CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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IN THIS ISSUE

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Ethical practice starts when study is designed and should be ongoing

Goal should be winning back the public's trust

Public trust in clinical trial research was damaged in the past year because of conflicts of interest issues that arose with the NIH and by front-page media reports about drugs that had been studied and approved, yet were found later to result in deaths among some people who used them.

"What people don't often realize is that virtually every decision we make has an ethical component to it," says **Evan G. DeRenzo**, PHD, bioethicist at the Center for Ethics at Washington Hospital Center and an adjunct faculty member in the graduate program in biotechnology at Johns Hopkins University in Baltimore. "We live in a world where we compartmentalize things. [Researchers] think of it as science, and then they think about ethics after thinking about science; and that's not the way it works."

Many researchers often fail to understand the ethical components to their decisions, including their ties to industry that could be construed as conflicts of interest, several ethical experts say.

Likewise, most researchers will think of conflicts of interest with regard to financial matters, but there also are other types, including process conflicts, says **Edward Fuchs**, PA-C, MBA, a research associate on the faculty at Johns Hopkins University School of Medicine in Baltimore. Fuchs also is the associate director of the Johns Hopkins Drug Development Unit.

"Investigators, in order to get promoted, need to publish and get data, and in some ways, that poses as great a conflict as financial conflict," he says. "Also, in clinical practice, there is this issue of conflict that exists between the investigator role and the patient-subject role."

Because of these ethical challenges, the NIH Director's Council of Public Representatives (COPR) held a workshop in Bethesda, MD, last fall — "Inviting Public Participation in Clinical Research: Building Trust through Partnerships."

More than 80 participants discussed issues related to public participation and trust and developed a set of recommendations designed to enhance and improve the state of clinical research and build trust. **(See recommendations, p. 87.)**

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Editorial Questions

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

Regulatory guidelines, recommendations, and an institution's own policies regarding conflict of interest and ethical responsibility all are part of the base foundation for the house of ethical decision making, notes **Linda Strause**, PhD, executive director of global site development at Cancervax Corp. in Carlsbad, CA. Strause also is the chair of the IRB for San Diego Hospice and Palliative Care.

The regulations were never intended to be black and white, she says. "Each situation may be different, and we need to address that and balance it with educating the public."

Strause, Fuchs, and DeRenzo discuss some of the chief ethical issues the clinical trial industry faces today:

• **Address challenge inherent in physician-investigator roles.** "Possibly, the most inherently conflicted person is the physician who is also the investigator," Strause says.

"I believe physicians make decisions based on what's best for the patient," she says. "However, that decision may be conflicted when the physician is also the investigator and the patient is also the research subject."

In this case, the physician has agreed to follow a protocol and comply with good clinical practices, Strause says.

Part of the challenge is the traditional relationship between doctors and patients in which patients ask their doctors to tell them what to do, Strause explains. In the case of a physician serving in the role of investigator, the doctor cannot make this decision and cannot apply any influence over the patient/research subject's decision-making process, she notes.

"This is potentially coercive and may put undue influence on the potential subject," Strause says. "Some subjects are more vulnerable than others, such as children, individuals with life-threatening illness, or those facing end-of-life care." So the answer resides in better education for both physician investigators and potential research subjects, she adds.

• **Be aware of changes in ethical perceptions.** Research in recent decades has relied on an ethical model based on the Belmont Report, focusing on issues of respect, beneficence, and justice, Fuchs says. "We may be in a period where we're looking at something beyond the Belmont Report. In some cases, it's described as a relationships model."

According to the relationships model, there is a relationship established between the investigator and community and the investigator and research subjects, and this relationship begins before the

trial and should continue after the trial has ended, he explains. "There are issues that may not be what one considers directly relevant to the trial, but they play a role in issues of trust and perception." For example, although HIV investigators visited sites in the developing world and tried to do everything they could to protect subjects, the communities haven't always felt enough was done, Fuchs notes.

"There was a perception in the community that not enough was done for those individuals," he says. "The community wondered whether the subjects would receive the standard of care that the individual with HIV in the United States would have and, if so, whether they would get access to those medications once the study was concluded."

That disconnect between investigators' ethical perceptions and the community's ethical perceptions resulted in some trials being closed briefly until investigators met with local leaders to discuss and define the investigators' obligations to the community, Fuchs explains.

• **Learn an ethical process or analysis.** DeRenzo has been working on an ethical process model that would apply to whatever issue arises, and the result of this is an 11-step approach to decision making. **(See ethics analysis, p. 88.)**

Using an ethical process model in making decisions is one way of making the process a more neutral one, she says.

