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*An essential resource for managers of clinical trials*

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## IN THIS ISSUE



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# Post-marketing phase IV studies create opportunities for clinical research sites

*It's a double-edged sword for industry*

The FDA, pharmaceutical companies, and clinical research sites all have vested interest in post-marketing studies, but despite buy-in for this process and its recent growth, problems remain, experts say.

"It's a double-edged sword," says **Christopher Milne**, DVM, MPH, JD, an associate director of the Tufts Center for the Study of Drug Development in Boston, MA.

"Both industry and FDA are sticking to their guns that pre-approval research is not the problem and that enhancing the post-approval process is where you could get more bang for your buck," Milne says.

However, Milne found in a recent analysis published in the *Tufts Center's Impact Report* that post-marketing studies have had problems with delays, variable costs, and little improvement in product profile.[1]

Since 2001, the FDA has required drug sponsors to provide annual reports on certain phase IV post-marketing studies, and some post-marketing studies are mandated by law or part of a post-marketing commitment (PMC) with sponsors when more information is necessary about a drug to improve its use or quality.[1]

"We saw the FDA saying, by and large, that what they got out of the post-marketing studies with regards to improving what they knew [about a drug] was less than what they would have hoped for, or, less than the optimum," Milne notes.

Also called post-approval studies, phase IV research looks at how the drug is going to react in the market place in a larger subgroup of a patient population, says **Joan A. Chambers**, BS, director of strategic marketing and development for the Tufts Center for the Study of Drug Development.

"Once a drug has been approved, you can reach out to a larger group of patients and track other data that may not have been collected," Chambers says. "You might find that the drug helps patients for another ailment that it wasn't originally tested for in the clinical trial phase II or III."

Post-approval studies are becoming more common because of PMCs with sponsors and the FDA, Chambers notes.

Also, post-approval studies are growing because of changes in the industry's drug pipeline, which is not as robust as it once was, she says.

"You're seeing new strategies that need to be planned by sponsor companies," Chambers explains. "The numbers of new molecular entities are kind of dropping a little, or they're staying pretty status quo."

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Editor: **Melinda Young**.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403 (brenda.mooney@ahcmedia.com).
Associate Publisher: **Lee Landenberger**, (404) 262-5483 (lee.landenberger@ahcmedia.com).
Managing Editor: **Leslie Hamlin**, (404) 262-5416 (leslie.hamlin@ahcmedia.com).



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**Editorial Questions**

Questions or comments? Call **Leslie Hamlin** at (404) 262-5416.

A lot of companies have brand name drugs that are coming off patent protection soon, and so there are indications of more interest and growth in late phase or post-approval studies, she adds.

"And there are increasing research and development costs, so sponsor companies are looking for new and innovative ways to produce a drug that may be more cost-effective," Chambers says.

An example of this would be to take an existing drug approved for one indication, and through a post-approval activity trial, identifying a potential new treatment for that drug, she says.

Milne's analysis of post-marketing research found that about 45 percent of such studies were delayed because of slow enrollment, technical difficulties, and other problems.[1]

Also, most drug sponsors said the study results changed little in their understanding of a drug's safety, efficacy, or quality.[1]

That's not necessarily bad news, Milne notes.

"Theoretically, if a lot of drug sponsors said, 'We found this and this and this in post-marketing studies,' and if they said the studies were expanding what they knew about their products, then that would be worrisome," Milne says.

The Tufts analysis also found that between 1998 and 2005 sponsors spent an average of $5.3 million per clinical post-marketing study, and the range of study costs were from $100,000 to $33 million, with the variability related to patient numbers (ranging from nine to 10,071).[1]

"Some of these studies are fairly limited, looking at smaller populations, perhaps specialized populations and populations with comorbidities," Milne says. "Paying $5 million for a study today is not huge, but this is obviously research funding that could go into clinical development if it weren't being spent looking at possible risks, and some don't pan out to be real risks."

Post-approval clinical trials often serve another purpose of increasing product awareness and penetration and expanding product demand, Chambers says.

"Hopefully, they'll establish a positive relationship with prescribing physicians," Chambers adds. "And if you get more physicians prescribing the drug, then ultimately you'll reach your goal of market penetration."

Sponsors sometimes want to spread out post-marketing studies among more physicians who have the intended population for a specific drug, and this goal creates opportunities for new investigators, Chambers says.

"Post-approval studies are a nice entry into clinical trials for investigators," she notes.

This is why post-approval studies have both clinical and market objectives and provide benefits to both the sponsor and the physician and patient, she says.

