

# CLINICAL TRIALS ADMINISTRATOR

*An essential resource for managers of clinical trials*

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## IN THIS ISSUE

■ **Recruiting children:** Follow these tips for recruitment and retention of pediatric subjects . . . . . 52

■ **Targeted recruiting:** Expert explains how underlying attitudes can influence willingness to participate . . . 53

■ **Researchers develop a more creative informed consent process:** Informed consent kits help with international and domestic trials . . . . . 54

■ **Take a walk through an FDA audit:** Consequences of noncompliance are great but you can and will survive . . . 57

■ **News Brief**  
— Health officials testify before House Committee . . . . . 59

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## Best practices in pediatric clinical trials expand with help of 13 PPRUs

*Goal is to increase drug labeling for children*

Only 6% of the 80 drugs most frequently used in newborns and infants are labeled for pediatric use, and three out of four of all medications on the market do not have approved labeling for children.<sup>1</sup>

Nonetheless, physicians frequently prescribe drugs with adult labels to infants and children, and this occasionally leads to serious problems. For example, the antibiotic erythromycin, labeled for adults, was linked to pyloric stenosis among seven babies in Tennessee in 1999, and about the same time, life-threatening pancreatitis was reported in children and adults receiving valproate, a drug used for epilepsy, manic episodes in manic depression, and as a migraine preventative.<sup>2,3</sup>

Also, in 1999, a 9-month-old infant's death was attributed in part to the drug Propulsid (cisapride), used to treat gastroesophageal reflux, which had been approved for adults but not in children and was being tested with a hospital study in 100 children. Cisapride was pulled from the market by Janssen Pharmaceutica of Titusville, NJ, in July 2000.<sup>4,5</sup>

With a goal of improving the scientific knowledge of how various drugs work in children and also reducing medication errors and problems among pediatric patients, the National Institute of Child Health and Human Development began in 1994 to fund a network of Pediatric Pharmacology Research Units (PPRU). The PPRU network now consists of 13 sites and has conducted studies supporting pediatric labeling, as well as investigations into differences in how children and infants metabolize medication.

The PPRU project helped lead to the FDA Modernization Act (FDAMA), and has responded to increased demand for pediatric clinical studies as a result of FDA's 1998 Pediatric Rule.

"There has been a lot of progress in the last 10 years as federal regulations have changed, and I think the biggest change is a heightened awareness by the public of the needs of the pediatric population for clinical pharmacology," says **Janice E. Sullivan**, MD, associate professor in the department of pediatrics at the University of Louisville (KY). The University of Louisville began its work as a PPRU in 2004.

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## Editorial Questions

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"But I think we've hardly touched the tip of the iceberg," she says. "Still, 75% of drugs used for children are not labeled for use in children, so although we've made inroads in the last 10 years, we still have some ways to go."

One of the key strengths of PPRU is encouraging translational research projects, notes **Ross McKinney**, MD, associate professor in pediatrics and vice dean for research at Duke University School of Medicine in Durham, NC.

"We're trying to understand why drugs do what they do, including metabolism and genetic markers that show clearance of a drug," he says.

## Strength in networking

Duke and the University of North Carolina at Chapel Hill have formed a North Carolina collaborative PPRU, which has been active for little more than one year, in which one piece is the school of pharmacy and the other is the department of pediatrics, McKinney says.

The two research institutions combine their strengths in good clinical research design, study management, pediatric clinicians, and laboratory resources, he reports.

"In our perspective, this gives us an unusual amount of depth since we have a lot of people with skills that we can access fairly easily," McKinney says.

Another benefit of PPRU is that it has increased the collaboration of pediatric pharmacology investigators around the country, reports **Robert M. Ward**, MD, professor of pediatrics and a director of the University of Utah Pediatric Pharmacology Program in Salt Lake City. The University of Utah has been involved with PPRU since 2004.

"It allows us to share ideas about what drugs need to be studied, what ideas need to be investigated, and how to carry out those studies," he says.

"It also shows us how to add science that's important to understanding pediatric pharmacology to other studies that are about to be done," Ward adds. "We've even tried to encourage some sponsors to add certain measurements to their studies so we can better understand how developing children respond to drugs and metabolize drugs and excrete them."

Children's Mercy Hospitals and Clinics in Kansas City, MO, has one of the older PPRU programs, which has studied more than 50 different compounds in its 10 years of existence, reports **Gregory L. Kearns**, PharmD, PhD, a Marion Merrell Dow/Missouri Chair in Pediatric

Pharmacology and chief of the Division of Pediatric Pharmacology and Medical Toxicology.

