CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

April 2011: Vol. 9, No. 4
Pages 37-48

IN THIS ISSUE

Financial Disclosure: Editor **Melinda Young**, Executive Editor **Michael Harris**, and Nurse Planner **Elizabeth Hill**, DNSc, report no consultant, stockholder, speaker's bureaus, research or other financial relationships with companies having ties to this field of study. Physician Reviewer Raymond Plodkowski, MD, has a research affiliation with Orexigen Therapeutics, Abbott Pharmaceuticals, Lilly Pharmaceuticals and GlaxoSmithKline Pharmaceuticals. He is on the speakers bureau of Lilly, GlaxoSmithKline and Novartis.

AHC Media

Compliance Best Practices

Research institute establishes best practices in preventing trial mistakes

Use comprehensive corrective action plan

Research institutions need a best practice plan for preventing and handling regulatory issues whether they have 50 or 500 new studies a year.

"As with most institutions that have a lot of investigators, we have seasoned investigators and newer investigators," says **Marion Olson**, CIP, CCRP, supervisor of human research regulations at the University of Texas M.D. Anderson Cancer Center's Office of Protocol Research (OPR) in Houston, TX.

There were issues, so the institution's IRB office developed a corrective action plan (CAP) template that outlines compliance issues and lists steps taken to address those issues. *(See table on reasons for implementing a CAP, p. 39.)*

"Departments were struggling with what they should include in a CAP, and they were having difficulty with identifying a focus, so we saw a need," Olson says.

For instance, clinical research sites and investigators were writing corrective action plans that were not as comprehensive as the IRB required, says **Wanda Quezada**, CIP, CCRP, manager of human research regulations.

Compliance issues — both minor and major — needed to be addressed more consistently.

Minor problems could be an investigator having repeated patient visits outside the window detailed on the protocol. Or there could be major issues involving safety procedures, says **Evanna Thompson**, MPH, CIP, supervisor of human research regulations.

A CAP template provides a structure for dealing with any kind of research compliance issue. So the Cancer Center's human research regulations staff created a CAP template that could be used by investigators when compliance issues arise and also as a way to prevent problems.

"We wanted to be proactive and provide an educational tool for inves-

tigators and research staff, as well," Thompson says. "It's not mandatory, but we strongly guide or encourage our investigators because everyone wants to be compliant."

Investigators that choose to use the CAP also might find that they become more efficient with their time and resources, Thompson says.

The OPR staff discussed the CAP template at departmental grand rounds, which were attended by mostly departmental research staff, Olson notes.

"The departments would see there was a need, and they'd invite us to go to these grand rounds to present it and assist their department with implementing it," she adds.

Also, they presented the CAP template at OPR brown bag sessions, which typically have 160-200 attendees. They're held each Monday from 12 noon to 1 p.m.

"We announce new and updated policies and procedures at the brown bag sessions," says **Marci Montemayor**, CIM, supervisor of human research regulations.

"We also provide departmental training, new research staff training, and education for IRB-noncompliant investigators and research staff," she adds.

When departments first use the CAP process, human research regulations staff will ask to be included in their first working group meetings so they can answer any questions investigators might have about the development process, Quezada says.

"The investigators also work closely with our auditing groups," she adds. "We are all very accessible; the auditing group administers a research support clinic that is open once or twice a week, and principal investigators can go in and sit with staff one-on-one."

There is also a 24-hour helpline that goes directly to Quezada's pager after hours.

Since implementing the new CAP process, the IRB has had only minor suggestions that need to be implemented on studies with compliance issues that were handled through a corrective action plan, Olson notes.

"In the past PIs would submit a CAP that was not approved by the IRB, so the CAP template has been pretty helpful," she adds.

The new process also has built-in monitoring.

"We ask the departments to give progress reports on the CAPs," Thompson says. "They should be monitoring things to make sure the goals outlined are being met and achieved, and, if not, then the CAP may need to be revised."

Here is how the CAP process works:

• **Access:** Compliance problems typically are identified during an audit or monitoring visit. When this happens, the research site begins a comprehensive correction action plan, beginning with an investigation of the problem.

For example, the compliance issue could be that the site is missing blood draws on day 2 of the cycle. The investigation would determine how many subject visits were impacted, Olson says.

Clinical Trials Administrator (ISSN# 1544-8460) is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Clinical Trials Administrator, P.O. Box 105109, Atlanta, GA 30348.

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this educational activity for a maximum of 18 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 15 Contact Hours.

