CLINICAL TRIALS
ADMINISTRATOR
An essential resource for managers of clinical trials

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JULY 2004
VOL. 2, NO. 7 • (pages 73-84)

Two trials prove that recruiting women isn't as difficult as it sometimes seems

Simply asking goes a long way, advocates say

More than a decade after the National Institutes of Health (NIH) issued guidelines encouraging the inclusion of women as subjects in clinical research, they still are not fully represented in clinical trials that determine which drugs and treatments get marketed in this country.

Although progress is being made, advocates say, women still have a lot of catching up to do after decades of historical, cultural, and legal barriers that excluded them from both the benefits and risks of participation in medical research.

In fact, until 1993, regulations by the Food and Drug Administration prohibited the inclusion of women of childbearing age as subjects in early clinical trials. In the decade since those regulations were changed and the restriction removed, more women have been included, but we are just starting to see the results, says **Sherry Marts**, PhD, vice president for scientific affairs for the Society for Women's Health Research, a Washington, DC-based nonprofit that encourages the inclusion of women as research participants and research into gender-linked differences in health and medicine.

"Even though the guidelines changed in 1993, it's been like turning a battleship," she explains. "You have to consider trial design and finding ways to recruit and retain women into studies — that took a few years. It is really only in the last few years that some of the data are starting to emerge. That shows you how long it takes to change the system. Data that you collect today will be in front of the FDA in 10 years."

Though more women are being recruited and are participating in clinical trials, there is little evidence that researchers are examining the data to look for any differences in response that might be linked to gender, Marts says.

"That is sort of the follow-up issue to inclusion," she notes. "What's the point if you are not going to at least look to see if there is a difference?"

Historically, women were excluded from participation as research subjects because of the risk untested agents posed to their future

children, says **Georgia Sadler**, MBA, PhD, clinical professor of surgery in the Cancer Prevention and Control Program at the University of California-San Diego and director of the center's community outreach program. Even today,

Clinical Trials Administrator (ISSN# 1544-8460) is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to **Clinical Trials Administrator**, P.O. Box 740059, Atlanta, GA 30374.

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This publication does not receive financial support.

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Subscription rates: U.S.A., one year (12 issues), $349. With CME: $349. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. **Back issues**, when available, are $58 each. (GST registration number R128870672.)

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Editorial Questions

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investigators must take painstaking steps to ensure that participants are not pregnant when a trial starts and understand the importance of not becoming pregnant during the course of the trial.

"There is always the concern about doing harm; you want to weigh the risks and benefits," Sadler says. "You want more benefit than risk — that is the goal, especially when there could be another person involved, namely the child."

Prior to the change in regulation, women of "childbearing potential" — those who had not yet reached menopause or not undergone a sterilization procedure — were excluded from early trials of drugs that had not been tested for teratogenicity (the potential to cause birth defects).

Exceptions were made in instances in which a patient had a life-threatening condition and no other source of treatment was available, Marts adds.

"It meant that there were some women in cancer clinical trials, but it did keep them out of trials of most drugs and it certainly kept them out of the early phase trials," she says.

The male norm

And for a long time in medical circles, it was assumed that what worked in men would work — and work in the same way — for women and vice versa; drugs not proven effective in male subjects were assumed to have no value.

"For a long time in medicine, we had this thing called the male norm," Marts continues. "I say this in my talks, and it always gets a laugh, but it is true. It was just assumed that the male was normal and women were just small men with different plumbing and a hormone problem. Come to find out, we are not. Our biologies are very different and that has an impact on our health."

Recent experience has borne this out.

For example, the only two drugs currently marketed specifically to treat irritable bowel syndrome seem to be more effective in women. And there are drugs that are known to be metabolized differently in men and women.

"There are some drugs that women break down faster than men, so they may need a higher dose or more frequent dosing, and there are some where it is the other way around," Marts says. "It is very challenging to kind of break the data out and figure out exactly what is going on."

Pharmaceutical manufacturers have an understandable disincentive to discovering the need for different doses for different populations, she adds.

It is great if one dose works for everyone, but that's not always the case.

Although more women are being included in clinical trials, there is some residual perception that trials are easier with men as subjects.

