CLINICAL TRIALS
ADMINISTRATOR
An essential resource for managers of clinical trials

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

Financial Disclosure:
Editor Melinda Young, Editorial Group Head Eileen Rusnak, Managing Editor Alison Allen, and Nurse Planner Elizabeth Hill, DNSc, report no consultant, stockholder, speaker's bureaus, research or other financial relationships with companies having ties to this field of study. Physician Reviewer Stephen Kopecky, MD, is a consultant to GlaxoSmithKline and has a research affiliation with Bristol-Myers Squibb.

MARCH 2006
VOL. 4, NO. 3 • (pages 25-36)

Sites, sponsors need to reduce time spent on clinical trial agreements

Contract and budget negotiations were biggest cause of trial delay

Clinical trial contract and budget negotiations were cited most often in 2005 as the reason trials were delayed, and this was a change from 2003, according to Thomson CenterWatch in Boston.

"According to CenterWatch's survey, in 2003 the most often cited cause of delay was patient recruitment and enrollment," says **Norman M. Goldfarb**, managing partner of First Clinical Research in Palo Alto, CA. Goldfarb spoke about clinical trial agreements at the 2005 Annual HRPP Conference, held by the Public Responsibility in Medicine & Research (PRIM&R) and the Applied Research Ethics National Association (ARENA), Dec. 3-6 in Boston.

"The bottom line is it takes an academic site over three months, on average, to sign a clinical trial agreement," Goldfarb says. Community-based and free-standing investigative sites take about 35 days, on average, to negotiate these agreements, he adds. This bogs down the whole clinical trial process, Goldfarb notes.

Sponsors are becoming more concerned about the delays caused by the budget and contract process, says **J. Mark Waxman**, JD, a partner with Foley & Lardner in Boston. Waxman also spoke about clinical trial agreements at the PRIM&R conference.

"There are a lot of trials out there and to find the right patients and to go through the informed consent process for all of those trials is a significant undertaking," Waxman says.

From a clinical trial site's perspective, there are three key issues to keep in mind, Waxman says. These involve having the right team, doing budget homework, and arranging a fair payment schedule, Waxman says. (**See story about clinical trial issues in budgeting, p. 27.**)

Sites that sign agreements drafted by sponsors without negotiating often do not have experience recruiting research participants, further costing sponsors' time and money, Goldfarb says.

"There is about a 35% research site turnover every year," Goldfarb says. "These sites are not experts at good clinical practice, and they often are not good at enrolling subjects. In the average study, 30% of research sites enroll zero subjects."

NOW AVAILABLE ON-LINE! www.ahcpub.com/online.html
For more information, call toll-free (800) 688-2421.

Sites that enroll zero participants still cost sponsors an average of $15,000 to $20,000 each, he says. This makes the process inefficient, since that same money could have been spent on the successful sites, Goldfarb says.

"You could pay the good sites higher fees, which would motivate them to enroll more subjects and allow them to put more resources into the study," Goldfarb explains. "You would get more and better data as a result."

A slow contract negotiation process is costly and inefficient for clinical trial sites and sponsors, so it's in everyone's interest to shorten the time spent on clinical trial agreements, Goldfarb says. "Both sides need the appropriate expertise for negotiation, and both sides need to delegate authority and escalate negotiations appropriately," he says. "The sponsor should start with as realistic a contract template as it can stomach. The sites need to decide what the critical issues are and focus their negotiating time on those issues."

Goldfarb offers these suggestions for how the contract negotiation process could be shortened:

• **Manage the process solutions.** Each sponsor has its own clinical trial template, and they leave it to sites to find the missing information and draw attention to the wording they find objectionable, Goldfarb says.

Since many sites cannot afford to hire lawyers to comb through these documents, they may end up signing the agreement without fully understanding the financial implications. As a result, the site might become unhappy with the sponsor by the trial's end, and trust between the site and sponsor is jeopardized.

A potential solution is for sponsors and sites to work with a model clinical trial agreement, Goldfarb suggests.

Goldfarb has created the Model Agreement Group Initiative (MAGI) for that purpose. MAGI has members from over 500 organizations in the clinical research industry. Information about MAGI is at the First Clinical Research Web site at www.firstclinical.com. "MAGI's model agreement has multiple choices," Goldfarb says. "Some choices are sponsor-friendly, some are site-friendly, some are neutral, and some are just different approaches to the problem," Goldfarb says.

The model clinical trial agreement includes commentary that explains the differences. For example, a comment in the indemnification section suggests that sites could indemnify sponsors to the limit of their insurance coverage."

Sponsors can adapt MAGI language to meet their own objectives, and sites will have a better idea of what the contract means because it's written in clear and familiar language, Goldfarb says.

A site manager might say of a contract that uses MAGI language, "I've seen this clause, and it's acceptable," or "I've seen this clause, and I'm

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.