This activity is intended for research nurses and physicians. It is in effect for 36 months from publication.

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

SUBSCRIBER INFORMATION

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

Subscription rates: U.S.A., one year (12 issues), $299. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Back issues, when available, are $50 each. (GST registration number R128870672.)

Editor: **Melinda Young**.
Executive Editor: **Michael Harris**,
(404) 262-5443 (michael.harris@ahcmedia.com).
Production Editor: **Neill L. Kimball**.

AHC Media

EDITORIAL QUESTIONS

Questions or comments? Call Michael Harris at (404) 262-5443.

If an audit found that five out of 20 patients had missed blood draws, then this becomes a trend and a potential significant issue, she adds.

• **Evaluate**: The goal here is to conduct a not-for-cause analysis by identifying criteria, condition, and cause.[1]

For instance, it could be that patients do not arrive at the clinic on time and miss their blood draw appointments. Or maybe some of the patients live out of town and have difficulty coming into the clinic, Olson says.

The cause could relate to the lab never receiving the blood draw order, she adds.

Part of the evaluate phase of CAP is to analyze the compliance problem's impact on the research.[1]

"Maybe it's not a safety concern," Olson says.

• **Assign:** "Establish who is accountable for that problem," Olson says. "Assign and identify the person who could affect the change."

This would be anyone who is familiar with the research, including be the principal investigator, who could say whether the blood draw really is necessary and eliminate it if it's not needed, Olson says.

Or there might be other collaborators with the study who need to discuss ways to prevent this problem from happening again, she adds.

• **Devise**: "When devising measurable outcomes you look at what's happening and try to get a plan in place," Thompson says. "Look at the different roles and responsibilities of each person on the protocol."

As part of this phase, a research site would use internal controls, such as policies, training, and segregation of duties.[1]

"Look at the different roles and responsibilities of each person on the protocol and decide what's going on," Thompson says. "You can put more checks and balances in there, such as having another research nurse come in and make sure orders are in."

Or the PI could look at the scheduling to make sure patients are scheduled every hour instead of every 30 minutes, or they could contact the lab where the blood is drawn.

CR sites also could use a delegation log to define staff roles and responsibilities.[1]

• **Design**: In the design phase, a CR site would create a list of required tasks, set reasonable expectations and time frames, and seek IRB approval

Multiple reasons why sites should use a CAP

Non-adherence is # 1

There are many reasons why clinical research sites should use a corrective action plan (CAP) and keep a CAP process and template on hand.

Experts at the University of Texas M.D. Anderson Cancer Center in Houston, TX, offer this list of reasons for implementing a CAP:[1]

• **Non-adherence to the study design**[1]

— IV infusion not done in the required timeframe[1]

— Administration of drug not allowed on the protocol[1]

— Schedule of events not done[1]

— Incorrect radiation treatment given[1]

• **Lack of timely reporting**[1]

— Serious adverse events involving death[1]

— Unanticipated events such as problems with the study drug composition[1]

— Protocol violations[1]

— No reporting to the IRB of unacceptable audits conducted by the sponsor, institutional regulatory office, or the department[1]

• **Incomplete consenting processes**[1]

— No signature for the participant[1]

— No witness present when required (i.e., children, non-English speaking participants, etc.)[1]

— Inadequate consent — study not fully explained to the participant[1]

— No assent for a pediatric participant[1]

• **Documented and inadequate management of conflicts of interests**[1]

— Principal investigator (PI) has a large amount of equity in the sponsor[1]

— Supervisor of PI has significant conflict with the sponsor[1]

— No documentation of PI conflict in the informed consent document[1]

— PI still analyzing data from a study where he/she has a significant conflict.[1]

REFERENCE

1. Olson M, Quezada W, Thompson E, et al. Steps for the development of a comprehensive corrective action plan (CAP) to address regulatory deficiencies in the human subjects clinical trial process. Poster presented at the 2010 Advancing Ethical Research Conference by the Public Responsibility In Medicine & Research, held Dec. 6-8, 2010 in San Diego, CA. ■

prior to implementation.[1]

"You would meet with department heads and figure out how to place those resources so the problem won't happen again," Thompson says. "Then submit the plan for IRB approval."

It's important to create a plan that is practical and will use only the amount of resources a CR site has readily available.

"We tell PIs, 'Don't put something down that looks good on paper that you can't carry out,'" Thompson explains. "So if you can't allocate space for extra nurses, don't write down that you can hire extra staff."