"We understand perfectly that manufacturers have a profit disincentive to doing this because if they look for a difference and they find one, then they are going to have to label the drug as say, 'These people should take it,' or 'These people should not,'" she says. "When you're Drug Company X looking for the next blockbuster everybody's-gonna-take-this drug, then you have some advocacy group come along and say, 'But does this work differently in women than in men?' It is sort of like the reaction we get is, 'We don't want to know.'"

Recruiting and retaining female subjects

There still is the issue of the risk to a female subject who is in the early stages of pregnancy but does not know it, or, equally dangerous, who becomes pregnant during the course of the trial.

Both Sadler and Marts say this potential complication is overblown in the minds of some researchers.

"You can ask a woman, 'Is there any chance you might become pregnant?' By definition that means, 'Have you missed your period?" says Sadler. "Once you have determined that she is not pregnant right now, the next question would be, 'Are you trying to get pregnant or do you have any plans to get pregnant?' If you have someone who says they are, then you could exclude them because of the potential to do more harm than good."

The riskier the product being tested, the more solid assurance the investigators will want that subjects are not going to become pregnant, she continues. "If you are doing things that are relatively safe, you might say, 'Well, being on birth control is probably adequate; but if you are testing a new drug for the first time in humans and it was highly toxic in animal models, you might say that unless the person has had her tubes tied or some other procedure, you might not want to take the chance."

It is also important, during the informed consent process, to emphasize this risk, emphasize the importance of not becoming pregnant and — should an unplanned pregnancy occur — that the investigators need to be notified immediately.

"It can happen, and that is when you need really good vigilance on the part of your research team," Sadler says. "What happens next is unique to every single trial. Every single investigator would be in close contact with the manufacturer of the drug and use his or her judgment about whether there are benefits to keeping her on the drug and whether the benefits outweighed the risks to the fetus."

Even with the change in the guidelines and attempts by many investigators to recruit female participants, women are not exactly knocking down clinic doors to get into trials.

Almost any conference involving research professionals will feature a session on recruiting women and minorities — and usually, it's a single session titled, "Recruiting Women and Minorities," as if they were one population, Marts notes.

"You still tend to hear investigators say, 'Oh, but it is so hard to recruit and retain women," she says. "I always ask them, first of all, 'Are you listening to your site staff?' Maybe they have some ideas about how to do this better."

Recent examples offer insight

There are some recent examples of large-scale clinical trials involving women and other populations thought difficult to recruit that can provide helpful lessons about how to recruit and retain study subjects.

The first, says Marts, is the Women's Health Initiative, which recruited many older women and followed them for several years.

"People said it could never be done; you could never recruit that many older women and keep them in the trial," she says. "But, as we know, they did."

Other examples can be found in the HIV prevention trials that involve women who are either drug users, partners of drug users, or professional sex workers.

There are some study sites that have had 98% retention rates over two-year periods with these populations, Marts says. The sites developed unique ways of maintaining contact with these women, even though the subjects may have moved frequently, sometimes in and out of homeless shelters, or work in dangerous and illegal conditions — not exactly conducive to regular follow-up visits.

"What they are finding is that it takes more than just herding people into the clinic, performing the visit, writing the next appointment on a notecard, patting them on the head, and sending them out," Marts says.

Became women typically shoulder the lion's share of responsibility for child care and household

maintenance, clinics that offer weekend and evening hours and those that combine multiple services (blood draws, X-rays, other monitoring) at a single visit are often more amenable to female participants, she says.

They also may be concerned about the safety of the clinic's location and whether security is provided.

Obviously, this is not a sole concern for female participants, Marts adds, and researchers may find that concessions they make to attract female participants may recruit more participants overall, too.

Did you ask?

Working on a contract with one of the HIV vaccine trials, Marts helped produce a video featuring the subjects talking about the benefits of participating in the study.

"There was one interview with a drug addict — who, in this instance, happened to be a man — and the interviewer asked, 'Why are you doing this? Why agree to be in the trial?' The guy looks at her and says, "Lady, I am a junkie. No one has ever asked me for nothing. These people came, and they asked me to do something for other people, and how could I say no?'"

Because clinical trials have, in the past, focused exclusively on men, it's possible that many women simply don't recognize this as something that is possible for them — they don't realize they would be able to contribute, Marts says.

"It is sort of a truism in the not-for-profit world that people don't volunteer unless they are asked. One of the things that occurred to us early on after they changed the guidelines was that half the population had been reading about medical research and seeing reports in the news and it was always about men," she relates. "Heart disease in men, men should take aspirin, etc. We imagined that women simply don't feel asked. They don't feel welcome to participate in these studies."