Thomson American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Thomson American Health Consultants designates this educational activity for a maximum of 18 credit hours in category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Thomson American Health Consultants is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Provider approved by the California Board of Registered Nursing, provider number CEP 10864. This activity is approved for 18 nursing contact hours.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This publication does not receive financial support.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (ahc.customerservice@thomson.com). Hours of operation: 8:30 a.m. -6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.

Subscription rates: U.S.A., one year (12 issues), $299. 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 $50 each. (GST registration number R128870672.)

Editor: **Melinda Young**.
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Eileen Rusnak**, (eileen.rusnak@thomson.com).
Managing Editor: **Alison Allen**, (404) 262-5431, (alison.allen@thomson.com).

Copyright © 2006 by Thomson American Health Consultants. **Clinical Trials Administrator** is a registered trademark of Thomson American Health Consultants.The trademark **Clinical Trials Administrator** is used herein under license. All rights reserved.

THOMSON
AMERICAN HEALTH CONSULTANTS

Editorial Questions

Questions or comments?
Call **Alison Allen** at (404) 262-5431.

3 steps to prepare for contract negotiations

Know your own costs is key goal

Clinical trial sites often are concerned about their ability to negotiate meaningfully with large companies, an expert says.

When negotiations are with small and new sponsors, sites also worry about what would happen in the event of a major lawsuit if the drug or device hurts a participant, says **J. Mark Waxman**, JD, a partner with Foley & Lardner in Boston. Waxman spoke about clinical trial agreements at the 2005 Annual HRPP Conference, held by the Public Responsibility in Medicine & Research (PRIM&R) and the Applied Research Ethics National Association (ARENA).

"Sites should logically discuss with their negotiation partner the value they bring to the task," Waxman says. "And with smaller sponsors they should decide how much business risk they're willing to take."

Waxman suggests clinical trial sites improve their budget and contract negotiations with sponsors by following these three key steps:

1. Put the right team in place.

"First of all, you have to make sure you have the team in place to do the trial," Waxman says. "That seems obvious, and that means they're trained and have competence and the ability to perform, including the ability to enroll the necessary population."

2. Know the budget in advance.

"One of the things that sites often don't do before they get started is to really make sure there's a budget, a method of keeping track of all the costs before they begin," Waxman says.

Determining costs is very important because there often are different payers involved, Waxman says. For example, the Medicare rules about what can be charged to Medicare are complicated, he says.

"The same thing is true with managed care contracts," Waxman says. "Carefully read to see what can be charged and what can't be charged."

Sites should check contracts to determine which charges would be reimbursed by third-party payers, he notes.

"You really have to look at these things before you start the trial to understand which box to check, which charges go where," Waxman says. "This also will help you determine whether this will be a trial where you lose money or make money."

3. Require payment as costs are incurred.

"In the best of circumstances, sites ought to be paid at the time the costs are incurred or shortly thereafter," Waxman says.

For example, a site would want a start-up fee to cover the initial costs, and then it would want periodic payments as trial costs are incurred, Waxman says.

If a site has difficulty enrolling an adequate number of participants and the trial must be dropped, then there should be something in the agreement that spells out what would happen in this event, Waxman says. Sites need to think about this possibility because sponsors are thinking about it, Waxman adds.

"This would be a matter of negotiation, and it goes back to the original comment I made which is that you have to be pretty clear you can get this done," Waxman says. ■

not happy about it, so I will propose an alternative from the MAGI and see if the sponsor accepts that," Goldfarb says. This streamlines the process and provides clearly stated alternatives to the ambiguous language that often is found in clinical trial contracts.

• **Set expectations and schedules.** The negotiation process should be managed with objectives, schedules, and setting expectations, he says.

For example, a sponsor could tell a clinical trial site that they have three weeks in which to reach an agreement, and if no agreement is made within that time period then all negotiation is over, Goldfarb suggests.

This will require the sponsor and site to work as a team during the negotiation process, he adds. If the site is too busy with other studies to take the time necessary during contract discussions, then it should pass on the study and not even begin the negotiation process, Goldfarb says.

Within the three-week deadline, the first milestone could be to have the site review the sponsor's contract draft and respond with issues and proposed language within seven days. Then the

sponsor would have one week to respond. The last week can be spent resolving any remaining issues, Goldfarb explains. "I don't know why they don't take this approach," he says. "Perhaps they don't want to take a chance on losing an investigator they want, but the cost they pay is a big delay in the trial."

• **Understand payment triggers.** Clinical trial agreements are complex, and the area that pertains to payment triggers illustrates this point.

Clinical trial payments by sponsors are triggered at different points. There often is a start-up fee as a nonrefundable partial reimbursement for the cost of getting a clinical trial started, Goldfarb says.

"Often, there are also advances," he says. Sponsors might advance a site the entire fee for one subject and deduct that portion from future payments, Goldfarb says. "The bulk of payments are activity-based, so when a subject comes for a visit, the site earns some set amount," Goldfarb says. "The fourth category includes miscellaneous fees, such as reimbursement for advertising, IRB fees, and payment for unusual incidents."