"About 98% of all the studies we do are early Phase I, II trials, which is a little different from most of the people around the country doing pediatric studies," he says. "We've done a fair amount of work that has characterized the age-specific dose requirements for drugs, and in many cases it's important information for sponsors to take with them in Phase III trials."

The PPRU network provides research strength in numbers of both subjects and in its access to some of the best clinical pharmacologists in the nation, Sullivan says.

"That's part of the reason we're interested in the network," says **Mary Jayne Kennedy**, PharmD, assistant professor in the department of pediatrics and a co-principal investigator on PPRU for the University of Louisville.

"One of our main goals was to generate some data in populations that would go to labeling drugs in children," she says. "The problem is no one site has the capability to generate that data alone."

### ***Born of necessity***

The PPRU network, which was created partially in response to the fact that there was little interest among individual sites in conducting drug trials in pediatric populations, provides the necessary critical mass with its 13 sites, Kennedy adds. **(See story on best practices in recruiting and retention of pediatric population, p. 52.)**

"We conduct Phase I to Phase IV clinical trials, and one study we brought to the network had 240 patients at eight out of 13 sites," she says.

Sullivan and Kennedy both have trained in clinical pharmacology, and the University of Louisville has established an inpatient/outpatient clinical research pediatric unit. Receiving the federal grant to become a part of the PPRU network carried the institution's pediatric research mission to the next level, Sullivan says.

Likewise, the PPRU network has evolved as sites like the Louisville one have been added, she notes.

"With each cycle of the PPRU network, the mission has matured," Sullivan says. "Initially, its mission was primarily for the labeling of medications for children, and now it's more focused on gaining an understanding of the ways children are different."

For instance, the Louisville PPRU staff work

closely with pediatricians and subspecialty physicians, often benefiting from their collaboration in a study, she explains.

"They have an understanding of the need for drugs for the disorders they're treating, and that's one of the biggest helps," Sullivan says.

The University of Utah PPRU is one of four PPRU sites with a neonatologist, which will increase the study of drugs in newborns it is hoped, says Ward, who is a neonatologist.

"I trained in clinical pharmacology from 1976 to 1979, and since that time there has been only a limited study of drugs in pediatrics," he says.

With the PPRU network, Ward says he is encouraged that scientists can begin to provide evidence for the practices neonatologists carry out in the newborn intensive care unit.

One potential benefit involves the study of an antimicrobial drug that would help reduce chronic lung disease in newborns, Ward says.

"Chronic lung disease is associated with developmental delay, prolonged hospital stay, and increased mortality," he explains. "If this drug is safe and effective, it could change the way we care for a very small baby."

The PPRU network also brings together different experts, who are scattered geographically across the country, Ward says.

"At the University of Utah, we have an extraordinary strength in drug analysis; and in Kansas City, they have a strong group in analyzing pharmacokinetics, how people metabolize drugs. Other sites around the country have different strengths," he reports. "Some have people extremely skilled in mathematics in how you analyze the data, and so this brings together those strengths from all around the country so that we can now share."

While PPRU holds promise for advancing pediatric drug research, there are some drawbacks, McKinney notes.

"PPRU grants are not huge," he says. "They provide some basic infrastructure, and you use that infrastructure to obtain funding from other projects, but it's not enough money to do a whole lot of research beyond the core infrastructure."

Also, while some of the PPRU sites have had a great deal of success in attracting sponsors for pediatric drug trials, others like the relatively new Duke/UNC PPRU have not, McKinney says.

"We have not seen greater interest among pharmaceutical companies," he reports. "There's a certain degree of reluctance among pharmaceutical companies to work with PPRU in general related to the fact that it's funded through the National

Institutes of Health." This is because federal funding comes with strings attached, McKinney explains.

"If federal dollars are used to support development of a new compound, there is the potential that if the drug's pricing doesn't fit the desires of the people who authorized federal support, then they have the ability to do a reach-through and change the pricing," he says. "This hasn't been exercised, but there are several times it's been discussed."

Also, pharmaceutical companies often want to control the design of a trial, while scientists generally want the clearest answer directly related to clinical care, McKinney says.

Nonetheless, there are some PPRUs that have had successful relationships with pharmaceutical companies, he notes.

Children's Mercy Hospitals is one example of a PPRU success story in that the site has 28 staff in the pediatric pharmacology program and has averaged 10-15 peer-reviewed publications per year for the past 10 years, Kearns says.