The studies also have benefits for clinical trial sites, which conduct about one-quarter of all post-marketing studies. Three-quarters of these studies are conducted in-house.[1]

"For every mandatory [post-marketing] study that's done, there are probably three to four studies that are done for marketing purposes, and these could be for anything," Milne says. "They could be looking for a new indication for the product and a new disease population."

These are the voluntary studies that the sponsoring company does to better manage the product application to a new patient population and to increase market penetration, he adds.

"This definitely is a growth area because as more of the emphasis of the market is on the global market, and you get multi-country applications where you're actually launching in more than one country pretty much simultaneously, then you're going to want to do post-approval studies in the country where you will market the product," Milne explains. "The condition of use is different from country to country."

The benefit of doing post-marketing studies is that the drug is being prescribed under a controlled situation, and a sponsor can look at actual use and other factors, including dietary, prescribing, and follow-up differences, he adds.

To clinical research organizations in the United States, these goals are an obvious benefit: the U.S. accounts for maybe 45 percent of the drug market and possibly as much as 60 percent of the profits, which means sponsors are motivated to conduct post-marketing trials here, Milne adds.

It's likely post-marketing studies will increase for other reasons, as well, Milne says.

"You'll have more mandatory studies, and payers are going to want to see it more," Milne says. "There also will be comparative effectiveness trials, and you now have to prove to a number of different audiences that your product works in different situations." ■

Reference

1. Milne CP, Faden L. Challenges loom for postmarketing study commitments; benefits unclear. Impact Report by the Tufts Center for the Study of Drug Development, Tufts University. 2007;9(3):1-4.

# Model center for research assists sites from A to Z

*Clinical trial staff benefit from one-stop shop*

A model research center in Maryland has become a major research entity that provides start to finish assistance to investigators and clinical trial professionals.

The Center for Cardiac and Vascular Research at Washington Adventist Hospital in Tacoma Park, MD, has become one of the top 10 enrolling centers in the United States since it was formed in 2001.

Prior to 2001, the hospital's research was physician-oriented and mostly conducted in individual physician offices, says **Dawn Shaddinger**, MSN, RN, CCRN, administrative director for the Center for Cardiac and Vascular Research.

Now, the research center, which is a hospital department, provides physicians who are interested in cardiac or vascular research with a place to bring their protocols, she says.

"We can see if the protocols are feasible and if there is an adequate patient population for enrollment and recruitment," Shaddinger says. "We'll take the protocol and totally prepare it for IRB submission, make sure we have all of the equipment that's needed, and that we have all regulatory documentation."

The one-stop shop frees investigators to focus on the research part of the study, leaving the paperwork to experts.

Prior to the center's opening, there were a handful of physicians who were involved in research, Shaddinger notes.

Now there are 20 to 30 physicians who conduct research, and many of them might not be involved in studies if it weren't for the center's assistance, she says.

"This structure has allowed for doctors in solo practice or who are new in practice to be involved in research," she adds.

"The other advantage is that because we're not run out of a physician office, we're able to get physicians from various physician practices to be sub-investigators on the protocol," Shaddinger says. "So, we'll get a higher enrollment and have a trained coordinator who can be a lead coordinator on the study."

When the center first opened, Shaddinger and staff used a marketing brochure to explain

its infrastructure and to show what services and skills the research center could offer physicians.

Marketing staff helped them with promoting the center's services, including putting information on the hospital's Web site, Shaddinger says.

Here are some of the services the research center provides:

• **Assess the protocol for feasibility:** Shaddinger, a regulatory expert, a research coordinator, and the principal investigator all will read the protocol, looking for answers to these questions:

- What are the requirements of the protocol?
- Does the institution have the necessary equipment to handle the protocol?
- If not, will the sponsor provide the equipment?
- Is there enough space for the equipment?
- How labor intensive is the study?
- Does the institution need to hire additional staff to handle the study?

For the next step, they look at the contract to assess whether the institution's and investigator's costs will be met, Shaddinger says.

The center's committee of four will evaluate the protocol subjectively and discuss their thoughts about its feasibility, she says.

Shaddinger has an Excel spreadsheet for the protocol's budget.

It includes a list of all charges, including overhead costs, she says.

Some sponsors present very reasonable budgets in the contract, and others are too low, she notes.

"So it's important to assess what your charges are, and for me it has been most beneficial to work with our finance people," Shaddinger says.

• **Begin IRB submission and contract negotiation:**

Most of the time they accept a protocol, and the center's staff will then begin to collect regulatory documents, Shaddinger says.