Activity-based fees can be problematic if they are timed according to the site monitor's inspection of case report forms, Goldfarb says. If the monitor visits once every eight weeks, and payment is quarterly, visits may not be paid for six months, he notes.

"Another issue is the hold-back by sponsors of 10% or more of fees until all data queries are resolved," Goldfarb says.

"Hold-backs are a reasonable strategy to ensure cooperation by sites, but not when the hold-back is 27% and the payment date is left open-ended," Goldfarb says.

For-profit sites often operate on profit margins as low as 5% to 10%, and academic sites often target a break-even balance sheet, he says.

"So it's possible on a cash basis that the study is cash flow negative until the hold-back percent is collected, and that might take another six months," Goldfarb says.

• Build trust in sponsor-site relationship: Problems occur in the negotiation of payment schedules because sponsors know that about a 30% of sites will never enroll any subjects, and many more miss their enrollment commitment, Goldfarb says. Since they anticipate that inefficiency, they are reluctant to write big checks at the start of a trial, he notes.

Likewise, sites are reluctant to invest in internal quality control when it doesn't increase the fees they can charge.

"The solution is to create long-term relationships between sponsors and sites so both parties can trust each other," Goldfarb says. "These are often called preferred provider relationships."

"If a sponsor has a site that always delivers the goods, it will feel more comfortable with larger start-up fees and smaller hold-backs," he says. "So you need to focus on building that relationship with them."

This sort of trust could lead to sites receiving partial payment before the monitor has checked all of the data.

While that might seem like a remote possibility, such trust already has been demonstrated in other industries. For example, there is an auto manufacturing plant that pays its suppliers as soon as they provide electronic notification that they've shipped the product to the plant, Goldfarb says.

"They wire the funds to the supplier without inspecting or even counting what is delivered because they have complete trust," Goldfarb says. "Sometimes there's a bad part or a miscount, but the cost that is avoided with this approach more than pays for those smaller problems." ■

Enrollment doubles with electronic reminder tool

Subject referrals had 10-fold increase

A new study suggests that clinical trial sites could significantly improve their subject recruitment with the use of an electronic medical record tool's physician reminder.[1]

The study found that during a diabetes clinical trial there was a 10-fold increase in referrals after the tool was used. In the 12 months prior to using the recruitment tool, there were five referring physicians who averaged 5.7 referrals per month. In the 12 months of using the tool, there were 42 referring physicians and 59.5 referrals per month.

The diabetes trial's actual enrollment doubled, with an enrollment rate of 2.9 per month in the 12 months before the tool was used, and a rate of six per month when the tool was used.

"The findings were remarkable," says **Peter Embi**, MD, MS, an assistant professor of medicine at the University of Cincinnati. Embi is the principal investigator on the study, which was conducted at The Cleveland Clinic.

While others have attempted to use emergency health records to remind clinicians of trials, no

studies have been published showing such a significant benefit in the number of physicians making referrals and their recruitment rates, Embi adds.

The diabetes study was receiving subject referrals from five endocrinologists prior to the use of the electronic health record alert tool.

After the tool was used, there were an additional 36 general internists and sixth endocrinologist who made subject referrals, Embi says.

"There was an eight-fold increase in the number of physicians participating," Embi adds.

The study's success shows that many physicians would make referrals to clinical trials if there were reminders and a simple process for doing so.

Some of the obstacles to physician referrals include a lack of time, unfamiliarity with the trial, and forgetfulness, Embi says.

"In my practice, I noticed I had missed a lot of potentially eligible patients for trials we had ongoing, and it was just because it wasn't the first thing on my mind," Embi says.

This revelation gave Embi the idea of creating a tool that would remind physicians about clinical research while they were meeting with patients.

Part of the tool's design also addresses the other obstacles, by having the tool do the initial subject screening and making the whole process very fast.

Since The Cleveland Clinic, which is where Embi practiced at the time, already had an electronic health record, he looked into adapting the tool to produce clinical trial alerts.

"The tool can be configured to alert for anything," Embi says. "Basically what you do is have it designate certain parameters."

Investigators decided to study the tool's new use as a clinical trial reminder during an ongoing diabetes study. So the tool was configured to alert physicians if their patients were likely to be eligible for the trial. The criteria selected to trigger the alert were the patient's diabetes diagnosis code, having a glycosylated hemoglobin level of greater than 7.4%, and being over age 40. "If those criteria were met, we had the alert come up during the patient's encounter with the physician," Embi says.

The system was also adjusted to give the physician an opportunity to click a button that would send a message directly to the study coordinator through the electronic health record, Embi says.If the physician felt it was appropriate, and the patient agreed to be contacted by the study coordinator, then the doctor would click on that button, he explains.

Clicking on the button would document within the system that the conversation took place between the patient and physician and that the patient had given permission for the study coordinator to review his or her medical records. This made it compliant with HIPAA privacy requirements, Embi notes.