• **Monitor:** The purpose of the monitor phase is to verify and assess the CAP's effectiveness, revising if necessary.[1]

Also, CR sites should schedule periodic meetings to discuss progress and deliver reports to accountable owners and the IRB.[1]

Once the CAP design is sufficient and implemented, it should be monitored by an IRB, compliance officer, or QA department.

"You can monitor this every 12 weeks or six months, depending on findings and whether more frequent monitoring is needed," Thompson says.

• **Measure:**The last phase involves measuring outcomes to see whether the objectives were met.

In this final stage, a CR site will also verify that the recommended changes have been completed, that training was implemented, and whether there have been any adverse events.[1]

"This is the chance for the department or PI to say, 'Have we met the goals of the CAP, or are problems still occurring?'" Quezada says.

If problems continue, then go back to step one, she adds.

"When the procedures put in place don't work, we ask the PIs or departments to report this to the IRB," Quezada says. "Also, the departments have to conduct internal audits and should assign a quality assurance person to go through and say which is working and which is not working in a protocol."

M.D. Anderson has a quality assurance person who monitors the IRB and PI regulatory files to ensure compliance with federal regulations, Quezada notes.

"Even while we preach the CAP process to investigators and departments, it's important for the IRB to have its own internal monitoring process to make sure we're practicing what we preach," she adds.

REFERENCE

1. Olson M, Quezada W, Thompson E, et al. Steps for the development of a comprehensive corrective action plan (CAP) to address regulatory deficiencies in the human subjects clinical trial process. Poster presented at the 2010 Advancing Ethical Research Conference by the Public Responsibility In Medicine & Research, held Dec. 6-8, 2010 in San Diego, CA. ■

Research institutions face exorbitant fines if accidentally release PHI

Privacy rule now has sharp teeth

Medical and research institutions have a great deal more to fear these days from aninadvertent release of protected health information (PHI).

"The biggest impact is going to be the fees [imposed by the federal government] when there's an unapproved disclosure of protected health information," says **Christina L. Gilchrist**, PhD, CRA, director of research at WellSpan Health in York, PA.

"Those fines are pretty severe," she adds. "We all want to be as careful as we can with our patients' information, and that has a lot of implications on security measures that need to be implemented."

The privacy rules put in place by HIPAA were reinforced with hefty fines when Congress passed the American Recovery and Reinvestment Act of 2009 and its Title XIII, the Health Information Technology for Economic and Clinical Health (HITECH) Act. HITECH strengthened criminal and civil enforcement of HIPAA.

Recent evidence suggests the government will be enforcing the rules aggressively.

For example, the U.S. Department of Health and Human Services (HHS) imposed a $4.3 million civil penalty under HITECH on Cignet Health of Prince George's County, MD, in February, 2011. The Office for Civil Rights (OCR) found that Cignet violated 41 patients' rights by denying their requests for access to medical records. Also, Cignet did not cooperate with OCR's investigations, according to an OCR media report, dated Feb. 22, 2011.

Health care and research organizations are required to make electronic records available to patients electronically, although they can charge to recoup costs, Gilchrist says.

The fines for violations for a privacy rule breach

in which the entity did not know there was a violation can range from $100 to $50,000 for each violation with a cap of $1.5 million for identical violations during a calendar year. If the violation was due to reasonable cause then the fines range from $1,000 to $50,000 per violation, also with a cap of $1.5 million.

HHS defines a breach as "an impermissible use or disclosure under the Privacy Rule that compromises the security or privacy of the protected health information such that the use or disclosure poses a significant risk of financial, reputational, or other harm to the affected individual."

As research facilities and medical centers fully transition to electronic databases, the potential for a privacy breach increases unless organizations take steps to prevent this problem.

"It is so easy to access protected health information now with electronic medical records," Gilchrist says. "For the purposes of research, easy access does not mean you should be accessing it, collecting it, or keeping it unless you have explicit permission from the institutional review board."

Electronic medical records also make it easier for an organization to have an accidental disclosure, she notes.

"If I'm a nurse on the floor, and I log into the computer to see a patient's record, and I don't log out, then theoretically a visitor walking by could see some protected health information," she adds.

Gilchrist offers these suggestions for how research sites can stay compliant with the regulations:

• **Create linking documents**: Researchers have legitimate reasons for collecting some PHI, but once data are collected, many people associated with the research project no longer need to have access to this information as it's broken down individually.