"We don't touch anything in terms of an industry-sponsored clinical trial that doesn't make new knowledge and result in publication," he points out. "We're certainly one of the most productive of the 13 sites; and programmatically, we have a huge investment in pediatric pharmacology."

McKinney expresses optimism for PPRU as a network, even though at present it does not have as many multisite trials as might be expected from a collaborative group.

"Our hope is over time it will function as a network," he says. "It has good scientists doing good work."

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# How to improve pediatric recruiting and retention

*Successful programs share best practices*

The University of Louisville (KY), is a new participant in the Pediatric Pharmacology Research Units (PPRU) network, but the site has history of success in recruiting and retaining pediatric clinical trial participants.

"In the majority of our studies, 90% to 95% of subjects who are approached and pass criteria join the study, and we have a 95 percentile retention," reports **Janice E. Sullivan**, MD, associate professor in the department of pediatrics.

Sullivan and other researchers at PPRU sites provide these tips for improving recruitment and retention of children in clinical trials:

• **Create infrastructure suitable for children:** "In some other places, they're trying to do pediatric research in an adult setting," Sullivan says.

At the Louisville PPRU, there are televisions in rooms where children wait, along with a play room with games and age-appropriate toys for young children to teens, she reports.

"When they're not giving a sample or doing other research things they can play in the research unit," Sullivan says. The children participants are given food or gift certificates for food as well.

The PPRU at Children's Mercy Hospitals and Clinics in Kansas City, MO, has a playroom outfitted for all ages of children, says **Gregory L. Kearns**, PharmD, PHD, a Marion Merrell Dow / Missouri Chair in Pediatric Pharmacology and chief of the Division of Pediatric Pharmacology and Medical Toxicology.

The research unit looks no different from the patient care unit, and the facility employs play therapists, who are similar to pediatric occupational therapists, and who interact with the children, helping them with crafts and other activities, during the long hours in which the children are waiting between research interventions, he says.

Since the children might spend 12 hours at the site and interact with research staff for about 1½ hours of that time, the play therapists play an important role in helping to recreate normal activities during the day, Kearns adds.

• **Make appointments convenient for families:** "Families like it if they can come in as part of the study and get the dental appointment done at the same time," he says.

"We try to integrate the research into the whole context of care, and part of that is educational too," Kearns says. "The reason we do clinical studies of new drugs is to improve therapy."

The University of Louisville site also coincides with study visits with participant's regular clinic visits, says **Mary Jayne Kennedy**, PharmD, assistant professor in the department of pediatrics and a co-principal investigator on PPRU.

"If patients are following up in the clinic, we'll do a follow-up for the study over here, so it's convenient for parents and their schedules," she says.

Also, parents of teenagers have the option of leaving the children at the clinic to return to work if needed. The research staff will call them when they're needed, Sullivan notes.

"We try to work with the family and because of school schedules, we do see some patients on the weekend if we need to," she explains.

• **Staff develop rapport with children participants:** "They spend a lot of time up front going through the consent forms and making sure the families have a good understanding of the study and what their responsibilities are throughout the study, and we build on that at each return visit," Sullivan says.

Study coordinators call patients to see how they're doing and to remind them of their study visits, she says.

To provide study coordinators with the time they need to develop this rapport, the Louisville PPRU has a unique staffing structure, Kennedy notes.

"All our coordinators do is interact with patients and do nursing activities," she explains.

Regulatory coordinators handle IRB paperwork, adverse event reporting, financial disclosure forms, and other research documentation, Kennedy says.

"Regulatory coordinators keep everyone informed of any changes in the regulatory arena and maintain regulatory binders," she adds.

• **Enhance informed consent experience:** "The parents of a child in a study are as much of a participant as that child," Kearns says. "So we want the parents to understand the reasons why a study is being done, and we want them to put a value on the potential contribution the study data will produce."

So study coordinators spend longer on education for a pediatric trial than they would for an adult clinical trial, he says.

"On average it takes our folks about an hour to

do an informed consent," Kearns says. "And even before the consent form is produced our study nurses and investigators will spend time talking to the parents about the problem for which the study drug is intended." ■

## Reach subjects through targeted recruiting

*Expert develops recruitment model*

There's a lot of focus on informed consent and compliance with human subject protection regulations. In the clinical trial process, that comes later. What comes first is getting people to volunteer for the trial.

According to **Diana Anderson**, PhD, president and CEO of D. Anderson & Co., a firm specializing in patient recruitment and retention, in the United States less than 6% of those eligible to participate in a clinical trial do.