"When you're talking about making ethical decisions on what to do in a protocol, whether to involve older adults who might be depressed and in a nursing home or older adults in a community population, you don't want a specific perspective," DeRenzo says. "You want a full-blown, expanded neutral ethics analysis."

Also, the use of an ethical model provides guidance that is not persuaded by personal relationships and opinions.

"Part of the problem with ethics is it's really not quite like other fields," DeRenzo says. "It's the art of justification."

For example, it doesn't provide clear-cut answers, only an opportunity to select between a weak ethical argument and a strong ethical argument, she says.

For instance, no one would consider asking a nonmedical family member or friend for a cardiology consultation, but everyone naturally seeks moral guidance from their family and friends, DeRenzo notes.

"You can see this qualitative difference about

COPR Recommendations for Building Public Trust

The NIH Director's Council of Public Representatives (COPR) held a workshop Oct. 26, 2004, called, "Inviting Public Participation in Clinical Research: Building Trust through Partnerships," in Bethesda, MD, for the purpose of learning more about strategies to build trust and partnerships in clinical trial research. Here are COPR's recommendations for improving and enhancing the state of clinical research in the United States:

- Incorporate into the NIH mission and philosophy that it values the involvement of the community in research and create language that expresses this value.
- Encourage change in the culture of the scientific community to ensure that medical research is viewed in the context of a long-term commitment to the community, not a one-time research study.
- Investigate ways to provide mechanisms that allow for follow-up health care when a clinical trial or treatment ends.
- Educate and reorient the current research community to the importance of treating the public as a partner in the research process.
- Set the expectation across the entire research community, NIH-funded research, and beyond that study results and outcomes should be shared with research participants and the larger community promptly and consistently. This will ensure that the research conducted in communities promotes translational research.
- Take action to interest community providers in clinical research and maintain their involvement.
- Provide incentives (not just financial) for primary health care providers and community specialists to play a role in clinical trials.
- Engage researchers, educators, and academic institutions in incorporating the public's perspective consistently at every level of training and in both the conduct of clinical research and the publication of findings from that research.
- Continue to develop and fund efforts to build a national identity for the NIH based on what NIH does best, research and education, as a basis for enhancing public trust in clinical research.
- Review the role and impact of institutional review boards and other patient protections in the clinical research process because the public views these protections as less effective than they should be.
- Document and publish best practices from efforts to re-engineer the clinical research enterprise as soon as the NIH begins to see results, so that progress in improving public trust in medical research grows rapidly and steadily.

Ethics Analysis and Thinking Through Issues

Titled "Thinking through the issue/problem case: Applying a systematic approach to ethics analysis," this concise process for ethical analysis was developed by **Evan G. DeRenzo**, PhD, a bioethicist at the Center for Ethics at Washington (DC) Hospital Center and an adjunct faculty member at Johns Hopkins University in Baltimore.

1. Who are all the possible interested parties? Think broadly — include not only persons and categories of persons, but institutions/organizations/professions/communities.
2. What are the full range of duties and obligations of each potentially interested party? Or at least the primarily interested parties? Think of parties as not only individuals, but institutions and groups, also.
3. How might various duties and obligations clash/conflict?
4. What might be short/long-term consequences of each possible course of action? How confident are you of your predictive accuracy?
5. What ethical principles are at stake? In tension?
6. What might be the intentions of the various players? Evaluate the praiseworthiness, or lack thereof, of persons'/organizations'/institutions' motives.
7. What appear to be the full range of the possible courses of action?
8. Weed out those possible courses of action that appear not to be justifiable based on potentially bad consequences, inability to meet duties and obligations, and/or the ethical soundness of intentions.
9. With the possible courses of action that are left, make explicit — either to oneself, or with colleagues/friends/family whenever possible — the justifications for taking each. Then vigorously scrutinize whether or not those justifications are ethically robust.
10. Act with moral courage.
11. Reflect on outcomes.

moral analysis and decision making," she says. "Most people think, and rightly so, of themselves as well-intentioned, decent people."

• **Incorporate ethics into the entire research process.** Ethical decision making should be a part of the thought process from the time a study is imagined, DeRenzo says.

For example, suppose an investigator wanted to study depression in the elderly and believed that enrollment could be achieved by using nursing home residents as subjects, she says. The investigator should be following an ethical analysis model before even deciding between the nursing home population and a community population, DeRenzo notes.