Also, when the physician clicked on the button, the system would send information about the clinical trial to an information sheet that would be handed to the patient as he or she left the clinic, Embi adds.

The written information would remind patients that they had given permission for the trial coordinator to contact them and that they might be called within the next couple of weeks. It also listed a phone number for them to call if they had any questions, and it informed them that they could change their mind about the trial at any time they chose, Embi says.

The Cleveland Clinic's electronic health record was implemented throughout the institution and at all clinical sites, Embi says. "So while you're in the room with the patient, you're actually logged into the computer, and you're doing your documentation and looking up labs for that patient."

The clinical trial alert system took less than a minute of doctors' time, Embi notes.

Investigators spent about an hour or two adjusting the electronic health record to include the clinical trial alert system, Embi says.

"The hard part was figuring out how we were going to do it," Embi says. "We didn't want to create something from scratch because that's what has been done in the past, and that tends to make it difficult to make the system portable."

Investigators had to decide which tools to combine, which criteria to use, and to which physicians to send messages. They ultimately decided to send the messages only to endocrinologists and internists, Embi says.

They informed clinic administrators of the new alert system and informed doctors that they would activate the system and would study the physicians' responses. In all, 48% of the physicians targeted responded to the alert notice, Embi says.

"At follow-up, even those who didn't participate said it wasn't intrusive and it wasn't much hassle, and they wouldn't mind seeing it in the future," Embi notes.

Although there was no cost analysis performed, anecdotal evidence suggests it was an efficient way to recruit subjects.

"From the perspective of the trial coordinator it was great," Embi says. "Her impression was that it was well worth it."

The clinical trial coordinator found the tool to be very effective when compared to other subject recruitment approaches, including some initiatives the site already was using, Embi notes.

Although there were more medical charts for the trial coordinator to review after the referrals increased 10-fold, it was fairly easy for her to determine which subjects would be suitable candidates without having to physically screen each patient referred, Embi says. "It was a little more efficient than it appeared," Embi says. "And it was very effective because it improved enrollments and didn't involve that much more time on the part of the trial coordinator."

The next step is to adapt the same alert tool to another health care system and another type of electronic health record. Since the initial tool was built into a vendor-based electronic health record, which is similar to many others used in the U.S., researchers are optimistic the tool will work in many different products, Embi says.

"We got this to work in one health care system and with one electronic health record, and the question is, 'Can we get it to work elsewhere?'" Embi says. "We think we can, but we need to demonstrate this." ■

Reference:

1. Embi PJ, et al. Effect of a clinical trial alert system on physician participation in trial recruitment. *Arch Intern Med*. 2005;165:2272-2277.

Competency tool not excessively burdensome

Use of subject advocates not as effective

Investigators who used a competence assessment tool as part of a large clinical study of antipsychotic drugs and a schizophrenia population have found that the tool's use during the study's informed consent process was not considered burdensome by most clinical trial staff and investigators.

"We took a relatively new instrument that had been used on a small scale, and we used it on a large scale study," says **Scott Stroup**, MD, MPH, an associate professor of psychiatry at the University of North Carolina at Chapel Hill. Stroup presented a poster about the tool's use in the study at the 2005 annual conference of the Public Responsibility In Medicine & Research (PRIM&R), held Dec. 3-6 in Boston.

Thirty percent of investigators said using the tool posed a significant burden on research staff, but most did not agree, Stroup says.

The study, sponsored by the National Institutes of Mental Health,was designed to compare the effectiveness of antipsychotic drugs over the long term, and it was begun in 1999, Stroup explains.

The main article was published in the *New England Journal of Medicine* in September 2005. "When we started the study there was a lot of controversy in the news and elsewhere about schizophrenia research," Stroup says.

A report by the National Bioethics Advisory Commission had suggested that people who have the potential for decision-making impairments should have their decision-making competence assessed independently prior to their inclusion in a trial, Stroup says.

Some psychiatric researchers felt this would be discriminatory toward certain subject populations and that it would be a significant burden and impediment to research, he adds.

One possible way to address some of the concerns about the report is to use a competency-assessment tool to assess subject's ability to provide informed consent. So investigators involved in the schizophrenia trial used the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) during the informed consent process. It took about 20 minutes to administer, although when first used it took up to 45 minutes, he says.

They found that using the instrument during a large-scale clinical trial was feasible, and it didn't greatly burden the sites or impede enrollment in the study, Stroup says.

Clinicians, research nurses, and clinical social workers administered the instrument and informed consent process, he says.

"Our evaluation showed that some people found it to be a very useful tool in assessing capacity and getting informed consent," Stroup says. "But if the goal of it was to screen out people who were incompetent, it really wasn't necessary."

Investigators found that fewer than 5% of subjects were screened out from the study due to the MacCAT-CR, Stroup says. "That doesn't mean that fewer than 5% of people with schizophrenia have substantial impairment, but only a small percentage of people the researchers thought

would be ready for the trial were impaired in their decision-making capacity," he explains. "So my interpretation is that investigators prescreened pretty well for the people who were able to understand the consent process and who would understand the research."