With 80,000-plus clinical trials, the need for participants continues to swell, says Anderson, who wrote the book, *The Guide to Patient Recruitment and Retention*. She was a presenter at the Association of Clinical Research Professionals annual conference held April 2-6 in Orlando.

To get a better understanding of who volunteers and why, Anderson's company surveyed 200 people from their database of participants and asked them questions about what motivated them to participate in a clinical trial.

### ***Altruism not always at the core***

In her ACRP presentation, Anderson said historically people volunteer for clinical trials for the following reasons<sup>1</sup>:

- they are not adequately treated with current therapy
- to seek new treatments
- to help future generations
- to get study-related treatment at no cost
- to comply with a physician's request
- to seek attention from physicians and staff

In Anderson's sampling, the reasons given were similar but she found that the way the questions were asked had an impact on responses. For example, when respondents were asked to provide an answer to the open-ended question: "What motivates you to participate in a clinical

trial?" 45% answered, "To advance medicine/science and help others."

However, when those same respondents were asked to choose among a list of answers, only 5% chose "Advance science and help future generations." The answer chosen most frequently — by 50% of respondents — was "To try new medicine to see if it works better for me." Only 20% provided that as an answer to the open-ended question.

### **Attitudinal segments**

In an effort to understand attitudes and needs, Anderson developed the Attitudinal Segmentation Model. The model hypothesizes that six primary attitudinal segments exist and have an impact on recruitment efforts. By knowing to which segment a targeted population belongs, recruiters can tailor their approach to be more effective at reaching and converting potentials to subjects.

The segments are "physician followers," "scared and seeking," "nothing to lose," "latest, greatest seekers," "financially frightened," and "content and accepting."

**Physician followers.** According to Anderson, this group is slightly less educated and highly influenced by physician recommendation or endorsement. "Fifty percent of the database indicated that the physician was a key component in the subject's decision-making process," Anderson says.

This segment relies on relationships, so those trying to reach physicians followers may want to use resources to educate physicians about clinical research.

"Only about 1% of physicians conduct clinical research," Anderson says. She suggests community-based outreach, such as physician dinners or seminars on how to become a successful investigator.

**Scared and seeking.** This group is newly diagnosed with long-term disabling or life-threatening disease, Anderson says. They are primarily women, and are motivated to drive farther and wait longer for treatment options that might improve their condition.

In order to reach this group, recruiters may want to think about developing relationships with diagnostic centers.

**Nothing to lose.** This group is in the more advanced stages of disease. Anderson says they typically have exhausted their treatment options

and are hoping for an advancement or looking to help others.

With this group, the emphasis on helping future generations would likely be effective. "Many may be thinking, 'This may not help me but I don't want my family or friends to go through this,'" she says.

**Latest, greatest seekers.** This group is made up of people who are advocates for their own health. They typically are well educated and affluent, and generally are women or those under the influence of a woman, Anderson says.

Ads in prevention-based publications could be effective in reaching this group. She points out that advertisements would need IRB approval.

**Financially frightened.** This group is highly motivated by offers of free health care. They typically are uninsured or underinsured. "Surprisingly, money is not a motivator in this group. It's the opportunity for treatment that is the motivator," Anderson says. She suggests partnering with indigent clinics and public health centers.

**Content and accepting.** This group is risk averse, Anderson says. They are satisfied with their current medical treatment. In spite of the potential for benefiting the greater good because they don't see participation as a gain for them, they likely won't volunteer.

"They are without question the most difficult group to recruit," Anderson says. "Because we don't know much about them, it's an area in which we need to conduct a lot more research."

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## **Informed consent kits improve process globally**

*Idea is to make informed consent user-friendly*

Investigators conducting HIV prevention research among married women in developing countries have found that standard informed consent forms and methods do not work for both cultural and comprehension reasons. A more creative approach to informed consent could help improve comprehension, says behavioral scientist **Cynthia Woodsong, PhD**.

“The concepts associated with research, such as randomization, placebo, and blinding are difficult concepts to provide to people in these settings where people don’t have any notion of research design,” Woodsong, a scientist in behavioral and social sciences division of Family Health International (FHI) of Research Triangle Park, NC, says.

FHI has been conducting clinical trials of topical microbicides that are inserted in the vagina to prevent HIV transmission during sexual intercourse. Even the concept of putting a gel or product in the vagina is alien to women in some of the countries in which the microbicide is being studied, she says.

Another problem with traditional informed consent is it’s based on the ethical principle of respect for persons and their autonomy in making decisions about their own bodies, and in some of the cultures in which FHI is conducting research, women traditionally are not permitted to make these kinds of decisions, Woodsong notes.