"If I don't stop and think at that point about what are the ethical issues raised by contemplating doing a study of depressed nursing home residents, then I'm already going down the wrong path," she explains.

Ethical questions to consider for the previously mentioned scenario include these:

— Could an investigator study late-life depression without studying nursing home residents?

— How would the nursing home residents' constraints on their liberty and rights affect the study?

— Is there something about depressed nursing home residents that would be more complex?

"Right from the get-go, ethical issues are going to be embedded in every aspect of running a clinical trial," DeRenzo adds. "So not to approach clinical research and development and design of clinical trial and its context with a heightened sensitivity to moral issues embedded in the study puts us at risk of ignoring those things and not paying enough attention to those things." ■

Use past performance to market your trial site

Experts offer guidance on improving site selection

The way clinical trial sites are selected is an antiquated process and yields predictably poor results, a research expert says.

"The process is designed to accommodate inexperienced people in site selection," says **Louis C. Kirby**, MD, medical director of Pivotal Research in Peoria, AZ. Kirby has been a principal investigator on more than 400 clinical research trials and has spoken about clinical trial site selection at national research conferences.

"Thirty percent of all sites do not enroll even a single patient into a trial, and approximately 80% of patients are enrolled at 30% to 40% of sites. The cost of this is a waste of resources to sponsors and clinical research organizations," he notes.

"No matter what side of the industry you're coming from, we're all hurt by identifying sites

poorly," says **Adam R. Chasse**, director of patient and site management services at Quintiles in Morrisville, NC.

Chasse also speaks at national conferences about clinical trial site selection.

Selecting sites that don't perform costs sponsors time and money because this prolongs the enrollment period and could result in delayed research, Chasse and Kirby explain.

"If sponsors don't do a better job of choosing sites, it takes that much longer to get studies done and drugs to market," Chasse says.

"Over 85% of clinical trials do not hit their projected original timelines for enrollment," Kirby adds. "And the ways sites are selected have not changed in response to that problem." What is needed is a robust database that takes the subjectivity out of the site selection process, he says.

Another problem that is exacerbated by poor site selection is the shrinking pool of physician investigators to conduct clinical trials, Chasse points out. "So not only does the current pool of investigators underperform on studies, the entire pool is shrinking," he says. "We as an industry need to know how to develop investigators, keep them doing research, and keep giving them more business."

Chasse and Kirby offer these suggestions for improving site selection and clinical trial quality:

• **Build on success.** "For sites that have been around for a while and have a reputation for doing work in a specific area, word gets around that they're fairly competent, and they get chosen for a lot of studies," Kirby says.

However, even these more successful sites have a finite patient base, and investigators may overestimate their capacity to enroll subjects, he explains. Also, popular sites may have several competing studies at the same time, and so they may not have many patients for the second or third time around with a sponsor, Kirby adds.

"So it goes back to the first argument that sites have some responsibility in this because it's an economic decision for all parties," he says.

Therefore, successful sites should not spread themselves too thin and end up hurting their reputation and their ability to succeed, Kirby notes.

Instead, they should take a realistic look at their capacity to enroll and communicate potential conflicts to sponsors, he says.

"Somebody should say, 'I don't know if this other study will start, but if we take on a second study, then we're stuck with it,'" Kirby says. "So the best dialogue to have with the second study's sponsor is to say, 'This other study is on hold, but if they cancel, I'm yours; if they do start the study, I'll honor my initial obligation to the sponsor.'"

• **Collect data and analyze performance.** "We're devoting an enormous amount of resources into finding sites we haven't worked with before and sending someone out there to work with them, find out what makes them tick, and to seriously analyze performance data on all sites we use," Chasse says.

"We want to know who the high performers are," he explains. "A sponsor might consider Dr. So and So a good investigator; but when you dig below the surface, you find out he didn't enroll as well as he should have, and the monitor was simply impressed with the nice facility."

Quintiles has spent a lot of time investigating sites and has developed a process for looking at performance data more closely, Chasse adds. "We can't afford to reinvent the wheel with every single study by not remembering that Dr. Smith did a great job and Dr. Jones did not, and then low and behold, we use Dr. Jones on the next study."

The most critical performance metric is enrollment, he notes. "Even if a site takes twice as long to get the regulatory contract and paperwork done, if they enroll twice as many participants, all is forgiven," Chasse says.

"We look at it on a time basis, so we look at enrollment per month from a number of different plotting points," he explains. "We make sure a site is not penalized for being added on late."