"I have a full-time regulatory coordinator who will prepare the documents for IRB submission and submission to the sponsor," she says. "At the same time, they go through all the elements the legal department requires."

These two activities can take four to six weeks to complete, and doing them simultaneously helps to ensure the process will be completed in a timely fashion, Shaddinger says.

"Our legal department has provided us with standard language they'd like to see in all contracts," Shaddinger says. "So when the sponsor sends the proposed contract, we red-line it with our specified language and then send it to our legal department for an initial review."

Once the legal department gives it a green light, it's submitted to the sponsor for approval and signatures.

• **Provide enrollment, study visit, and other assistance:**

"Research nurses will evaluate patients that are referred to us by the physician for inclusion and exclusion," Shaddinger says. "They look at lab values, medical records, and spend considerable time speaking with the patient and going over the protocol, making sure all questions are answered."

The staff nurses also will make certain each patient understands what the study is about and has a copy of the informed consent form, she says.

"We have them give us feedback, and we make sure they know how to get in touch with us if they have any questions," Shaddinger says. "We ask the patient, 'What are you agreeing to do?' and see if they can explain what a randomized study is."

If the patient's answers indicate he or she doesn't understand how the study will work, then the nurse will spend more time going through the informed consent and clarifying issues, answering all questions, Shaddinger adds.

The research center also assists with patient follow-up, setting up appointments in physician offices, if appropriate, she says.

"We make sure we get answers to questions as needed to the patient report form," Shaddinger says. "And if there are serious adverse events, we make sure we're getting records about it and all source documents that are needed, including medical records from outside hospitals, physician offices, and maybe even a copy of the death certificate if a patient dies."

Once the research center has collected all of the adverse event documentation, the investigator needs only to review the information and sign it, she adds.

"If it's a serious adverse event, then we submit documentation to the IRB and sponsor," Shaddinger says.

The research center handles all regulatory visits, as well, Shaddinger says.

"If a physician is notified of a Food and Drug Administration visit, then I'm the next phone call," she says. "If the IRB requires additional information, we do it." ■

# Here's how to improve study budgeting and policies

*Administrator offers look at best practices*

It's not uncommon for research institutions to lose money on studies because of unexpected expenses, but this problem can be prevented by using a thorough budget worksheet and following budget policies.

"We did a major initiative for budgeting, focusing on how to budget and how to know the true cost for research conducted here," says **Jana L. Lacera**, RN, BSN, MSA, human protections administrator and director of the IRB and Bio-Ethics at Community Healthcare System in Munster, IN.

"This was one of our main focuses because everybody kind of knew how to budget, but there wasn't a formal process or spreadsheet they could use to identify costs up front," Lacera explains. "And we felt it was very important in negotiating contracts with sponsors to know what it would cost us."

Lacera devised a six-page Excel spreadsheet that lists activity details, hours per activity, total number of hours, dollars per hour, projected expense and expected revenue. **(See sample of budget worksheet, p. 90.)**

She also wrote an eight-page budget policies and procedures for researchers and research staff to follow.

"I took the budget worksheet and new policies to the clinical research staff, and they tested the budget worksheet, using data from old contracts," Lacera says. "Then we took it to our legal counsel for review, and they thought it was a good idea and approved everything we had done so far."

The institution has used the research budget worksheet for about a year, and there have been no problems with its predictions, so far, she says.

"We just finished revising it to make it more user-friendly," Lacera notes. "It was good to begin with, but it needed those fine revisions."

Here is how Lacera helped the research office improve its budgeting and contract negotiation process:

**1. Create a model clinical research agreement.**

Policy manuals can describe what is expected, but what if clinical trial professionals have questions about reviewing a clinical research agreement with a sponsor?

Community Healthcare System made this process easier for staff by developing a checklist of items that a clinical research coordinator and principal investigator could look at in a CR agreement, Lacera says.

"And we have a model clinical research agreement we worked on with our legal counsel," Lacera says. "We looked for language in the agreement that they recommended."

The model agreement is meant to help CR staff become familiar with such contracts, she notes.

"I asked our legal counsel to come in and speak with the staff, giving them a few sections on how to examine a clinical research agreement and about negotiation," Lacera says.

The 16-page model agreement includes language, such as the following:

- **"Study Conduct:"** 1.1 Institution, Investigator, and all sub-investigators agree to use their best efforts and professional expertise to conduct the clinical research described herein (the "Study") in accordance with the Protocol and the terms and conditions of this Agreement, provided however, that Institution and/or Investigator may make such deviations to the Protocol as they deem necessary to protect the health and welfare of Study subjects. Institution will promptly notify Sponsor of any such deviations to the Protocol."