To help remedy that problem, the society initiated its "Some Things Only a Woman Can Do" campaign, which included a web site, brochures, and other educational materials that encourage women to consider participating in clinical trials.

"It emphasizes that you don't necessarily have to have a disease or condition to participate and women are really intrigued to find this out," she says.

Conducting clinical research on essentially one population — white men — has handicapped medical research in a number of ways. Clinical trials that include diverse groups of people can yield better information faster, says Sadler, whose research focuses on improving recruitment of both women and minorities.

"It is important, for example, to have women of childbearing age represented in clinical trials. Let's say you are looking at blood pressure medication for hypertension; you would not want to exclude women between the ages of 18 and 50 — that is a large segment of the population that will eventually take this medication," she says. "Would you want them to take it without it ever having been tested in that population? That is essentially what happens now. If you have a study and you don't have a large enough representation of African-Americans, Hispanics, or Asians, it is the same thing."

The issues go beyond just genetics and gender, she continues. For example, say a particular drug does really well in subjects who are Asian women, but none of the other participants. Researchers would then look to see why. Perhaps it is something in the diet that these women all had that enhances the drug's efficacy? Once that is determined, that information could be included in the drug's labeling.

Conversely, say a certain group does poorly in a trial. For example, all of the Hispanic men don't respond. Perhaps there is a reason there. Once the likely cause is found, then researchers can recommend a possible solution.

However, if these people are never represented in clinical trials, this information is likely to never be found. Say the drug that worked so well for Asian women is only tested in groups of Caucasian men. It is found to not work well and is dropped, without researchers ever knowing its true potential.

Or a drug that has significant complications for people with certain dietary habits or genetic differences makes it to market. Patients who do not respond to the drug, or worse, experience a poor reaction, are rarely noted.

Outside a clinical trial, Sadler says, individual complications or adverse events are too far apart for their significance to be noted.

"One of the reasons we spend so much time educating health professionals and the public is to try to help communities to understand that no participation is really no voice," Sadler says. "So, someone has to step up to the plate. Obviously, we are not saying everyone should do everything, but keep your eyes and ears open and don't have a knee-jerk negative response." ■

In-process QA soon may be standard for research

Here comes PAT

In a never-ending quest to make clinical trials safe for participants and learn from unfortunate incidents that may have occurred during a clinical trial, the Food and Drug Administration is not only scrutinizing corrective and preventive action plans (CAPA), but also looking outside of health care for effective quality assurance processes.

Specifically, the FDA is interested in the concept of process analytical technology (PAT) in which there is a continuous quality assurance check throughout the clinical trials process, rather than saving this check for the end of the process.

Currently, the FDA web site lists a definition for PAT as follows: a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

"Through PAT you are looking all along at which process can be more cost effective and safer," says **Sandy Weinberg**, PhD, senior director of Fast Trak GE Healthcare in Atlanta. "Then you know it's safe and the final check is a confirmation."

The FDA is expected to complete a final draft of guidelines for PAT within a year or two, he notes.

"Anyone who is FDA-regulated ultimately should look to see whether it's applicable," Weinberg says. "The first place it will be applied is with the manufacturers; secondly, the labs and, third, clinical trials."

Improving risk analysis

Besides adopting PAT, clinical trials managers also may improve process quality through improving their risk analysis process.

"There are two ways of thinking about risk methodologies and using risk control to improve quality, costs, and to improve regulatory compliance and regulations," says **Victoria V. Lander**, market development manager for NuGenesis Technologies of Westborough, MA.

"People use the terms risk analysis and management interchangeably, but they're not the same thing," she says. "Risk analysis is the overall process of stepping out and thinking — whether in clinical trials, manufacturing, or quality control — and figuring out the risks or hazards that could or do occur."

According to the FDA, CAPA procedures consists of these basic steps:

- Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data.
- Investigating the cause of nonconformities relating to product, processes, and the quality system.
- Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.
- Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.
- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
- Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

Tips for improvement

Lander and Weinberg offer these strategies for improving CAPAs and PATs:

- **Document risk assessment.** A documented risk assessment and risk analysis should show how each critical system fits into the overall picture, Lander explains.

For example, for a 21 CFR Part 11 compliance, the idea is to make certain all electronic records and signatures are reliable and legally defensible, she says.