For example, if a study involves 40 sites and six months into a study the enrollment is poor across the board, then some sites are dropped and replaced with others, Chasse adds. "Those new sites may only enroll four patients in four months, and another site in 10 months has enrolled eight patients. I'd argue the backup site is better at enrollment per month."

Also, Quintiles compares a site's performance to the mean and median of a study to avoid bias from statistical outliers, he says.

"People here are trained to look at a variety of factors so they can come up with the best possible potential site list to hand back to teams," Chasse explains. "We don't place as high a priority on the other factors as we do on enrollment."

The other factors include:

— time to do enrollment;

— screen failure rates when appropriate;

— patient retention rates;

— how effectively a site uses its advertising budget and how that translates into subject enrollment numbers.

"Past performance should not be the only way sites are assessed," Chasse notes. "We have to understand the process for problems and how proactively we put procedures in place so there won't be any problems."

For example, is there a project manager who can fix problems before he or she has to call the site and persuade them to fix it? he asks.

• **Introduce customer relationship management techniques.** Investigators should be viewed as a tactical advantage from one sponsor to another, Kirby says.

"If you identify highly qualified investigator sites, who reliably produce clean data and adequate enrollment, it will shorten the timeline and ultimately cost less money," he says.

"So the goal is to identify consistently producing sites, and this requires knowledge of the site," Kirby explains. "It requires planning, senior level management decisions and infrastructure, and costs, and etc. — all of which are over and above what senior managers have to do."

If the goal is to accelerate the timeline in clinical development, then the research industry is going to have to do some planning and structure changes in order to change the system, he says.

Sponsors and CROs should view investigators as customers and ask themselves whether they know what makes a particular doctor's site work, Kirby says. "They should spend time with the senior level person and engage in conversation to identify key parameters that the clinical trial site will follow," he adds.

• **Take prospective measures of site performance.** While it's important to know a site's past performance before selecting sites for a study, it's also necessary to prospectively measure performance, based on what are identified as leading indicators of performance, Kirby notes.

Sponsors or CROs could develop a set of indicators, measure for these, and then measure their ability to predict success across multiple sites and studies to determine how accurate they might be, he suggests.

"Look back at your analysis, and say, 'Which of these are positive indicators for future performance, and which of the others didn't help much?' It's a matter of collecting data and looking at them," Kirby points out.

Some examples of potential indicators include:

— During a pre-site visit, how has the investigator led the protocol?

— How does a site manage internally?

— How does a site produce an ad?

— How does a site measure response?

Prospective measures might be a more accurate way of assessing a clinical trial site's performance than simply going by enrollment, Kirby says.

"Sometimes, a site doesn't have great enrollment for one trial, but is pretty good overall, and there may be extenuating circumstances," he notes. "So you should know from a customer relationship what kinds of things keep a site from enrolling."

For example, Pivotal Research has had cases where a sponsor ran out of money and provided no funding for advertising, Kirby explains. "So it took 12 months to get six patients because the company didn't provide any money."

The other advantage to prospective measures is it requires some telephone conversations with the site, and this is a good way to develop trust, he adds. "This helps get you on a first-name basis with each investigator," Kirby says.

And it will give a sponsor or CRO some additional data about a site's capability to adapt and take on new study projects.

"A site may have a good sense of a study and is flexible and able to innovate, and it may turn out to be one the best sites even if it has never done this trial before," he says. "Once you figure out what a site is good at then you want to keep using it." ■

You can improve your chances of being selected

Make circumstances work for you

While it will take a commitment by sponsors and the entire clinical trial industry to make major changes that will improve trial enrollment and study quality, experts say there are some things that individual sites can do to improve their own quality and desirability as a clinical trial site.

One of the first steps is to collect data on your own site's performance, experts suggest.

"I think any business needs to be familiar with what its performance is, and that's not something that has been paid attention to a lot by enough people in the clinical trials industry," says **Adam R. Chasse**, director of patient and site management services for Quintiles of Morrisville, NC.

"No matter what your product is, you should make sure you have a feel for how effectively

you produce that product and make sure you're giving much due regard to quality," he says.

By performing well and documenting this performance, a clinical trial site can build both a reputation and a marketing tool, says **Louis C. Kirby**, MD, medical director of Pivotal Research Centers in Peoria, AZ.

Kirby and Chasse offer these additional suggestions on how to make a site a top pick by sponsors:

• Develop personal relationships with sponsors.