Since investigators didn't know what the cut-off point would be on the MacCAT-CR, they used the instrument with a low threshold score, leaving the final decision up to the physician, Stroup says. "We didn't want to set an arbitrarily high threshold that would keep people out of the study," he says. "But what we found was that a lot of people were way above the threshold we established."

Another investigator, **Scott Kim**, MD, PhD, at the University of Michigan in Ann Arbor is using the study's data to try to determine an appropriate cut-off point with the instrument, Stroup notes. "That's one spin-off from this project," he says. "Another thing is we used the instrument throughout the study, so if someone discontinued treatment, we used the MacCAT-CR, as well."

Once longitudinal data from the instrument's use are analyzed researchers will know if there were significant fluctuations in subjects' capacity during the trial, Stroup says.

The study also involved another informed consent innovation: use of a subject advocate, Stroup says. "Our subject advocate procedures could use some improvement," Stroup says. "Ideally, we asked people to designate a family member or friend or caregiver or case manager as their advocate."

However, with a schizophrenia population, there may not be many people in their social network, so the study also had to assist subjects find volunteer advocates, he says.

"We had to find other people who weren't part of the research project who could pinch hit and fill in," Stroup says. "In some places they found people from local advocacy groups to serve as subject advocates, and others might have a case manager who worked at their agency but who wasn't involved in the research."

Research subject advocates were expected to be present during the consent process and to understand the subject's motivation for participating in the trial, he says.

Advocates also were expected to understand the risks and benefits, so if the subject's capacity lapsed, they could be consulted by investigators, Stroup notes.

"If investigators were concerned about a lapse in decision-making capacity, or if they felt like there had been a lapse in capacity, they could check with the advocate to make sure it was reasonable to keep the person in the study," Stroup says.

A study of the use of the research subject advocates found that only a third of respondents thought the use of advocates had aided retention in the study, and most thought there had been no effect.[1] More than a third of respondents thought the use of advocates had a positive effect on subject autonomy, but, again, most found no discernible effect.

The study also revealed that almost no respondents found that the use of subject advocates had any negative effects on subjects' rights or retention.

"Some people liked using subject advocates because it helped to engage family members and others into the study, and it reassured subjects that someone else was looking out for them," Stroup says. "It reassured investigators that other people were involved in the study, and participation was reasonable."

Also, IRBs tended to like the study having research advocates, and advocacy groups liked it, so there were collateral benefits, Stroup notes. ■

Reference:

1. Stroup TS, Appelbaum PS. Evaluation of "subject advocate" procedures in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study. *Schizophrenia Bulletin*. 2006 Jan;32(1):147-152.

Write a comprehensive data safety monitoring plan

Plan complements protocol

Developing a data safety monitoring plan is good practice for all research protocols, an expert says. Data and safety monitoring plans may be developed as a general plan for a research institution or center; a global plan for a protocol or as the specific plan for a protocol conducted at a local research site.

"Not only should each protocol have a DSMP, but it should also be specific to that site" says **Lori T. Gilmartin**, RN, a consultant with Halloran Consulting Group, a private clinical trial management and organization consulting firm in Boston. Gilmartin is also a research subject advocate at Boston University School of Medicine, General

Clinical Research Center and has spoken about developing data and safety monitoring plans at clinical trial industry conferences.

She defines a DSMP as a plan/process unique to a study for optimizing participant safety and maintaining the integrity of the study data for unbiased evaluation. The need for a DSMP should not be overlooked because of lack of intervention. Safety, and integrity of data collected from human subjects is indication for a DSMP.

There are six steps to developing a DSMP:

1. Assessment of risk: "First, have the investigator take a realistic look at the protocol itself and make an assessment of risk within the protocol," Gilmartin advises. "What are the factors within the protocol and the research environment that elevate the risk?"

For example, here are some factors to consider:

- Does the study involve a vulnerable population?
- Does the study involve an unapproved drug, device, or treatment?
- Is it a blinded study?
- Is it a multicenter trial?
- How is the drug/device dispensed?
- Who is controlling the drug or device?
- Who is monitoring the drug or device and how often?
- How is the drug's risk being minimized?

The risk assessment includes a look at vulnerability, demographics, condition of health, intervention, logistics, outcomes, blinded study, and medical risk, Gilmartin says.

2. Identify data set: In developing the DSMP you should include a review of the protocol to make sure that what is being collected is documented, she says.

"You want to have control over what you have identified as data for the study, because in addition to assuring appropriate documentation, you don't want to collect more than you need, and you don't want to collect less than you need," Gilmartin says.

This is an excellent opportunity for principal investigators to take a final look at all the data points to be collected, she says.

"Remember, if you collect the data, it should have a purpose, answer a question, and needs to be monitored," Gilmartin says. "Why would this be a concern?"