When FHI discussed the study with community leaders and others to find out what would need to be done to improve its acceptability among the population being recruited for the trials, investigators kept hearing that the women’s husbands needed to be informed and involved, she says.

“What often comes back is the women want their husbands to approve it or the community leaders say, ‘You can’t enroll women without their husbands,’” Woodsong says.

So FHI developed a creative informed consent kit that included information that could be provided to husbands or boyfriends and would explain the clinical trial process in a way that is easily understood by women from various cultures, including women in the United States.

The result is an informed consent process, with 10 versions of materials in eight languages, which has been used in a clinical trial involving 3,200 women at seven sites in six countries, including the United States and five nations in Africa, Woodsong reports.

“In the United States, increasingly, we have health research done amongst minority and marginalized populations, folks who are not tuned into the mainstream concept of research,” she says. “Even though women are able to read the words on a consent form, they may not understand.”

Through the use of illustrations and consent materials, women subjects of the HIV-prevention studies have a better understanding of what to expect, and there is more of a dialogue in discussions with research coordinators who initiate the

informed consent process, Woodsong explains.

“We’re seeing that this was developed in response to a particular need in one microbicide trial, and now three different groups are using it in microbicide trials,” she says.

Here are some of the chief features of FHI’s creative informed consent process:

- **An illustrated booklet:** Researchers developed a 20-page booklet, made from 8.5-inch by 11-inch paper folded in half.

“I call it the user-friendly version of informed consent,” Woodsong says.

“For each clinical trial the consent forms are lengthy with 10-plus pages of typed information,” she notes. “The user-friendly version hits on the basic elements of informed consent, but not the nitty-gritty details.”

Research professionals meet with subjects to discuss informed consent, giving them the booklet to review as they talk about the various elements of the trial, Woodsong says.

“There are pictures and text on each page of the booklet, with lots of white space,” she describes. “The text is consistent with everything in the informed consent form, and all of it has to be approved by an ethics committee.”

In the U.S. version of the booklet, there are illustrations depicting these scenes, among others:

- A calendar with a day circled to show that women in the study will see a nurse each month;
- A picture of a woman leaning close to another woman who is pointing to papers, which is intended to illustrate how participants will be counseled and treated;
- A picture showing four different women, smiling and sitting comfortably close together, above another picture of four women in white coats; this is intended to show how the medical/research team will compare the experiences of the different women involved in the study;
- A picture of a medical professional putting a key in a filing cabinet to show how all information collected about each woman is kept confidential;
- A picture of a woman holding up her hand in a “stop” sign to show how one method of prevention is to say “No” to having sex; another illustration shows two hands pulling a condom out of a package.

Other illustrations feature a hand holding a small blood tube to demonstrate how a little blood would be drawn as part of the study, Woodsong says.

“We know from previous work that people are

concerned about how much blood you are taking, so we have the hand holding a blood draw vial so they can see it's a small amount," she explains.

While text explains the same information on each page of the booklet, researchers expect that most women will not read the text, so the illustrations serve as a memory device, as well, Woodsong says.

- **Research subject mascot:** FHI had a graphic designer draw illustrations of a woman, called Serena, who is featured throughout the booklet and shown in various scenes that highlight different parts of the clinical trial process. For each culture in which the trial is conducted, Serena may look a little different, reflecting that culture's typical woman, Woodsong says.

"We pilot-tested the pictures in communities to make sure the illustrations are appropriate for each cultural setting," she explains.

Through the pilot-testing process, investigators discovered that one image of Serena that was slated for the cover of the booklet would not work. In that image, Serena had her hand on her chin, which was intended to suggest she was contemplating joining the study, Woodsong explains.

"I was told if you have your hand on your face, that means something is wrong in the African cultures we were studying," she says. "So we moved that picture to a page about the trial's risks to show she was concerned."

In the U.S.' illustrations, Serena's features have been changed to reflect a multicultural woman who could be a combination of African American, Hispanic, or white race, Woodsong says.

"Serena is of nebulous race because both trials in the U.S. are enrolling blacks, whites, and Hispanics," she explains.

The venues in which Serena is depicted also vary according to where the trial is being held. For instance, for the Philadelphia trial, Serena is shown in a storefront clinic; for African trials, Serena is shown in a marketplace setting, Woodsong says.

- **Additional consent materials:** The informed consent kit includes items that help demonstrate the way the clinical trial intervention works.