"The short answer is that people currently give clinical trials to people they like," Kirby says. "I'm on the phone constantly with pharmaceutical companies. I go to investigator meetings, and I spend time with pharmaceutical staff getting to know them."

Kirby says he spends time finding out what pharmaceutical staff like and dislike and what their fears and weaknesses are. "If I'm working with a new company, I'll say, 'Let me give your staff a talk about this and what works and what doesn't. I offer to be a resource to them."

Any site that is starting out should talk with sponsors, making personal communication.

• Know your own strengths and weaknesses.

"Collect your own numbers and present these to sponsors," Chasse suggests. "What sites that are doing all these things well need to do is know how to really sell that success."

The clinical trial industry is competitive, so they need to know how to make themselves stand out to Quintiles or to whomever, he says.

"Then when they get in the door and perform well, they should make sure the company remembers that they performed well, and that needs to be part of the business strategy," Chasse notes.

But it's also important to be able to describe a problem-solving or process improvement strategy, he says.

"What would impress us is for a site to be able to describe to us how it would go about fixing a problem if it happened," Chasse continues. "If the enrollment fell behind, or if the monitor noticed on three visits that certain paperwork is not in order, then does the site have a system where someone can step in and fix it?"

Also, another question to consider is how qualified are staff to perform the study, he says.

"Are we going to be surprised by something we find in the audit or something the FDA finds later down the road?" Chasse asks.

"A good site has standard operating procedures in place, and everybody is enforcing those SOPs," he explains. "But if your acknowledgement procedure is just that everyone has to read them and never look at them again, then that's not an adequate quality assurance program."

• Contact referral sources.

"Sometimes, universities have a population that's unique," Kirby says.

Referral centers go there for certain groups of patients, so it's a good idea to identify those types of opportunities, find universities, contact them, and let them know you have a patient population that's important to their development and that you have a site that can handle a clinical trial, he adds.

"You get on the phone and talk about what you have and what you can do, because if they don't know you're out there, the phone is not going to ring," Kirby notes. "It's amazing how many doctors don't put in the time it takes in order to develop the relationships." ■

Fair budgets lead to better research

Capture every possible penny

The budget chargemaster prepared by the clinical trials office at Louisiana State University (LSU) Health Sciences Center in Shreveport is so detailed and complete, capturing every conceivable research cost, that it's rare for the site to lose money on a clinical trial.

"Sponsors will say, 'That's the highest budget I've ever heard,' and I say, 'We're the best site you've ever seen,'" says **John P. Rowell**, RN, MSN, CCRC, clinical research educator for the department of medicine/division of research at LSU Health Sciences Center.

The site handles about 100 studies a year, but may turn away as many protocols because budget negotiations fail or because the protocol doesn't meet the site's budget feasibility, he says.

"One of the advantages of being a big site is we turn some down before we get to the budget phase," Rowell adds.

"It's not unusual for the budget that I've worked up to be twice what the sponsor originally sent out to say they would pay," he notes. "But I won't come down below our costs. We won't lose money doing research — we can't afford to."

Rowell speaks at research conferences around the country, converting others to his budget chargemaster and negotiation process. He's also published the secrets behind his budget process, preferring that the entire clinical trial industry improve the research budgeting process rather than having an edge on competitors.

One of the biggest problems in the research industry is the high turnover rate of investigators, many of whom will work on one clinical trial and then lose money and enthusiasm for the process, Rowell says.

"Most sites accept a budget as is from the sponsor," he notes. "And the latest I've heard is 25,000 investigators a year do research once and never do research again because most lose their shirts and can't make any money at it."

While the quality of research is better with experienced research sites, including sites that invest in strong education and training programs, such as the LSU Health Sciences Center, sponsors sometimes will just go with whoever says they can do it the cheapest, Rowell says.

"My position is a full-time research educator, and most sites don't have that position," he says. "We put a lot of effort and money into education, so that makes us a better site, but it adds to our costs in the long run."

So the most likely way the budgeting process will improve is if academic and other larger research sites work to more fully capture all research costs in their chargemaster, Rowell explains.

"I keeping hoping that it will happen, that research budgets will get better," Rowell says, adding that at his most recent conference an industry representative walked out on his presentation, saying she thought he was giving sponsors the shaft.