"Put different controls in place," Lander adds. "Some are stringent and require major system revisions."

However, if a clinical trials manager has decided that a particular system or process is low risk, then it's unnecessary to go through the extensive process of replacing the system, she says.

"You might put procedural controls in place — something not as expensive and resource-consuming," Lander says.

Then when the FDA conducts an audit, it's crucial to have a documented risk assessment that justifies the actions taken to control the risks in that particular system, she says.

• **Develop a cost-effective strategy for processes.** "The FDA's new focus is on making sure there's a cost-effective strategy for any regulation," Weinberg says.

Many pharmaceutical manufacturers already follow this strategy for their manufacturing process, but it's not always employed in the clinical trials process, he says.

"Every once in a while you hear in the news that a trial is halted because the results are so dramatic, and that's what we're talking about — make adjustments as you go along," Weinberg says.

"This is a codification of good policy," he says.

• **Write standard operating procedures.** The first thing to do to either create or improve a CAPA is to write standard operating procedure (SOP) guidelines for how to proceed with each step of the process, Lander suggests.

"A lot of companies create risk management files and put in the results of everything they do and then assign a risk index, a probability of occurrence, and severity of consequences," she says. "So they're ultimately assigning value to every system: high, medium, low, or a numbering system."

For guidance on writing SOPs, review published risk management protocols in and outside of the clinical trial world, Lander says.

Also, it's a good strategy to form a cross-functional team, consisting of a quality manager in a contract research organization, a professional skilled in regulatory issues, and others, to decide which type of risk management protocol will be put in place, she says.

There are many different types of protocols that could be reviewed, including ones used in the aerospace industry, the military, the food industry, and others, Lander adds.

Some examples include the failure mode effects and criticality analysis, which is from the aerospace industry, and the hazard analysis and critical control points from the food industry, she notes.

"Look at the protocols, and if you like them adopt them wholeheartedly," Lander says.

• **Don't overlook the simplest approach: training.** One of the simplest ways to manage risk is to make certain clinical trials staff are well trained, she says.

"Think about the fact that people who are running these trials need the background and experience to do it," Lander says. "One of the simplest ways to control risks is to make sure the key personnel have the right background and are trained and then document the training."

In short, the risk management process might be reduced to these steps: make certain people understand the process, monitor their progress, standardize the approach, train people, identify the right tool for the right job, and validate the equipment, she summarizes.

"That's the basic structure for a quality plan," Lander adds.

• **Be proactive with instituting PAT.** "Too often in our industry, we become reactive instead of proactive," Weinberg says. "Nothing hits the radar screen until the FDA announces it, and then we are surprised."

But in the case of PAT, clinical trials managers have an opportunity to be proactive. They have two or more years to prepare for the inevitability of putting PAT in place, he adds.

"I think PAT is a logical approach, and it's often used in our industry without that name, and it is an appropriate way to produce critical research in a cost-effective way," Weinberg says. "The whole industry is gearing now to understand that cost is an important factor.

"We used to be a cost-plus industry where we cared about quality and whatever it cost we would spend," he says. "Now we need to maintain the quality and at the same time use cost control measures to make sure we are at a place where people can afford the kinds of products our quality produces." ■

Think of 21 CFR Part 11 as a business issue

An expert advises how to best comply

Slipping away are the days of pen-and-paper record keeping. Here to stay are electronic records and electronic signatures

"In 2004, technology plays a huge role — you can't exist without a computer system anymore, so you employ automated systems to process data, payroll information, etc.," says **Leonard Grunbaum**, president of META Solutions of Warren, NJ. META Solutions provides regulatory consulting services for the pharmaceutical and

related industries, and Grunbaum speaks at professional conferences about the regulations governing electronic data collection.

The 21 CFR Part 11 provides the control objectives that must be met when clinical trials data are collected in an electronic format, Grunbaum says.

He advises clinical trials managers and investigators to consider the electronic processes the same way they consider designing protocols and methods by asking these sorts of questions:

- How do we do this?
- What do we write in the plan?
- What process or system do we use?
- How does this process meet our needs?
- What are we hoping to show and how do we show it?
- How do we test the system?
- Is the system tired, true, and tested?

The 21 CFR Part 11 is chiefly concerned with allowing FDA to trust and rely upon the information collected.