Since many of the women in the developing world were unfamiliar with the concept of inserting a tampon or gel into their vaginas, study coordinators use props to demonstrate how the microbicide gel is applied, Woodsong says.

Investigators took a pelvic model and added a plastic vagina to demonstrate how the microbicide gel application device works, she explains.

"This allows the people doing the consent to demonstrate how to do an application, and it's

used during the consent process to allay concerns and fears," Woodsong says. "It's intended to show how the applicator won't hurt you or get lost in the vagina, so there's nothing to fear."

Even in the United States, certain minority groups are unfamiliar with tampon use, so the kit could be used in conjunction with the booklet and its illustrations, which also explain how to insert the applicator, she adds.

The kit also uses flip charts for a table top and other visual aids, Woodsong adds.

- **Fact sheets:** The trial uses fact sheets with information similar to what is on the consent documents to describe aspects of the trial that may be of special interest to male partners of the women participants, she says. The fact sheet designed for husbands is one page, front and back, and it's written in the spirit of "Men, here's what you need to know," Woodsong says. It uses the same illustrations of Serena and includes a male character named Sam, she adds.

At African trial sites, where most of the women participating are married, Sam is portrayed with his arm protectively around Serena; while in the U.S. where the female participants typically are not married, Sam is portrayed casually strolling alongside her, Woodsong says.

Interestingly, although the fact sheets were created in response to feedback from pilot studies in Africa, they also have been popular in the United States, she says.

"At the U.S. sites, women want to hand the men something to read," Woodsong notes. "It's less of an expressed need because women can make their own choice about this; but if they have a steady boyfriend, they often want to give him the fact sheet."

The fact sheets help to alleviate male concerns about how the microbicide might affect the penis when it is exposed to the product, and it's been a gesture of good will in the African communities, Woodsong notes.

"We do a fair amount of social and behavioral work before we start trials, and that's how we learned that you've got to get men involved," she says. "So in a number of country settings, we also developed male informational sessions for a Saturday afternoon when men can come and learn more about the study."

In the microbicide's Phase II trial in New York, investigators have encouraged women to bring their partners to the consent visits so the men also can receive some safety explanations, says Woodsong.

Sometimes men will say that they feel like they need to give consent as well because their penises are going to be exposed to the product, she says.

"Because in Phase II trials we have less safety data than we do for Phase III trials, we feel a little more inclined to go out of our way to answer men's needs for information," Woodson says.

If it's a Phase III trial and men have questions, study coordinators will explain that the product has been tested extensively for safety, and there's nothing to be worried about, she says. ■

## Compliance Corner

### Good documentation helps when FDA knocks on door

*Consequences of noncompliance are serious*

While the FDA's enforcement efforts in the clinical trial industry has not changed much over the years, one reality remains: Many clinical trial site staff and administrators do not fully appreciate the consequences of noncompliance, an FDA enforcement expert says.

"You need to understand the worst-case scenario and what could happen if things went downhill dramatically," says **Michael A. Swit**, JD, vice president, life sciences, at The Weinberg Group Inc., a scientific consulting firm in Washington, DC. Swit often speaks about FDA regulatory and enforcement issues at national conferences, and he is scheduled to give a talk on this topic at the Drug Information Association's 41st Annual Meeting, June 26-30, 2005, in Washington, DC.

Clinical trial staff should understand the criminal penalties and how any serious violations that can be linked to a serious health consequence or a subject's death increase the potential for strong FDA enforcement consequences, he says.

"The FDA has the power to enjoin violations of the law and seize products in violation of the law," Swit reports. "If there's a very serious problem the FDA is aware of then the agency will step in and put a lot of pressure on you to stop the trial."

Another repercussion would be for the FDA to

decide a trial has been done so poorly that its data are unreliable and cannot be included in a published report, Swit says.

This level of enforcement is not common, but it is a potential risk of noncompliance, Swit says.

"The FDA has a number of more informal administrative ways to achieve the agency's objectives," he notes.

Swit provides these examples of enforcement activities and best practice responses:

- **FDA inspection/audit:** The most common is a clinical auditor inspection in which FDA inspectors are specifically trained to look at a clinical trial site's patient records, compliance procedures, inclusion/exclusion criteria, and training of clinical trial staff, he says.

FDA auditors will examine whether the clinical trial site has gone through appropriate IRB procedures with sign-offs before initiating the clinical study, Swit adds.

During the exit interview, the FDA provides the site with a 483 inspection form that lists allegedly violation conditions identified during the audit, Swit says.