His chargemaster divides the research site budget into six phases, capturing every research cost in each. Here's how it works:

1. Preparation phase

"The most important phase is the preparation phase, which is what you start before you ever get a protocol in your hand," Rowell says. "You go through your site and determine what things cost at your site**." (See story on the budget preparation phase, p. 93.)**

2. Protocol review phase

"I brag that I can budget a complete study in less than 30 minutes because I've learned to read the protocol and am very familiar with my chargemaster," he says. "For the average person, it takes an hour to review the protocol."

Everyone who will be involved with the protocol should review it and let the budget person know where there might be a problem, Rowell advises.

Those reviewing the protocol include the administrator, principal investigator, X-ray room staff, research nurse, research pharmacist, regulatory staff, and others, he says.

The person putting together the chargemaster should then calculate cost by taking the salaries of each of the people involved and multiplying it by the number of hours they spent on reviewing the protocol, Rowell notes.

Some of the commonly overlooked budget items include these, he says:

- screen failure compensation;
- payments for unscheduled procedures, adverse events, visits, tests, screening failures;
- application of overhead to unscheduled visits or adverse events;
- consent process of 45 minutes to one hour;
- increase in operating cost over the course of a long study;
- visits not considered visits by the sponsor because they're not on the flowsheet or due to adverse events;
- advertising;
- third-party drug dispensing.

3. Budget submission phase

Typically, sponsors will want a budget broken down with some itemization of costs, Rowell points out. They may request the budget to be broken down into per-visit costs and other details.

"So I might say it costs $450 for visit one and $200 for visit two, etc.," he explains. But the important thing to remember is that if some charge is for research purposes, the sponsor has to pay for it. "If there's even a question at all, then we don't bill the patient's insurance," Rowell says.

If a sponsor says the PI can go back and use a past lab result for the study, then there would be no additional lab charge; but if someone on the site has to draw lab work for the study, then the site cannot bill the patient, he adds.

"And you have to have these costs in your budget," Rowell says. "The sponsor may think it's a standard of care charge, but our site will say, 'No, it's only for research.'"

Rowell will include a charge based on time and salary for the process of submitting and negotiating a budget.

4. Budget negotiation phase

When a site fully captures its research-related costs and comes up with budgets that might shock sponsors, then it's important to have a great deal of enthusiasm and confidence in the quality of your site's product, he says.

Whoever negotiates the budget needs to be the person who has the power to say "yes" or "no," Rowell adds.

They also need to be familiar with the protocol, and they need to know how to negotiate, he says.

"A lot of people have no idea they can negotiate," Rowell notes. "A lot of budgets from sponsors say they are nonnegotiable, and I negotiate them every time, but an inexperienced PI wouldn't think to negotiate it and would take it at face value."

The key to negotiating the best price is for the negotiator to know both the budget submitted to the sponsor and the bottom line costs budget included on the chargemaster under "real cost," he says.

Ideally, a site would be paid for the budget submitted, but when that's unlikely, it's important to not settle for less than what it realistically will cost to do the study, and that means being willing to walk away when the sponsor simply won't budge enough, Rowell adds.

5. Review acceptance phase

"This is when the sponsor sends the contract back to you to make sure everything is listed there and the money is all right," he says.

"A lot of times you agree on a budget and get the contract and see that it has a different figure in it," Rowell says. "You may have agreed on including variable costs and then the contract accidentally left it out, so you have to make certain that everything agreed upon is in the contract," he says. "It only takes a few minutes to review the contract."

6. Post-study review phase

"This is where you say, 'For such and such sponsor I enrolled so many patients — they asked for eight, and I was able to get 12,'" Rowell says.

"And this information is all on the Excel spreadsheet, so if the sponsor comes back to us, I can tell by looking at the Excel sheet how good they were for us and how good we were for them," he says. "That helps with negotiations."

The post-study review process is the time for clinical trial staff to look at why a study that was accepted with high expectations ended up doing badly, Rowell explains.

"Maybe the population wasn't there that you thought was there, or maybe a new investigator wasn't as enthusiastic at the end of the study as at the beginning," he adds. "Or maybe the study coordinator quit half-way through the study, or it takes more time with a certain population."

Once the study's budget results are analyzed, staff are given a post-mortem and everyone who reviewed the study initially begins to talk about the problems or successes of the study, Rowell points out. "Did we make any money or lose money on it? Was one department in the hospital extremely hard to work with or easy to work with?"

The next time the site takes a similar study, the post-mortem answers will assist with the decision-making process.

