regulations, they are not as useful for an international audience, Rivera says.

Since FHI's goal was to have a globally-accepted training program, when the training curriculum was completed, FHI sent it to be reviewed by international experts, Rivera says.

"We have a number of reviewers from international organizations, like the World Health Organization and local people who are responsible for research ethics programs in their respective countries," Rivera says. "We asked them to be sure they believe it is internationally correct and that it is something that addresses the subjects in a manner that is acceptable for an international audience."

The reviewers returned many comments about terminology, informed consent, and other items, he notes.

"They care very strongly about informed consent and thought we were presenting it more like a form, so they wanted us to look at developing it as a process," Rivera says. "They wanted more focus on why you have to do research this way and not just because it's a regulatory requirement."

After incorporating the reviewers' concerns, FHI came out with a new version of the training program and then conducted field testing with the program, Rivera says.

"What we do commonly is select reviewers who may be members of research ethics committees and then ask the person to conduct training in their location," Rivera explains.

"Since they reviewed the training material they know how to do it, and they tell the audience that they are field testing a training instrument, and they want to hear what parts the trainees don't understand."

The field testers completed a structural template, send it to FHI, and that information was incorporated in the final version of the training program, Rivera says.

"It's a long and painful and costly process," Rivera says. "But it works, and that's the only way of doing it."

Each training program took about a year to complete, he adds. ■

Research training trends and methodologies

Expert offers look at best practices

Requirements for research staff education may not include hard and fast regulations, but they might be part of the expectations held by regulators, sponsors, and others in the research industry. So it's important to design staff training and education programs in a way that will meet all of these expectations and provide information that

staff will retain, says **Carol A. Connell**, RN, DrBA, director of development operations team lead at Pfizer Inc. in Groton, CT.

For instance, training that relies solely on lectures is less effective than hands-on training, Connell says. "Only 10% of what we hear we retain after two weeks," Connell says. "But we retain 90% of what we say and do." It's important to realize that parts of the education won't be retained, so the most important information will need to be emphasized in repeated training sessions, she says.

When a study involves international sites, there are additional considerations that must be kept in mind. "There are different religious and national holidays, like the Festival of Lights in India, which lasts a whole week," she says.

Also, each country will have its own local requirements and regulatory agencies, and since health care and communication infrastructures vary from site to site, these differences also have to be considered, she says.

"A lot has to do with understanding what the requirements are and finding someone locally who knows this and has contacts within the community," Connell says. "I have worked in a number of countries and areas where you need to get tribal approval for a protocol." In some countries if the trial involves women, the investigators must speak with the men in the community to make certain they're comfortable with the trial, as well.

When an institution collaborates with international research sites, it's important to determine the direct and indirect costs of setting up training, including labor and facility costs, Connell notes.

Some of the goals that might be set for research training include:

• **Establish expectations:** "Prior to starting any trial, the staff conducting procedures in the trial need to be aware of what needs to be done in the protocol and in imparting informed consent," Connell says. Then during the course of the trial, as new staff join the study, there should be refresher training and education, she says. It's the monitor's job to make sure the investigator and coordinator understand procedures and are running the trial with integrity and best practices, Connell notes.

"I would expect the monitor would talk with sites to make sure they're aware of the different requirements and to see if they see something that's not done quite the way it should be," she adds.

• **Focus on the protocol:** "The protocol is a huge document today, and many people do not read it in its entirety from cover to cover," Connell says. "At the initiation visit, we go through the protocol page by page with the relevant staff," she explains. Pfizer usually asks that study coordinators be included in protocol meetings, Connell notes.

People often miss procedures on the flow chart if they're not highlighted adequately, so a good strategy for preventing this problem is to add laminated cards to the packet clinical trial staff use. Research staff could use the cards during study visit procedures as a quick guide to making sure all procedures are done correctly, Connell suggests.

It's also helpful to provide study coordinators with research training along with their protocol education because this helps them understand why they're being asked to do various protocol requirements, Connell says.

• **Use initiation visits for training purposes:** At initiation visits, education might include standard operating procedures, case report forms, information on the protocol, documentation, regulatory requirements, drug/device accountability, among other items, Connell says.

"We bring to the site samples of packaging so we can show people what to do with it," Connell says.

"And we have special procedures done that are part of the protocol, and we show staff exactly what we want done." For example, if the protocol calls for reading a chest X-ray, the instructor will show the clinical trial staff precisely how to measure heart size, Connell says.

Other strategies for making certain staff have learned to standardize the procedures include using laminated cards and using electronic data capture with links to information that can bring the standards to the people who are entering data, Connell says. ■

COMING IN FUTURE MONTHS

- How you can improve subject recruitment, retention
- Russian researcher discusses global investigator training
- Competence assessment of a vulnerable population
- Improve your site's data safety and monitoring plan

CE/CME Objectives / Instructions

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- **review** pertinent regulatory mandates;
- **develop** practical clinical trial oversight strategies;
- **review** best practices shared by facilities that successfully conduct clinical trials.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

CE/CME *questions*

5. One strategy for improving the informed consent process is to assess whether participants understand what they've been told. Which of the following questions is NOT a good approach for assessing their actual understanding?
A. Would you please tell me what you think is the purpose of this study?
B. Would you please tell me what is the benefit to you personally for joining the study?
C. Do you have any questions?
D. What do you think would happen if you decided to drop out of the study?

6. If investigators would like to improve the readability of an informed consent form, which of the following would be the best size for the type font?
A. 8 point
B. 10 point
C. 12 point
D. 14 point

7. When a decision has to be made about whether to provide continuing access to a study drug, which of the following is not a good question to consider in the risk-benefit analysis?
A. Severity of disease: Does study involve treatment of a serious or life-threatening disease?
B. Market availability of drug: Is product on market in country of study and can be lawfully prescribed for the disease?
C. Phase of development of drug: In what phase of development is the drug?
D. All of the above are good questions

8. According to The Common Rule, in order to ensure that a research participant receives the necessary information to make an informed decision, it is important to provide each participant with which of the following information:
A. Description of the research and participant's participation, including identification of experimental procedures; description of reasonably foreseeable risks; and description of expected benefits.
B. Potentially advantageous alternatives to participation; explanation of confidentiality; explanation of compensation for injuries; who to contact about the research and participants' rights; explanation that participation is voluntary.
C. Both A and B
D. None of the above

Answers: 5. C; 6. D; 7. D; 8. C