**2. Obtain more information and feedback.**

"I went to other people's Web sites and found only one budget worksheet," Lacera recalls.

So she read as much as she could about the budgeting process and called some institutions to see if they could help her learn more by sharing their budgeting tools.

Once she obtained a great deal of information on the subject, Lacera began to build a budget worksheet and budgeting policies and procedures that would be suitable for Community Healthcare System. **(See sample of budgeting policy and procedure, p. 91.)**

Lacera also meets, as needed, with clinical trial staff to identify areas that need to be improved, such as the informed consent process.

The meetings are more frequent with departments that are newer to research, and these same departments are the ones that report finding a great deal of value in the budget worksheet and other tools, Lacera notes.

She obtained buy-in by having research staff involved in the process from the beginning.

"They said they found the budget worksheet very helpful," Lacera says. "And since they were in on the process from the beginning, they could

see the importance of budgeting and knowing what a budget was because people tend to buy into things if they're involved."

**3. Learn as much as possible about the costs of clinical research.**

"I started with the study activities, determining how much time it would take for the principal investigator and clinical research coordinator to actually prepare for a study," Lacera says.

She identified a variety of areas that would take time, including the following:

- Meeting regulatory concerns;
- Going through the budget contract;
- Conducting a legal review;
- One-time start-up fees;
- Study conduct fees;
- Having a site selection visit;
- Having a site initiation visit;
- Having interim visits;
- Closing out a study.

Research coordinators fill out the worksheet from the very beginning, noting the estimated number of subjects, and then they complete information for all of the activities that are listed, Lacera says.

"I tried to capture all of the expenses, such as were they going to solicit the use of pharmaceutical services within the hospital?" Lacera says. "Or, what else would they have to use to do this study that would impact their budgets, including the lab and the radiology department."

Lacera also included a section on the cost of test procedures and treatments, detailing the actual costs and physician interpretation fees.

"There's a place where you can identify whether a test or procedure is the standard of care or related to research," Lacera says. "I did that for the obvious reason that you're identifying which it is right up front so it won't get confused along the way and lead to double billing and fraud problems."

There is an easy reference sheet for clinical research coordinators to review, she adds.

"In our system, it's the clinical research coordinators who fill this out, and if the standard of care versus research care is not evident in the protocol, then the protocol is not written well," Lacera says. "If they don't spell out who is responsible for paying for what then I have a problem taking that protocol to the IRB because if you don't know who pays for what then you can't inform your subjects."

On the last page of the worksheet, there is a budget recapitulation in which all of the totals are listed and there is a 25 percent indirect cost added to it, plus the IRB fees.

"Then it lists what the expected revenue will be from the research," Lacera says. "Hopefully, your expenses are less than your revenue." ■

# Sample clinical research budgeting worksheet

*Institution shares its tool*

Community Healthcare System of Munster, IN, has created a thorough clinical trial budget worksheet that is used by clinical research coordinators prior to the institution's acceptance of a study contract.

Here is a sample look at the worksheet:

In an Excel spreadsheet, it contains these columns:

- **Study activities**
- Subject recruitment
- Subject visits
- Subject visits
- Study activity
- Study activity
- **Activity details**
- **Subject identification:** pre-screening and total identification fees
- **Subject screening:** subject screening, screen failures, and total screening fees
- **Subject consent:** Prepare consent packet, investigator inform subject, clinical staff inform consent process, update of study spreadsheets, and total consent fees.
- **Baseline patient visit:** prepare for visit, investigator participation, clinical staff participation, randomize subject and complete paperwork, clinical research form completion and filing, update of study spreadsheets, query resolution, and total baseline visit fees.
- **Treatment visits:** Customize this section per the protocol; be specific as to activity details and number of visits. It may include: visits, patients seen in MD office, for completion of case report forms and drawing blood, time spent shipping out specimens, time spent by the physician with the patient, and total treatment visit fees.
- **Follow-up visits:** Customize this section per the protocol; be specific as to the activity details and number of visits. It may include: study personnel time, physician time, and total follow-up visits fees.
- **Study closeout activities:** preparation, time

spent with monitor, physician time spent with monitor, follow-up, and total study closeout activities.