Rowell suggests asking these questions during the review phase:

- Did the budget reflect the work performed?
- How much money did the site owe?
- How much money did the site earn?
- Have all IRB fees, advertising, etc., been paid?
- Did the site get stung by extra procedures? ■

Budgeting begins in the study preparation phase

Expert offers advice for capturing all costs

The first step to developing a complete and accurate chargemaster for every study is to determine all of the costs that would be included in a one-time charge, such as the costs needed at the start of looking at a protocol.

These are the costs that can be plugged into any protocol's chargemaster, depending on the protocol's risk severity level and other factors.

Also, these start-up costs should be paid up-front and are not refundable, says **John P. Rowell**, RN, MSN, CCRC, clinical research educator for the department of medicine/division of research at Louisiana State University Health Sciences Center in Shreveport.

He divides the study preparation costs into four categories, including the following:

- **Start-up costs:** "This is what it takes to get the study up and rolling at your site, before you enroll the first patient," Rowell explains.

Start-up costs include:

— IRB fees;
— IRB preparation;
— IRB presentation;
— protocol review time;

— budget preparation;
— copies;
— equipment (new and upgrades);
— chart reviews;
— database reviews;
— pre-study visits;
— pharmacy setup;
— lab setup;
— administrative;
— regulatory requirements.

• **Per-patient cost:** "This is what it costs to handle the patient, the direct costs," Rowell explains. These costs are put directly into the chargemaster, which could involve complicated software, or it could be a simple Excel spreadsheet, which is what Rowell uses.

"I put in every cost I can possibly think of for my site, including starting IV dosing, pharmacy, preparing the dose, X-rays, MRIs," he says. "And I find out what the costs are for those, because usually in an academic center, we have to pay someone else to do those things."

Rowell's chargemaster has five columns, including the charge item, the real cost, the site's charge, quantity, and total.

Whatever the charge might be, he will add a percentage to it to cover a profit margin. The site's charge provides insulation against mistakes and miscalls that could run up costs of a clinical trial.

So if an X-ray's real cost is $100, he enters that amount under that column. Then he might add $25 to that price, to cover overhead costs, and enter the amount of $125 in the column for the site's charge, Rowell explains.

Sponsors never see the chargemaster during the negotiation process, but having one helps a site determine a bottom line for a budget, he says.

Also, it helps to keep an electronic version of various site costs and charges because sponsors have begun to keep records of their own, Rowell notes.

"These charges should be consistent because most sponsors now keep some record on you," he says. "So if you charge $100 for this study, then they expect you to charge $100 next time, and they know that and will tell you that."

• **Variable cost:** "These are things that may or may not happen, and I bill sponsors as if they do happen," Rowell says.

Variable costs typically are not captured in the protocol, he adds.

Variable costs include the following:
— serious adverse events (SAEs);
— safety reports;
— extra monitor visits;
— making source documents;
— change of clinical research organizations in the middle of the study;
— change of monitors in the middle of the study;
— protocol amendments;
— need for additional advertisements.

"I try to figure these out by the estimated time involved," Rowell says. "Who will it involve, and how much time does it take, and time is our No. 1 biggest expense anyway."

For example, SAEs take a lot of time in completing paperwork because SAEs must be reported to the sponsor within 24 hours, plus require a follow-up report and a report to the IRB, he says.

Variable costs also might include a visit by the FDA, which could be a strong possibility of a site has the highest enrollment for a study, Rowell adds.

"Normally, when the FDA comes in, it takes three days, and it will tie up your coordinator for three days — so you have to figure the salary for those three days," he notes. "Then you have the principal investigator involved for one to two hours per day, and you take that salary."

The same calculation should be done for the regulations manager, who also would be involved with an FDA visit for one to two hours per day, Rowell adds.

• **Closeout cost:** "These are all the things that go on at the end of the study, including the pharmacy closeout, the administrative closeout, stored documents, and closeout visits," he says. ■

Improve relationships with research faculty

Research site brown bags it for staff education

Being more service-oriented to faculty has been a priority goal for the research staff at Northern Arizona University of Flagstaff in recent years, and improving communication is one way this has been accomplished.

"We have tried to be more service-oriented to our faculty and to provide good one-on-one contact with them, developing a good, direct working relationship," says **Bobbie Ursin**, grant and contract administrator.

"By having a good working relationship with

faculty, we're able to communicate ideas and concerns to them, and they pay attention to us," she says.

Besides one-on-one contacts, the research office has set up informal training for faculty, including a brown-bag series of educational updates, Ursin says.

During one semester, faculty were invited to a variety of research topics, including a session on post-award financial management, compliance issues, NIH and National Science Foundation (NSF) updates, and conducting funding searches. Each topic featured a staff or guest speaker and was held for 1.5 hours at noon. Participants were encouraged to bring their own lunches, she adds.