"Part of what you need to do regardless of whether you have paper-based or an electronic system is to check records and make certain they are safely stored and have backup systems," says Grunbaum.

"With a computer system, what's different is that you have to make sure people can't get into a computer system, steal the data, or that it won't be corrupted or lost," he says. "Firewalls and those kinds of concepts are the means whereby you can protect your records with an electronic system."

Another aspect of 21 CFR Part 11 involves electronic signatures, which must be designed in such a way that they cannot easily be forged, Grunbaum says.

Electronic signatures could be protected through identifications and passwords or through biometrics and thumbprints, he says.

"There should be controls in place to make sure no other person has your password," Grunbaum says. "When a form or document is generated, it says this was signed electronically by XX on this date, and this signature means XX approved it as reviewed — so there's meaning to the signature."

Six basic requirements

Grunbaum explains the basic requirements of the regulations under Part 11 this way:

1. There must be an ability to generate accurate and complete copies of records. "The purpose here is that when the inspector comes in, he or she needs to be able to touch and feel the data; just because you can see the data on a screen doesn't mean the data exist," he explains.

The Food and Drug Administration will need to confirm that there are accurate and complete copies in readable form, Grunbaum adds.

"Any system you employ should be designed so that any and all records can be copied," he says. "There need to be accurate and complete copies because the way systems are designed, sometimes you don't get all of the related information, such as meta-data, explanations of codes, and dictionaries."

The copies may be obtained electronically or in printouts, and the system needs to be tested to make certain the copies can be obtained, Grunbaum adds.

"Any system built for regulatory purposes should be done according to a formal methodology, meaning that you know exactly what the system is supposed to do, see how it's designed, how it's tested," Grunbaum says. "The testing should be done in your own environment to make sure it meets all requirements."

2. Protect records. Computer firewalls and similar systems should protect the electronic system from unauthorized access into the network, he says.

Another aspect is physical security, making certain people can't walk into a computer room and access data or walk off with a laptop computer, Grunbaum says.

"Deal with the physical security first, making sure computers are secure and can't be tampered with, can't be destroyed or stolen," he explains. "And then deal with logical security, which is the identification information, passwords, so not everyone has access to the system."

3. Generate systems controls. "When you build a system to do certain things, you build in certain controls," Grunbaum says. "For example, if you have a double data entry process, you can't allow a second entry before you have a first entry."

Also, it's a good idea to have edit checks for the purpose of eliminating bad or invalid data, he notes.

"Build those kinds of things to maximize getting valid data and minimize getting invalid data," Grunbaum says. "Make sure that these functions are specified as requirements and then build or buy to these requirements."

4. Validate the process. "People get hung up on the term 'validation,' when validation is simply providing evidence that a system is doing what it's supposed to do and that it will continue

to do it," he explains. "Part of what you need to be able to show if someone wants to rely on your information is that this is your process; this is how you get information; this is how you rely on it and then provide evidence that it works."

This is good business practice, even though the clinical regulations do not spell it out this clearly, Grunbaum says.

When a clinical trial manager or investigator validates the process, he or she is providing evidence that the system works, he says.

"When you develop and test the system the evidence is available for inspection, and if an inspector comes in from a potential sponsor or the FDA or business partner, the evidence can be viewed," Grunbaum adds.

Sometimes companies will decide to save money and they won't test their systems adequately in the beginning, he says.

"What happens then is they don't work sometimes, and the company has to go back and redo the system or redo the studies," Grunbaum says. "We knew of one company who had seven different systems, a clinical trials system, a system to capture lab information, a system that did statistical analysis, and others, and they didn't validate any of it, and they couldn't use the information and had to start a remediation effort that cost over a million dollars."

5. Provide an audit trail. "This allows you to reconstruct any part of your study process," he says. "Almost every regulation requires that you show what happened, when it happened, who did what, and whether anything was changed and who changed it and why it was changed."

The audit trail makes it possible to go back and figure out what happened throughout any aspect of the study, Grunbaum notes.

"The system should be designed to collect it as a by-product," he says. "Just put in a subject with data and then go back and make changes without erasing the original record."

By the end of study, there undoubtedly will be a massive amount of data that include the audit trail of any changes, Grunbaum adds.

6. Train personnel. "Every regulation will talk about people being qualified to do their assigned activities," Grunbaum says. "What Part 11 does is say specifically that people who develop and maintain systems need to have the training."