- Number of hours per activity
- Total number of hours
- Dollars per hour
- Projected expense ■

## Here's a look at a budgeting policy and procedure

*P&P accompanies worksheet*

Community Healthcare System of Munster, IN, has an eight-page budgeting policy and procedure form that provides clinical research staff with explanations and descriptions to help them complete the budgeting worksheet tool.

Here are some sample items from the budgeting P&P form:

**Section Three: Additional Fees:** The usual expenses accrued during the conduct of business that can be attributed to the study and are outside of the scope of the other line item expenses.

**Cumulative Time for Specialty Professions:** The expenses during a research study by specialty professions (i.e., nurse, therapist, technician, and pharmacist) for accurate cost recovery to that professional's department cost center. This section should not include any expenses that were attributed to any fees charged to the study in the One-Time Fees Section. The documentation should specifically list the Specialty Profession performing the service, the type of service delivered according to the protocol, and the salary cost associated with the Specialty Profession. The salary cost will be based on an average of that specialty's average salary plus the CHS calculated benefit cost of 26.4 percent. The Clinical Research Coordinator will obtain the average salary information from Human Resources.

**Budget Calculations:**

1. Number of hours per activity X number of activities = Total number of hours.

2. Total number of hours X Fee of Specialty practitioner performing activity = Projected Expense

**NOTE:** Fee of Specialty Practitioner performing activity = Average salary + 26.4 percent

Subject Stipend, travel, parking: List of items that the sponsor has designated in the contract that the sponsor will reimburse to the subjects.

**Other Expenses:** List of other expenses that can be expected to accrue as a result of the research study for which the sponsor is responsible. This list could include:

a. Copying medical records, films, etc. to be sent to the sponsor

b. Postage

c. Packing materials, dry ice

d. Outside lab or other interpretation fees

**Budget Calculations:**

1. Number of hours per activity X number of activities = Total number of hours

2. Total number of hours X Standard Fee of practitioner performing activity = Projected Expense

**Budget Calculation for Additional Fees:** Total all Additional Projected Fees for this section = Total Additional Fees. Transfer Total Additional Fees to Section 5: Budget Recapitulation. ■

## View IRB process as a help, not an obstacle to research

*Informed consent is a process — not a form*

Investigators and research staff often take a sour view of the IRB process, thinking of it as a burdensome hurdle to starting a clinical trial.

It would be more productive to view the IRB review process as a way to clarify the risks and benefits of a study and to improve the informed consent process, experts note.

Ideally, IRB staff will be trained to triage protocol applications and work with investigators and clinical trial staff when an application needs improvement, says **Dawn Dowling**, BS, CIP, compliance administrator at Carnegie Mellon University in Pittsburgh, PA.

"They can make sure the investigators give them all of the necessary information and have it written clearly so there won't be any questions," Dowling says. "They can be an advocate for the IRB and understand what a study is about."

This ideal world scenario isn't always possible because of the often understaffed IRB office environment and the increasing paper burden placed on IRB office employees, says **John Chinn**, MBA, compliance director at Carnegie Melton University. Both Chinn and Dowling spoke about the IRB application process at the Northeast Section

of the Society of Research Administrators International Conference in Newport, RI, held April 21-25, 2007.

"Some institutions have six IRBs, and each may review three or four new protocols a month, plus dozens of modifications and renewals," Chinn says. "And if you have a staff of four IRB administrators, it's really tough for the administrators to read entire protocols and try to figure out what the investigator is missing in it."

IRB administrators should do their best to help investigators and clinical trial staff complete the application, and the form should not be so burdensome that it discourages investigators from going to the IRB, making it difficult to get through the process, Chinn adds.

"So, if each institution could balance the risks that it takes when determining what information is absolutely necessary for an IRB to make an informed or good review of the clinical trial protocol or IRB protocol, and then balance that with the burden of the documents to the investigator, that would be helpful," Chinn says.

Clinical trial administrators and investigators can improve their own IRB applications by following these tips:

• **Understand what IRB wants from informed consent:** "When you put together an IRB application, what you need to do first of all is come up with a lay abstract that everybody understands," Chinn advises.

"It doesn't have to be written at sixth or eighth grade level, but it should be in a format that someone with that level of education could understand," Chinn says.

Pharmaceutical companies often give investigators a sample consent form with its own language, explaining what the study is about and what the risks and benefits are, Chinn notes.

"Many investigators are short-staffed, and they don't have a whole lot of time to reinvent the wheel, so they cut and paste examples from the pharmaceutical company's form and submit that to the IRB," Chinn says.