For instance, an investigator might write out a list of tests he wants conducted for a study, and then some time later in the trial process, he might reconsider the need for all of that data, she says. "So why collect it and put the subject through the process if you didn't use it?"

For example, suppose an investigator has developed a cardiac study, and the protocol includes the collection of an EKG, Gilmartin says. The first three subjects have an EKG, but the next five do not. The doctor makes the comment, "I really don't need that anyway. It doesn't matter," Gilmartin explains.

The following scenarios could result:

- The IRB approved the original protocol as it is written, so the investigator is out of compliance and must file deviations.
- If the investigator doesn't really need the information, he needs to file an amendment to the protocol and see if he receives an approval.
- If the investigator really didn't need the data, then why did he include that test in the first place because it is a waste of time, money, and subject time.
- And in the worst case scenario, if the IRB approved it because the board felt the test was necessary to prove the theory, but the investigator didn't do the EKG for the remaining subjects and this omission was never monitored and reported until the study's closure, then the hypothesis could not be proven. And all of the subjects had been placed at risk and possibly without the potential for any benefit, Gilmartin says.

It's important to check the protocol line-by-line to make sure all data points are indeed being collected and captured appropriately and not missed due to paperwork design problems, she adds.

3. Data and clinical trial material/device integrity and accountability: Without this factor, the study's validity is in question and subjects have been placed at risk and may be without the possibility of benefit, Gilmartin says.

"The data and clinical trial materials have to stay valid throughout the trial, and you have to maintain accountability of them," Gilmartin says.

For example, when using computer-based data, there should be routine back-up of electronic data in case of an accident or disaster that threatens the data integrity. Documentation should have provisions for minimal access, security, and destruction of records, she says.

This would include maintaining the integrity and security of randomization. Likewise, clinical trial staff should check expiration dates on drugs and maintain logs, looking at batch numbers and noting when and how drugs are received, dispensed and/or returned, Gilmartin explains.

Clinical trial sites should maintain appropriate storage parameters for temperature and containers, as well as follow all shipping criteria, she adds.

4. Minimization of risk: "Before you start the trial, you want to take into account all the things that you can do to prevent any problem you can imagine," Gilmartin says. "So for a simple example, if you know there's a risk of breach of confidentiality in your electronic data, you would want to maintain the data under password protection, or, maintain minimal access to your files."

Many of the protocol-related issues will be spoken to directly within the protocol, often within the exclusionary, Gilmartin says.

"Many of the minimizations of risk have been included as part of the protocols global DSMP," she adds. "But if it's a site specific item or additional item of concern you would put it in the local data safety monitoring plan."

Other questions to consider in this category are:

- What are the endpoints or stopping rules for safety or efficacy?
- What would make you stop the study?
- What are specific training requirements you might add?

The plan might include having all staff receive human subjects protections or good clinical practice training or perhaps training for a specified intervention to be performed within the protocol. Or the minimization might be treatment related. For instance, a study involving a drug that was known to cause a significant number of subjects to have hives could include minimizing such reactions, such as giving subjects Tylenol and Benadryl 30 minutes prior to the onset of study drug, Gilmartin suggests.

5. Monitoring: Monitoring data safety is one of the most important aspects of the DSMP. The three main decisions to make are who will monitor, what will be monitored, and how often will monitoring take place, Gilmartin says.

Monitoring could be handled in a wide range of ways. Monitoring encompasses a large spectrum from the individual principal investigator through a formal Data and Safety Monitoring Board (DSMB).

It is the earlier steps in the DSMP development phase that will help the investigator and the review boards determine the level of monitoring required, Gilmartin says.

They will take into consideration the level of risk of the study. For instance, in a small, well-controlled phase I study it may be appropriate for the investigator and clinical trial staff to be the people who are monitoring the study, Gilmartin says. In other cases it might be more appropriate to have an independent reviewer or to rely on the monitoring that's being done by the clinical research organization (CRO), she says.

If an outside, CRO monitor is utilized — not in-house/real time, the local DSMP should still identify who the local person is who will be reviewing/receiving the data for safety, and how often, Gilmartin notes.

At the highest level of oversight, a DSMB may be convened. This is a formal board that acts under charter. By NIH guidelines DSMBs would be required for a phase 3 clinical trial, but they may also be requested upon review by the IRB due to the level of risk of a study.

Some sponsors choose to form boards of their own volition, Gilmartin says.

"It is important to note that the board acts without conflict from the sponsor or investigator," Gilmartin says.

"A board provides independent review of the data, but is not local," she explains. "While the DSMB's action would effect protocol change, its action would be slower than the action that could occur on the local level." Therefore, it is still important to identify within the site DSMP which person will be reviewing/ receiving safety data, Gilmartin says. A local member could perhaps prevent an AE from elevating to a serious adverse event.

The DSMP should include wording about what will be monitored, including these examples:

- Subject conduct and compliance;
- drop-out and enrollment rates;
- laboratory data;
- non-laboratory data;
- key data points for safety;
- adverse events

It will be the individual review committees' decisions to determine whether the selected monitor(s) and the frequency of the monitoring are appropriate, Gilmartin says.