So anyone who is developing or maintaining a computer system needs to be trained to do so, he adds.

"You have to verify the fact that the vendor has training and qualifications to develop and maintain the system," Grunbaum explains. "You need to know the activity, and you need to know who is doing it on the organizational chart and what the person's job description is and match against the person's curriculum vitae and training records." ■

An oversight process can improve quality

An expert explains how to do this

Investigators and physicians may be experts on research and medicine, but it's up to the research compliance staff and the clinical trial managers to be experts in the interpretation and application of regulations governing clinical research.

This is one reason some institutions have begun to focus on quality improvement and in-house monitoring of clinical trials.

"When we first set up the research compliance monitoring office, the charge was to go forth and monitor," says **Deborah Waltz**, MS, CIP, director of the Research Compliance and Quality Improvement Office for Human Research at the University of Pennsylvania School of Medicine in Philadelphia.

It's not enough to rely on federal monitoring and peer reviews of federally funded research if the goal is to prevent major problems, she notes.

For instance, the National Institutes of Health (NIH) might send a group of oncologists out to review research conducted by other oncologists, Waltz explains.

"Political dynamics and personal relationships come into play," she says. "There's a code of behavior and conduct in the medical field where physicians are very reluctant to criticize fellow physicians."

While these peer reviewers may catch some important mistakes and will evaluate adverse events, this still isn't as detailed a review as it could be, Waltz adds.

"Don't confuse a physician medical review with source data verification and review for research compliance and protocol adherence," she explains.

"In general, peer review and/or medical monitoring is not going to identify potentially important compliance gaps because there is a different focus in the review itself," Waltz says. "This doesn't mean that someone's wrong and someone's right; they are just different disciplines with different focus."

Therefore, it's a good idea for institutions and clinical trials managers to establish their own monitoring and compliance program, which also could serve as a vehicle for educating clinical trials staff and investigators, Waltz says.

The numbers tell a story

Waltz offers these suggestions for what to include in such a monitoring program:

• **Establish a risk rating standard.** At the University of Pennsylvania, all centers agreed to a standard for rating risk. They agreed on a rating system that included minimal risk, low risk, moderate risk, and high risk, Waltz says.

"It took an extraordinary effort to get the centers to agree on the language," she adds.

Now, when an investigator proposes what he or she thinks is the risk and the IRB agrees with this, it is entered into a database where the study is stratified according to its risk rating, Waltz explains.

"Being able to stratify research according to risk levels is a powerful tool when trying to maximize the impact of your monitoring program because it allows you to use a risk base strategy in allocating monitoring resources," Waltz says.

• **Add another level for review for IND studies.** "We also review another element of risk if our investigator is conducting an investigator-initiated trial where he is an IND holder," she says.

"What we have them declare is who is the regulatory sponsor," Waltz says. "What we found to be a problem in many institutions is that investigators didn't understand the difference between a regulatory sponsor and a funding sponsor."

In other words, investigators sometimes would erroneously believe that the NIH was the regulatory sponsor, when in fact the NIH frequently is only the funding sponsor, and the investigator is expected to fulfill the responsibility of the regulator sponsor, she explains.

"Since the regulatory sponsor of the trial is responsible for ensuring that the trial is conducted in compliance with the protocol and the regulations, if there is not clear understanding — right up front — about where this responsibility for regulatory sponsorship resides, then there is a much greater risk of compliance issues," Waltz says. "It comes down to a matter of ensuring that someone has taken ownership of the regulatory compliance of the trial.

"From the institution's perspective, it can be a matter of 'Who's the one who's going to be on the headline in the newspaper if you make a mistake? Who's in control of the study?'" she adds.

• **Assess how much research an investigator is conducting.** One facet of the monitoring process focuses on the investigator's combined work, including assessing how many protocols the investigator has and what the enrollment is for these protocols, Waltz says.

"We have encountered investigators with more than 50 studies," she notes. "That's something we certainly want to take a closer look at."

There may be a reasonable explanation: for example, the investigator may be simply doing blood draw studies, or there may be a number of substudies under one large protocol, Waltz says.

It may be a situation where only two or three are actively enrolling subjects, she notes.

"But it also may be a symptom of an investigator who doesn't know how to close out a study," Waltz adds. "Within every institution, you will find a couple of well-intentioned investigators who simply submit zero enrollment to the IRB every year because they don't have the time, resources, or understanding of the regulatory requirements to properly close out a study.