"But the IRB reviews it and looks at the informed consent form from their own institutional culture," he says. "And there may be language they find unacceptable to that particular culture or institution."

For example, some institutions require stricter language about the disclosure of pregnancy results in a study in which participants cannot be pregnant and are tested regularly, Chinn explains.

"If the investigator is working with minors, the IRB might require that the parents be informed about the results of the pregnancy test," he adds

It's also crucial that informed consent forms include clear language on who will pay for the various procedures included in the clinical trial, Chinn says.

"Because of the current health care environment and the insurance company paying for extra procedures, it's important the subject realize he or she may not be responsible for any of the additional costs of research tests," he says.

For instance, if the study was about asthma, and three chest x-rays were required while a subject was taking an asthma drug, it might be that the patient's insurer will only pay for the one X-ray which is the standard care, Chinn explains.

"So, someone has to be responsible for the other two X-rays, and it's important that the consent form tells the subject who the person is that will pay for the additional chest X-rays," Chinn adds.

"For clinical trial research, I believe the risks and benefits usually are adequately disclosed, but there's often confusion about clinical standard of care versus research," he says.

Depending on the subject population, clinical trial administrators and investigators need to make certain the risks and benefits of a trial are equally distributed, Dowling says.

"You need to know that informed consent starts at the start of the study, during subject recruitment," Dowling adds. "You need to know everything a participant would see and do, including recruitment materials and debriefing."

Make certain that the person who is signing the informed consent is legally able to sign it and is able to understand what they are going to do, Dowling says.

These institutional and cultural considerations challenge the investigator to understand the protocol more fully so they can rewrite the informed consent form in a way that will satisfy the IRB's concerns, Chinn adds.

Also, investigators should keep in mind that the informed consent process doesn't stop when the patient signs the form and leaves, Dowling says.

"Informed consent is a process that continues throughout the entire study, maybe for years and years," Dowling says. "Informed consent can be taken away at any time."

Participants need to be informed that they can withdraw from a study at any time, for any reason, she adds.

When Dowling audits a clinical trial, she'll ask the investigator to walk her through the informed consent process.

"I say, 'Treat me like a participant,'" Dowling says. "The informed consent process starts with either a flier or email or phone call."

Investigators need to be careful to not make promises they can't keep and to let subjects know if they can't answer a question, she notes.

"Don't give them a false answer," Dowling says.

"I think the people who are going to be talking to subjects, the nurses, researchers, and doctors, need to understand the study and make sure they address all of the patient's concerns appropriately and accurately," Dowling says.

- **Thoroughly plan statistical sampling:** Part of the Belmont Principle involves the benefits to society and respect for the people participating in research, Chinn notes.

"You don't want to use more subjects than you really need, but if you don't get enough subjects to result in significant power in the study, then you've wasted all of the subjects and these resources," Chinn explains. "So that's why the IRB looks at the number of subjects you plan to enroll."

It's important for investigators to show clinical significance in their protocols, and this work should be done right before the protocol is submitted for IRB review, he adds.

If there is a problem with the protocol's enrollment projection, then the IRB might say, "We don't believe you have significant power to find your answer," Chinn says.

"And they'll have the investigator go back and recalculate and suggest a different number," he says.

IRBs have different resources and offer different services, but at least one institution Chinn knows there is a statistician who works with the IRB, and this person helps investigators determine the correct sample size for their research, he adds.

With pharmaceutical company-sponsored trials, a statistician typically has helped the proposed study determine the optimal number of participants, Chinn says.

Typically, there will be no change in the number of participants during the course of a trial, unless the trial is going very well at one particular site and the sponsor organization asks that site to enroll more participants, Chinn notes.

"Where you find an increase in numbers is when the site has been so successful that they've reached their limit of their initial request for recruitment," Chinn says. "And the pharmaceutical company says, 'You're doing so great, will you please continue recruiting, and so the investigator will submit an IRB application to recruit additional subjects."

- **Provide IRB and ethics training to staff:** Training for principal investigators and clinical trial staff is very important, Dowling says.

"You need to make sure researchers and anyone who is going to interact with human subjects or human subject data is trained," Dowling says. "This can be on-line or through internal education courses."

Even the people who do nothing more personal than analyze the data need to understand that it's human subjects data, and they need to know how to treat it, Dowling adds.

Clinical trial staff need information about why the IRB asks for particular documents, she explains.

It's not enough to know what's required by the IRB, the staff should understand why it's important to the IRB, Dowling adds.

For example, investigators need to know why the IRB pays detailed attention to the language in the informed consent form, Chinn says.