"Toward the beginning, we had a very good turnout," Ursin explains. "And the session we had on the NIH was very well attended."

A representative from the NSF was the lecturer for the NSF lecture, and that session also was well attended, she says.

Providing training as needed

In another example of how the research staff worked to improve service for faculty, one of the administrators will make presentations about funding opportunities and grant applications for faculty and their departments on an as-needed basis, Ursin notes.

"She has a special presentation for graduate students or post-docs in providing training to them about the research process," she says.

Another administrator is very skilled in the financial management system and works closely with departments, faculty, and staff to help them with their post-award financial management, Ursin explains. "She provides a little better oversight on those kinds of issues and can be proactive in working with staff and faculty," she notes.

When news arrives from NIH, NSF, or the Environmental Protection Agency (EPA), it's posted on the institution's web site and is distributed to faculty through a written summary, Ursin says.

"I think the key is being service-oriented," she adds. "We're here to help the faculty, and I think they perceive our office in that way rather than thinking we're here to institute some regulations and make them jump through hoops."

By maintaining a friendly atmosphere with staff ever ready to provide personal assistance, the research office demonstrates concern for the institution's and faculty's needs, Ursin notes.

For example, frequently there are staff who work on grant proposals to the NIH, and they might not be aware of all of the stipulations on human subjects research and the content of those proposals, she says.

"So I put together an outline of the questions they need to respond to within their proposal in a particular area," Ursin explains. "And I sent them that early in the process, instead of in the last few days when I'm reviewing a proposal."

This way the faculty researchers know all of the details that are needed before they research the proposal and write it, she says.

Another example of the office's service is in how research staff make faculty aware of such seemingly minor details as NIH's preferred font style, Ursin says. "As soon as I hear someone is going to work on an NIH proposal, that's one of the first things I alert them about. People use Times New Roman as a standard font, but that's no longer acceptable font style for the NIH." Rather, the NIH prefers Arial and Helvetica fonts, she adds.

"Another instance is with an NSF proposal — if you are asked to submit a revised budget, and if the revision involves a greater than 10% change in your budget, then you also have to submit an impact statement," Ursin explains. "So I let faculty know that some text is going to be required, and if they need to change the scope of their work, they'll need to explain that in the impact statement."

Whenever Ursin works with a new researcher, she tries to provide him or her with the information and guidance needed to develop and fine-tune a budget.

"Or I might draft a budget for them, knowing basically what a faculty member is going to be proposing," Ursin says. "I have found that our faculty are very appreciative of our comments and direction." ■

COMING IN FUTURE MONTHS

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- Handy protocol and risk management tools
- Assessing decision-making capacity
- Can small research programs handle accreditation process?
- Obtain cooperation with IRBs for efficient review process

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CE/CME instructions/objectives

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

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

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

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

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

CE/CME *questions*

5. Which of the following is one of the recommendations made by the NIH Director's Council of Public Representatives following a workshop, "Inviting Public Participation in Clinical Research: Building Trust through Partnerships"?
   A. Investigate ways to provide mechanisms that allow for follow-up health care when a clinical trial or treatment ends.
   B. Educate and reorient the current research community to the importance of treating the public as a partner in the research process.
   C. Take action to interest community providers in clinical research and maintain their involvement.
   D. All of the above

6. Experts on clinical trial site selection say which of the following is not one of the problems resulting from poor site selection for trials?
   A. Most clinical trials do not hit their projected original timelines for enrollment.
   B. About one-third of sites never enroll a single subject.
   C. About half of sites are overburdened with trials because too many sponsors come to them.
   D. There's a shrinking pool of physician investigators, a problem exacerbated by poor site selection.

7. Some of the commonly overlooked clinical trial budget items include all of these except which of the following?
   A. Final subject visit
   B. Payments for unscheduled procedures, adverse events, visits, tests, screening failures
   C. Application of overhead to unscheduled visits or adverse events
   D. Consent process of 45 minutes to one hour

8. In writing a budget for a clinical trial, which of the following contains the four main categories of the preparation phase of the budget?
   A. Start-up costs, per-patient costs, variable costs, closeout costs
   B. Start-up costs, overhead costs, variable costs, closeout costs
   C. Overhead costs, first visit costs, pharmacy costs, lab costs
   D. Per-patient costs, per-unit costs, start-up costs, closeout costs

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