"No inspector worth his or her salt comes out without a 483 unless the company is perfect," he says. "And depending on how extensive the 483 is, you might have a situation where you're in substantial compliance with no major worries or maybe have a list with violations they've observed that may or may not require immediate action."

- **Responding to 483:** "The first thing you have to do is to respond to the sectional report," Swit says. "You need to promptly respond in a way that shows you appreciate what the FDA said and are addressing concerns. When you respond to the 483, start off with each observation made," he says.

Then it's appropriate to say how the site has addressed or plans to address the concern or whether the problem noted is not valid.

For instance, clinical trial sites cannot administer study drugs to patients until after the informed consent document has been signed, and to do so before the consent has been signed is a violation, he says.

So if the 483 form notes that drugs were administered before the consent was signed, the clinical site should respond that "Yes, that did occur," Swit says.

"You can't lie in these cases, but try not to admit that you were in violation," he suggests. "Explain that you investigated the incident and

found out how it happened, such as maybe you didn't get the consent signed, but did go through the consent process."

While technically it wasn't done correctly, at least there is an explanation for what happened, Swit adds.

"So put in your response what you have found and how you will address it, including measures you will take to give the FDA assurance that you have taken actions to prevent the violation from occurring again," he says.

"Often if you respond to the 483 aggressively from the standpoint of making sure you're really responding to the FDA's concerns, then that may be the end of it," Swit says. "But if the violations are serious enough, the FDA may think your system problems are so extensive that patient safety is an issue, and then the FDA may issue a warning letter."

Occasionally, the FDA will include a concern that is not valid. Perhaps the FDA has misread something or has based the concern on old information, he notes. You should respond to those charges as well.

• **Warning letters:** Unlike the 483 form, which are available to whoever requests it, but are not made readily available on the FDA's web site, the warning letters are made public, Swit says.

"If you receive a warning letter, the FDA posts that on the web site within a week or two of when it was issued," he says.

Even the 483 forms could have some impact on a clinical trial site's ability to recruit new trials, but typically the FDA will provide the site with an opportunity send in a detailed response, and then will give the site a verbal "OK," Swit says.

"You can try to get some input from the agency that you can communicate to others, but you typically don't receive a formal letter," he explains. "If you get a 483, that's fairly innocuous and you can turn it over to the sponsor and say, 'These are minor issues; here's our response,' and many times it's all right."

However, any responses from the FDA regarding a warning letter is put in writing and will have repercussions, Swit says.

"If you get a warning letter, that changes the public complexion of it," he says. "There have been warning letters issued on occasion that go out before a site has been able to respond to the 483, and that's when the FDA is not happy with what they found."

In other instances, there might have been an inspection that found some problems, and the

warning letter was issued 3½ years later, Swit says.

When there are warning letters, the repercussions can be severe, such as the FDA disqualifying a clinical investigator from doing clinical trials or conditions being placed on how a site can conduct clinical trials, he notes.

• **Responding to warning letter:** "You have to provide a detailed response and make sure the allegations in the warning letter are true," Swit says.

"If you're a very small operation you may have direct knowledge of whether it's true or not, and there may be things that are not accurate," he adds. "Particularly if there's a delay between the inspection and the warning letter, you may have corrected the violation."

It's important to send the FDA a carefully worded but comprehensive response that addresses each one of the matters raised in the warning letter thoroughly and appropriately, Swit says.

"Many times what people will do is bring in an outside consultant and law firm to help them address the issues and to work with them to make sure the necessary procedures are put into place," he explains.

Clinical trial administrators also can request to meet with the FDA to discuss the situation, Swit notes.

• **Preventing enforcement problems:** "What I say to any institution regulated by the FDA is the mnemonic: Please Teach Risk Avoidance," he explains. "The 'P' stands for procedures that are designed to address FDA compliance," Swit says.

"The 'T' is for training employees on those procedures; the 'R' is for recording the results because procedures and training don't do any good if you don't have good records that are designed well and are faithfully used."

Often when there's a failure to record a significant action, it's because a site might have the best procedures in place but lack good record keeping, he notes. "If it's not written down, it didn't happen, and the procedure won't defend you from a violation," Swit adds.

And the "A" stands for audit, meaning clinical trial sites should conduct their own audits to make certain they are following the best procedures and record keeping, he says.

"If you don't occasionally audit and make sure all the stuff is being done, you could begin to be out of compliance," Swit says.

Small mistakes sometimes can lead to a worst-case scenario in which a subject dies because

someone wasn't paying enough attention during the inclusion/exclusion process and didn't document a subject's hypertension, which should have excluded the person from the trial, he says.