"We tell investigators that this is a teaching opportunity," he explains. "They're teaching participants about what kind of research they're doing." ■

## Know protocols before signing on bottom line

*Form team and tools to help with process*

Every investigator and research administrator should make certain they understand what's in a protocol and what will be expected of them before they sign the contract.

"The protocol is your clear standard, roadmap," says **Alane J. Drexler**, RN, BS, MS, clinical research coordinator at the Florida Hospital Institute of Translational Research in Orlando, FL.

"Before an organization knows what is in the protocol, how can they determine whether the contract will be feasible or not?" Drexler says.

If researchers sign the contract before analyzing the protocol, then their options are limited.

Each research institution should have a system for reviewing protocols, Drexler advises.

This could be having two or three people look at the protocol or having a number of people in

different departments take a look, depending on the size of your organization, she says.

Drexler offers these suggestions for how to check a protocol for a good fit with your research institution:

**1. Know your own organization's research goals.**

"The bottom line is, What is it about the research that makes you want to do research?" Drexler says.

Asking these questions allows the organization to measure whether the protocol being evaluated matches the organization's goals for doing research.

For example, if the bottom line goal is financial, then the protocol will need to be carefully evaluated for costs to see if the contract amount will cover all expenses, she says.

Another goal might be to promote translational research.

"Are you improving the care of patients? Is that something that's important to you for a study?" Drexler says.

There might be a study involving oncology drugs for breast cancer, and the drugs are an improvement over existing therapy, for example, Drexler says.

"This study might be a way of trying to improve care and outcomes for patients with breast cancer with this new cocktail," she says. "Or maybe the drug being studied has fewer side effects."

In either scenario, the study might help move patient care forward, and that would help fulfill a goal of the organization that focuses on translational research, Drexler says.

Another goal might be to conduct landmark research, the study of new and novel therapies.

For instance, a study might be made of therapeutic hypothermia in which a patient's body temperature is artificially cooled after a witnessed out-of-hospital ventricular fibrillation cardiac arrest, Drexler says.

In an example of this, there was a patient who received therapeutic hypothermia after a ventricular fibrillation cardiac arrest on Christmas Eve, and by April he was well enough to walk his daughter down the aisle at her wedding, Drexler says.

"Would you and your organization like to be a part of that kind of landmark therapy?" Drexler says.

Other examples of novel therapy include stem cell research.

Whatever goals an organization has, it's important for the people evaluating the protocol to keep these in mind and know how the goals are prioritized.

"This way when you receive a protocol you can measure it according to what your goals are, and it helps you to establish your mission, your purpose, and why you're doing research, and why you're going forward with these projects," Drexler says.

**2. Check a protocol's feasibility, following thorough steps.**

There are different stages to reviewing a protocol for feasibility, Drexler says.

"First, when you get a protocol, you should do a quick initial overview because the sponsor company will want to know if this is something you might consider doing," Drexler says.

If there are clear red flags in a new protocol, it shouldn't take time to quickly turn it down, she notes.

Review the protocol first for ethics because the study would have to be ethical for the organization to be involved, Drexler advises.

Also, review the protocol for its science and its possible conflicts with standard of care, she adds.

"If the protocol does conflict with standard of care, is there a way for patients to get back on the standard of care if they need to be?" she says.

Finally, look at the financial aspects of the protocol and see if the numbers will work.

"At this point, make a go/no-go decision," Drexler says. "If you have enough questions and don't want to get involved with the protocol any further, then it's a no-go, and let the sponsor know."

Alternately, if the protocol continues to hold promise, then it's time to do some more detailed exploring, Drexler says.

If the protocol is not given a thorough review when it's received, then research professionals might make the mistake of thinking the protocol sounds good, only to have to backtrack once they take a detailed look at it, Drexler says.

"You put it in place and get to the middle of it and find out it's more difficult to implement than you thought, and, maybe, the costs are high because there are little surprises in there," she says. "So doing a feasibility review up front can be a good way to predict whether the study will work for an organization."

## *Research feasibility team*

If the protocol passes the quick initial review, then it's time to set up a research feasibility team. This process can be simple or complex, depending on the time available and the commitment from team members, she notes.

"This would be defining in your organization who would need to be a part of this," Drexler

says. "Determine who would have final say and who needs to have input."

For instance, an institution's research professionals, including research managers or coordinators who do the hands-on work, should have some say over the protocol, Drexler says.

"You also need to look at the resource staff," she says. "For example, who in your lab is a go-to person if you have questions on lab pieces in a protocol?"