6. Reporting: The DSMP should identify to whom the monitor will report findings and when this reporting will take place. This part of the plan will depend on the regulatory agencies involved, and at the very minimum reporting will take place to the IRB, Gilmartin says.

Together with the protocol global DSMP, and the Institutional DSMP, the site specific DSMP offers strength to the complete DSMP structure as it applies to human subjects protection, Gilmartin says. ■

Russian research expert discusses training

Russian sites have high enrollment

[Editor's note: In this Q&A interview, ***Anatoly Gorkoun****, MD, PhD, project manager of clinical operations of PSI Pharma Support International in Saint Petersburg, Russia, discusses some of the differences and similarities of clinical trial research in Russia and how U.S. investigators might prepare to collaborate on these projects. In this issue, Gorkoun discusses investigator training and best practices. In a follow-up story that will appear in the April issue of* Clinical Trials Administrator*, Gorkoun discusses trial audits, monitoring international sites, and regulatory considerations.]*

CTA: *How has clinical research expanded in Russia, and why has the country attracted more interest from the United States in recent years?*

Gorkoun: First of all, a piece of general knowledge: Russia has its population up to 150 million inhabitants, and it has an 11-time-zone territory. I need to admit that our company has got a unique geographic experience, involving sites in all the biggest cities from the West to the East. Thus, there are clinical trial sites in the city of Kaliningrad, which is on the Baltic Sea, the most Western Russian point on the map, and in Sakhalin, one of the remotest Far Eastern locations, bordering with Japan.

In the recent years more and more clinical sites are getting involved in clinical research. There are two main reasons for such intensive expansion:

1. Russian sites provide high enrollment. The phrase, "Go where the patients are," explains one of the reasons the country attracts more interest. I would say that most of Russian sites never experience problems with enrollment, and it's applicable to most of the investigated diseases/pathologic conditions.

2. Russian sites produce data of a high quality, which was confirmed by numerous sponsors' and Food and Drug Administration audits.

Despite this overwhelming involvement of sites all over the country, there still is a huge potential that can be used if the expansion process continues. The local sites have advanced facilities, sophisticated modern equipment, and very experienced medical staff. Maybe some of the investigators don't have an extensive clinical research experience, but proper training can easily improve the situation.

CTA: *What are the chief training objectives/considerations for investigators working on or with clinical research sites overseas and, specifically, in Russia?*

Gorkoun: The main training objectives applicable for Russian investigators, are the same as for American or Western European investigators. Of course, there might be different training requirements for some other countries. For instance, those which don't have an extensive, many-year experience in clinical research, might need basic training in safety reporting or source documentation maintenance, but it's not applicable for our case. Most Russian investigators have extensive hands-on experience in clinical research, and in most cases only study-specific training is needed.

Previous investigators' clinical research experience is evaluated during site selection visits and thus, we identify needs for training if a particular site is selected for the study conduct. From our long-term experience, in most cases there are study-specific training issues such as study protocol, investigational product, study-specific procedures, study-specific requirements for safety reporting, etc.

If some of the investigators need to have their general clinical research knowledge refreshed, let's say in good clinical practice [GCP], they will be provided with this additional training.

And only in those rare cases when a clinical research-naïve site is going to be involved into the study conduct, the site will be provided with all basic training prior to the study's start. It can be the case when some site with insufficient research experience has a broad clinical expertise, access to a wide target population, and sophisticated equipment. If additional sites are needed to be open , this site can be considered as a candidate and, after the successful respective training, can be approved to run the study.

Speaking about training goals, I would like to highlight that it's important not only to provide the investigators with the respective information, but also it's very important to make sure the information is understood in the right way.

CTA: *Would you please describe a best practice model for general training for investigators?*

Gorkoun: 1. At site selection/evaluation visits, investigators' level of expertise is clarified.

2. Training is provided at an investigators meeting. Who attends the investigators meeting? The principal investigator and one of the sub-investigators, who are MDs. In addition, there are the site data manager/research coordinator, who is an RN, or a required specialist, such as a lab specialist or

radiologist, etc. Normally, two or three people from each site attend the investigators meeting.

Since the investigators meeting is assigned for a large audience, it's possible to train all participating sites simultaneously. From our experience, training at the investigators meeting is very important for future compliance and quality of data. And we pay special attention to the investigators' meetings preparation. The investigators' meeting cannot be considered as only a social event with the main purpose "to socialize."

3. Training prior site initiation visits may be provided, if needed. Especially, it's applicable to the sites less experienced in clinical research. Usually it's for one-day, on-site training right before the site initiation visit. It can be general clinical research training in GCP, as well as study-specific training.

4. Training at site initiation visit. If during the site initiation visit the monitor identified a lack of study-specific or general knowledge, additional training is provided at this visit, and it's documented on the site initiation visit report. So it can be considered as on-site, additional re-training/training in study procedures/protocol, if needed.