"When you see those things, you want to look closely because that's a huge risk to have one investigator exposed to that kind of volume of research and patients, unless as an institution you can be sure that he has the proper support system and infrastructure to properly manage it," she says.

"It comes down to a matter of exposure," Waltz says. "Some diseases are so rare that you might find one patient on each of 50 protocols; is that OK? I don't know; it might be, but it really depends on a number of variables — the point is that we certainly need to take closer look at this."

Look out for noncompliance

• **Watch for conflicts of interest.** Reviewers will follow the conflict of interest committee's recommendations for managing conflicts of interest, and they'll make certain conflicts are managed according to the recommendations, she says.

"If an investigator is a patent holder, and the conflicts of interest committee has recommended they not be directly involved in the research, then we'll go in and make sure that it's actually happening," Waltz says.

• **Monitor local compliance units.** For example, suppose an institution has a cancer center with its own compliance program and local monitoring program, then the key is to evaluate the local monitoring programs as a way to extend the

office and to push oversight to the local level, she says.

"When we have investigators processing or manufacturing any of the components of what's being delivered to the patient, including the blinding of the study drug, then we need to make sure the manufacturing has appropriate controls and standards in place," Waltz says. "We also need to be sure the investigational pharmacy has adequate controls and standards in place if they are managing aspects of the blinding or randomization for the study."

• **Look for triggers of other areas of noncompliance.** For instance, if an IRB sees something amiss with the documentation supplied by an investigator to the IRB for either initial approval or continuing review, then the IRB will turn it over to the monitoring office for review, she says.

"If an investigator had a total enrollment of 210 patients last year and on this year's continuing review there are only 180 patients, then that's a problem," Waltz explains. "IRBs have become more sophisticated and have raised the bar."

IRBs now expect the investigator to submit accurate and complete information or they are not going to grant approval, she notes.

"At the risk of oversimplifying this, it is obvious that someone isn't paying careful attention to the IRB paperwork, naturally you should be curious about what other aspects of the research might be suffering from lack of careful attention," Waltz says.

What's next?

• **Have a plan for dealing with what you find.** For many institutions, implementing an oversight process and quality improvement program amounts to changing standards and expectations around clinical research.

The trouble is that if you raise the bar, then you have to be prepared to deal with the people who are under the bar, Waltz adds.

"One of the first things we did was develop protocols for the management of compliance or serious noncompliance," she explains. "We established what is serious noncompliance and what is important noncompliance that requires serious oversight."

Having policies like this in place ensures the fair and consistent management of compliance issues, Waltz says.

It also lets investigators know ahead of time that the institution takes compliance issues seriously, and if an investigator is the subject of some compliance remediation, the investigator doesn't feel as though he or she is being singled out or treated unfairly, she adds.

• **Note the experience of clinical trials staff and other items.** "We look at the staff assigned to a project and their level of experience," Waltz says. "We look at things such as compliance with reporting adverse events to the IRB, the phase of the research and the IND status of the research."

Reviewers also assess protocol performance, rate of accrual, study design, and number of centers involved, she says.

"It raises the risk level if it's a multicenter trial," Waltz notes. "We also look to see if it has a vulnerable patient population and if there have been previous government inspections or previous inspections from other sources."

• **Follow investigators closely if they've had past problems:** Past performance is considered, and if an investigator has been found to be in need of important improvements in the clinical trials process, then reviewers will monitor that investigator closely to ensure sustained compliance, she says.

"Depending on the nature of specific needs, we may customize the follow-up monitoring, including monitoring of the consent process," Waltz explains. "We evaluate whether they comply with inclusion criteria and whether informed consent of the patients was properly obtained."

Reviewers will return at various intervals to verify the accuracy of the data and case report forms and to make certain source records and data are collected in compliance with the protocol, she says.

"In starting our program, one thing we found was that investigators didn't have case report forms in a lot of cases, and then we found that if they did have them they'd wait very long to fill them out — not just weeks, but months or even longer," Waltz says. "Investigators are generally well intentioned: they always meant to fill them out, but never got around to it."

This is where investigators can be educated about regulations, compliance, and documentation.

In general, the investigators have come to understand the importance of compliance and the benefit to both in terms of human subject protections and data integrity, Waltz says.

One important aspect of a sound compliance and quality improvement program is that when compliance problems are encountered, the program should provide the strategy, education, and

resources to help the investigator achieve sustained compliance, he notes.