"Remember one significant issue: Good clinical practice is an evolving standard," Swit says. "What exists in the FDA regulations is the minimum standard, and the FDA also has a guidance document that goes into more detail about how we expect people to implement various requirements in the regulations." ■



## Health officials testify before House committee

Pandemic flu preparations already are under way, said government health officials who testified in mid-April before a congressional subcommittee.

"The threat of a pandemic is now felt to be greater than it has in decades," said **Bruce Gellin**, the director of the national vaccine program at the Department of Health and Human Services. "This is in large part because of the highly pathogenic bird flu, an influenza virus classified as H5N1, which is established and endemic in many different species of birds across Asia."

Most alarmingly, researchers have established that the same strain has crossed into 74 people in the past year, killing two-thirds. And those figures "probably represent the tip of the iceberg," said **Julie Gerberding**, head of CDC, who also sat before the House Subcommittee on Labor, Health and Human Services, Education and Related Agencies.

In an effort to head off that danger, testing of vaccines and antiviral therapies is in progress

under the watch of the National Institute of Allergy and Infectious Diseases. Its director, **Anthony Fauci**, told the subcommittee that initial clinical testing of an H5N1 vaccine produced by Sanofi-Pasteur is under way, and that the Swiftwater, PA-based company is under contract to produce 2 million doses of the product.

Other clinical trials of the same vaccine will be held later this year, and simultaneous research on three attenuated H5N1 vaccine strains is being conducted, as are studies on an attenuated vaccine strain of H9N2, another avian virus that has jumped into humans.

Also, since the antiviral drug Tamiflu (oseltamivir, from F. Hoffmann-La Roche Ltd.) is effective against H5N1, the federal government has stockpiled 2.3 million units. In its budget request for the coming fiscal year, HHS requested an additional \$120 million to support its pandemic preparedness activities, such as ensuring a year-round supply of chicken eggs to provide for a secure vaccine supply and shifting manufacturing to cell culture technologies.

Concurrent with those actions, Gerberding stressed the importance of international cooperation.

Although the gathering focused primarily on pandemic flu preparations, members of the subcommittee, part of the House Committee on Appropriations, also quizzed the public health trio on preparations for the coming flu season. Concerns were raised about a lack of domestic manufacturing.

An underlying concern of the subcommittee was directed at last year's flu vaccine shortage, which Gerberding addressed by saying that the myriad government health agencies are preparing for all scenarios connected with the challenges associated with annual flu vaccine manufacturing.

"We are not going to assume anything about the supply," she noted, adding that despite manufacturers' optimistic outlook to date, plans are in place to initially provide vaccines to those most in need. "The priority for us, as a health protection agency, is to get vaccines to those who need it most," she said. ■

### COMING IN FUTURE MONTHS

■ Develop airtight noncompliance policy

■ Here are best practices in protocol deviation reports

■ Make the best use of time in investigator meetings

■ Improve informed consent training

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## CE/CME questions

17. Benefits of Pediatric Pharmacology Research Units (PPRU) include which of the following?
  - A. Increases collaboration of pediatric pharmacology investigators around the country.
  - B. Encourages translational research projects.
  - C. Improves the scientific knowledge of how various drugs work in children.
  - D. All of the above.
  
18. Which of the following is not one of the alternative and creative informed consent strategy that has been employed by investigators providing informed consent during HIV prevention trials conducted internationally and in the United States?
  - A. Using drawings of a mascot woman to illustrate a booklet that details the clinical trial and informed consent.
  - B. Asking male partners of the female participants to sign the informed consent and initial each page.
  - C. Using an informed consent kit that includes a pelvic model for demonstration of the insertion of the microbicide applicator.
  - D. Providing fact sheets about the clinical trial that can be distributed to husbands and lovers of the women participants.
  
19. When the Food and Drug Administration conducts an audit and sends a site a 483 form, what is the best way to respond?
  - A. Start off with each observation made and say how the site has addressed or plans to address the concern or whether the problem noted is not valid.
  - B. Send a certified letter to the FDA audit division, noting all extenuating circumstances that may have contributed to the citations listed in the 483 form.
  - C. Call the auditor to discuss the 483 and to find out what should be the next course of action by the site.
  - D. None of the above.
  
20. It a violation of federal regulations for clinical trial sites to administer study drugs to patients before the informed consent document has been signed.
  - A. True
  - B. False

**Answers: 17-D; 18-B; 19-A; 20-A.**

## CE/CME instructions/objectives

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.

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. ■