5. Ongoing training or re-training in the course of the study are done at routine monitoring visits or by the phone. This is provided by monitors, and in Russia, most monitors are MDs.

The general training means GCP and/or any other clinical research-related experience that can be useful for any clinical trial. It's not study-specific. They can be the principles of ICH GCP, ethics issues, investigator's responsibilities, study documents, etc.

In Russia there are several GCP courses the investigators can attend, where MDs and medical/registered nurses can get the necessary basic knowledge. After the investigators successfully pass the respective tests, they obtain GCP certificates. But it's not mandatory to attend the courses.

The other places where the investigators can get general knowledge are congresses and conferences, both national and international, where they can listen to the respective clinical research-related presentations. Also, clinical research workshops, organized by Pharma companies or clinical research organizations (CROs) are useful. It might be GCP workshops, or some specialized workshops, like "informed consent process in pediatrics," for instance. These workshops are very valuable since they are concentrated on narrow issues.

And finally, the investigator meetings are a place for training. They are dedicated to discussing study-specific issues. Normally, at each investigator meeting at least one presentation is dedicated to discussing the most critical GCP questions, such as the informed consent process, the investigator's responsibilities, study documents, etc.

The trainers are CRO or sponsor's project managers, senior clinical research associates, experienced clinical research associates, safety officers, data managers, and others.

We think that investigators have been provided with proper training if we can see throughout the study these objectives:

- proper maintenance of source documents;
- GCP, regulatory, protocol, and procedure compliance;
- adherence to ethics standards;
- absence of violations or misconduct;
- reasonable number of explainable deviations, low rate of data clarifications.

CTA: *What are some of the major challenges with delivering training uniformity in global trials?*

Gorkoun: The main challenges are the following: different languages, different cultures and social conditions, sites' locations in different countries and continents. One of the challenges is diversity of the languages the investigators speak. It's obvious that the study documents, issued mainly in English, which is the industry's language, must be understood in the right way by each investigator at each site and in each country. Incorrect treatment of the study protocol or procedures can lead to irrecoverable consequences. So, before the site is initiated, we need to make sure that the investigator got everything correctly.

Speaking about site location, in Russia sites are scattered from West to the East within an 11-time-zone territory. It's a long way from one part of the country to another. The flight from St. Petersburg, Russia, to one of the Far Eastern sites takes about eight or nine hours. Of course, it's a challenge to manage face-to-face training, and it's even not very easy to handle training by the phone, taking into account the seven-hour or more time difference. ■

COMING IN FUTURE MONTHS

- Develop a process for reporting non-AE information
- Research site provides oversight of innovative therapy
- New approach to clinical trials might save time, money
- Healthy workplace tips for dealing with overwork

Editorial Advisory Board

Stephen L. Kopecky, MD
Medical Director
Mayo Alliance for Clinical Trials
Rochester, MN

Elizabeth E. Hill
BSN, RN, DNSc
Assistant Professor
Director
Clinical Research
Management Program
Duke University
School of Nursing
Durham, NC

Edwin V. Gaffney, PhD
Executive Director
Clinical Research
Baptist Health System Inc.
Birmingham, AL

LaDale George, JD
Senior Counsel
Health Law Department/
Health Care Business
Counseling Practicing Group
Foley & Lardner
Chicago

Ellen Hyman-Browne
JD, MPH, CIP
Director
Research Compliance
New York University
Medical Center
New York City

Barbara LoDico, CIP
Executive Director
Human Subjects Protections
University of Medicine &
Dentistry of New Jersey
Newark

Tamara Dowd Owens
RN, MSN, MBA
Clinical Research Manager
Governor's Institute on Alcohol
and Substance Abuse
Research Triangle Park, NC

Lynette M. Schenkel
Director
Office for Responsible
Conduct of Research
University of Oregon
Eugene

CE/CME Objectives / Instructions

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

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

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

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

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

CE/CME *questions*

9. According to Thomson CenterWatch, the reason most cited for why clinical trials were delayed was which of the following?
A. Clinical trial contract and budget negotiations
B. Patient recruitment and enrollment
C. Regulatory audits and monitoring
D. Human subjects protection education and training

10. A new study found that during a diabetes clinical trial there was an increase in referrals during a 12-month period after an electronic alert tool was used by physicians during patient visits. What was the increase in referrals?
A. referrals doubled
B. 4-fold increase
C. 7-fold increase
D. 10-fold increase

11. A study of the use of the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) during the informed consent process of a schizophrenia trial found that what percentage of subjects were screened out from the study due to the MacCAT-CR?
A. 21%
B. 12%
C. 8%
D. Fewer than 5%

12. When assessing a protocol's risk, which of the following is not a factor to consider?
A. Does the study involve a vulnerable population?
B. Does the study involve an unapproved drug, device, or treatment?
C. How expensive is the drug/device?
D. Who is monitoring the drug or device and how often?

Answers: 9. A; 10. D; 11. D; 12. C