Also, find the same person in radiology and other units, Drexler says.

"Find people who would interact with this process and people who are committed and willing to review the protocol in a timely manner," she suggests. "Once you have that team in place, then you're ready to start looking at protocols."

**3. Develop tools to break down protocol components.**

The key is to develop whatever tools will help one's own organization better review protocols for feasibility, Drexler says.

It's helpful to have someone break down the protocol's components into details that will help an organization flag which items will work and which won't, Drexler says.

A look at the pull-out components should answer these questions:

- What do the investigator and coordinator need to do?
- What are the inclusion and exclusion criteria?

Another useful tool would be a checklist for recording the various protocol pieces, and this checklist could be broken down by category, such as below, Drexler says:

- investigator;
- pre-study;
- radiological result needed to enroll patient;
- number of visits.

"Pull all of those details out from the protocol and put on a checklist, organizing them by category, so you're not just flipping through it page by page," Drexler says. "Do this for the other reviewers, and include a column where you found that piece in the protocol, such as a page number, so they can go back and reference the written part."

In some cases, a thick protocol could be broken down into a two- or three-page Excel spreadsheet in which all of the essential details are spelled out for the feasibility reviewers, Drexler suggests.

"You could have demographic data on top," she says.

Other sections would include the investigator's initial activities, including physical exams, Drexler says.

### *Site evaluation of protocol*

Another step is to conduct a site evaluation of the protocol, by asking these questions:

- What about this type of protocol has worked successfully before?
- What about this type of protocol has been a problem before?

The answers to these questions might produce quick thumbs up or thumbs down on the study.

"If you know you can't get that type of patient then that might be a no-go answer to whether you'll take the protocol," Drexler says.

"Evaluate future protocols by these kinds of questions, and then once you have these questions all put together and have them broken down, send the information out to the feasibility team," Drexler suggests.

"For example, let's say several different visits involve a lab draw, then you have the lab resource person look at it to see how much blood is drawn over a period of time," Drexler says. "And you'd need a scoring system for evaluating the findings."

For instance, in answer to the question of whether the protocol is desirable, a scoring system might be one to three with one meaning "no-go," and three meaning "absolutely," Drexler says.

Another helpful took is a feasibility flow chart that identifies who has the protocol at any point in the review process, Drexler suggests.

## 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.

## *COMING IN FUTURE MONTHS*

- Center formed to address health and research disparities
- Optimize clinical trial efficiency using these strategies
- Here's how to improve patient recruitment and retention
- Provide better site start-up support

"I would want to know that Dr. Smith in pathology is looking at it and will get it back to me tomorrow," she says. "If I was sending a protocol around a big building, I'd want to know where it's at, and if I sent it out simultaneously to many people, I'd want to know who sent it back to me."

**4. If it's a 'Yes' then move to next phase.**

Once an organization decides whether to go ahead or turn down the protocol, it's time to notify the sponsor and keep the communication lines open, Drexler says.

"Don't hesitate to contact your sponsor when you have issues because the sponsor can clarify questions as you go along," she says. "And once you decide you want to do the protocol, finish the budget negotiations."

Part of the budget negotiations may involve financial details, such as who will pay for the minus 80 degrees freezer that the study will require, Drexler says.

"If you accept the protocol and then realize that you need this freezer half way through the study, you'll have a problem," she says. "You don't want surprises, and you want to know if you can afford the study before it starts."

Once the financial details are worked out, it's time to start the regulatory submission process, including the IRB process, Drexler says. ■

## CE/CME *questions*

5. A Tufts Center for the Study of Drug Development analysis of clinical post-marketing trials found that the cost range of such trials was between $100,000 and $33 million between 1998 and 2005. What was the average cost?
A. $5.3 million
B. $12.1 million
C. $17.0 million
D. $19.9 million

6. In assessing a protocol for feasibility, which of the following questions is important to answer?
A. What are the requirements of the protocol?
B. Does the institution have the necessary equipment to handle the protocol?
C. How labor intensive is the study?
D. All of the above

7. Which of the following questions could be used when assessing a protocol's feasibility?
A. What do the investigator and coordinator need to do?
B. What are the inclusion and exclusion criteria?
C. Both A and B
D. None of the above

8. Which of the following is not among the activities that should be considered when preparing a study budget?
A. Meeting regulatory concerns
B. Going through the budget contract
C. Physician's commute from office to research site
D. One-time start-up fees

**Answers:** 5. (a); 6. (d); 7. (c); 8. (c)