"We try to make sure the investigators we've worked with are model citizens in terms of data collection, data organization, and understanding what it takes to conduct a study," Waltz says. "These are the people we want to have go out and mentor up-and-coming physicians." ■

Petition for stem cell policy change circulated

A bipartisan group of 206 members of Congress asked President Bush via a petition to rethink the embryonic stem cell policy that is being blamed for damaging cutting-edge research in the United States.

Reps. Diana DeGette (D-CO), Randy Cunningham (R-CA), Michael Castle (R-DE), and Calvin Dooley (D-CA) led the effort.

At issue is the president's policy limiting federal funding for stem cell research to 78 lines that were available Aug. 9, 2001, the day Bush announced his decision on the subject. (Originally Bush cleared 64 lines; the other 14 were added to the count some months later.) In the years since the policy was implemented, many scientists have complained that some lines are not viable or accessible.

In a prepared statement, the Washington-based Coalition for the Advancement of Medical Research said the lines that qualify for federal funding are not genetically or racially diverse enough to meet research needs.

Furthermore, it might be impossible to develop future therapies with the current lines, since cell lines cultivated in the past were exposed to mouse feeder cells, and might not be acceptable under federal regulations on biological materials drawn from more than one species.

Many scientists argue that therapeutic cloning applications could lead to revolutionary therapies for Alzheimer's disease, Parkinson's disease, spinal cord injuries, diabetes, heart disease, and other debilitating conditions. Others say there are alternative approaches and therapies that eliminate the need for human embryonic stem cell research. ▼

Stem cell research moving forward

An upcoming ballot initiative in California may pave a path for that state's scientists to better direct their stem cell research.

A proposal to allocate $3 billion over 10 years to such research will go before voters in November. If it passes, the bond-backed bill could circumvent current federal limitations on the use of human embryonic stem cells.

Such studies remain limited by government regulations on the number of cell lines currently available for research in the United States. At present, 19 federally sanctioned lines are offered, a figure critics point to as a hindrance to furthering research. ▼

FDA initiative seeks to speed up approvals

Pressure from Congress and the public to gain access to more efficacious, less expensive drugs and biologics has caused the Food and Drug Administration to rethink its role in the drug development process.

Earlier this year, the agency introduced the critical path initiative, a project to create a new generation of performance standards and predictive tools aimed at providing better and quicker results on safety and effectiveness of investigational products.

FDA officials over the last several months have taken the podium at conferences in Washington looking to sell the plan as a positive step for drug companies and recently kicked off its campaign, "The Critical Path, From Concept to Consumer."

Each year, new guidance on different diseases or indications will be issued under the critical care

COMING IN FUTURE MONTHS

- Ins and outs of emergency department research
- Cultural sensitivity in clinical trials
- Informed consent for opinion surveys
- Recruiting under-represented populations

initiative. For example, if an obesity drug were the subject of a critical path, the FDA would provide descriptive guidance about what is expected in the clinical and regulatory process from concept to bedside. Also, the FDA expects to provide scientists, investors, and companies with information on the types of diseases needing new treatments and on research grants available through the National Institutes of Health in Bethesda, MD.

The initiative also calls for the FDA to work with the industry, academia, and other government agencies to develop the "Critical Path Opportunities List," which is designed to identify areas that would most benefit from a modernized path of medical product testing and manufacture. ■

CE/CME objectives

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. ■

CE/CME *questions*

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.

1. Prior to 1993, the Food and Drug Administration restricted the participation of what group of people in early phase clinical trials?

A. Asian men
B. Women
C. Black men
D. Children

2. Which of the following procedures was not included in a list of the Food and Drug Administration's corrective and prevention action plan (CAPA) basic steps?

A. Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data.
B. Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.
C. Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
D. Notifying the FDA about all information related to quality problems or nonconforming product.

3. The 21 CFR Part 11 involves electronic signatures. Which of the following is a requirement for the designing of electronic signatures?

A. They must be protected through identifications and passwords or through biometrics and thumbprints.
B. They must be designed similarly to the electronic credit card signature process used at many retail stores.
C. They must require a three-part pass code and verification process.
D. All of the above.

4. Part 11 does states that people who develop and maintain systems need to have the training.

A. True
B. False

Answers: 1-B; 2-D; 3-A; 4-A.