However, no one wants to make the PHI irretrievable, so the solution is to create linking documents.

For example, the medical record number is by far the most commonly-used PHI data, Gilchrist says.

"A lot of people don't think about it as protected health information," she explains. "But the regulations say if the information can reasonably be used to identify someone then it's a PHI."

The solution is to create a linking document that assigns a study number code to the medical record number. Then lock that linking document away for use in the event a particular subject needs to be re-identified, Gilchrist says.

"If we see something where we have a moral and ethical obligation to contact that particular person, then that would be a legitimate reason for accessing that linking document," she adds.

• **Use encryption on all computers**: "All of our laptops now are encrypted," Gilchrist says. "We also have an encryption program for any media device like a pen drive, so if I put a pen drive into my laptop to take information off of it, then the pen drive itself is encrypted, and I can't access data without a password."

Research institutions walk that fine line between making available necessary data for research versus safeguarding against privacy breaches.

"We're trying to make access to data for studies simple while making access to the identifiable information difficult," Gilchrist says.

"I've been working with our health information management team to discuss a potential option that will encrypt all of our identifiable information," she explains. "Then researchers would have access to it based on their role and security clearance level and their need to know."

• **Ensure business associates know their responsibilities:** Under HITECH rules, business associates of research sites also are held responsible for PHI breaches. They could receive the same fines and penalties for breaches.

"One of the biggest recent changes is institutions rewriting business associate agreements," Gilchrist says. "We have to let them know they are responsible to the federal government and regulatory authorities and that when they sign our business agreements they are assuming that responsibility."

Business associates previously were not held accountable because they were not considered "covered entities" under HIPAA. Now they can be fined or otherwise receive civil and criminal penalties, including letting patients receive financial compensation for a violation of their privacy.

Included as business associates are employees and independent contractors.

• **Write SOPs for handling a privacy breach:** Medical and research organizations are required to make a notification of breach when an incident occurs. Each CR site should have its own standard operating procedures (SOPs) addressing how to handle these situations.

For instance, if a researcher loses his or her pen drive with study data on it, including PHI, the research site would have to investigate the incident

and determine if the breach involved unsecured PHI.

"Unsecured protected health information is protected health information that has not been rendered unusable, unreadable, or indecipherable to unauthorized individuals through the use of a technology or methodology specified by the Secretary in guidance," HHS guidance states.

If an investigation determines the breach included unsecured PHI, then the CR site would have to notify all the individuals impacted by this breach, conduct a full investigation, and advise HHS and others, Gilchrist says.

First, the site would need to send a written notice by first class mail to subjects impacted by the breach. The notice would need to tell them that their private health information was accidentally breached.

"I'd have to let them know everything we're doing to mitigate it and our plan for preventing further breaches," Gilchrist says.

Secondly, the CR site would need to notify the media in the event there's a breach involving more than 500 residents within a jurisdiction, she says.

"You have to notify prominent media outlets serving that state or jurisdiction," she adds.

The third step is to notify the Secretary of the Department of Health and Human Services, again if the breach involved more than 500 people.

"If there are fewer than 500 people then we just keep a log of the breaches and after 60 days from the end of the calendar year, you can provide a notification at that time," Gilchrist says.

"Send the elements of what happened, your mitigation plan, and corrective action plan to HHS and the individuals," she says. "You give a description of what happened, dates of discovery, say what the individual should do, what the research site will do to mitigate the harm, and list a single point of contact for more information." ■

CR sites increasingly have to make their own source documents

Here is advice on how to do so

Clinical study sites are carrying a greater part of the compliance burden these days as sponsors increasingly are shifting responsibilities their way — such as the task of making source documents, an expert says.

"For years the sponsor supported us in making source documents and providing them to sites," says **Cindy Mendenhall**, CCTA, clinical research coordinator at Evergreen Healthcare in Kirkland, WA. Mendenhall also is the founder of a consulting firm called CRC Services that focuses on clinical research.

"More and more lately, sponsors have stopped making source documents because they don't want to get blamed for missing something," she adds. "So as sites we need to make source documents ourselves."

The U.S. Food and Drug Administration (FDA) has certain rules about source documents, and one is that research sites should not simply use copies of case report forms, she says.

"It's not good clinical practice," Mendenhall says. "Your source document needs to have some sort of change, whether it's adding in time or something else; you have to change it a bit and not copy the case report form verbatim."

Mendenhall offers these tips on how to create or improve source documents:

• **Determine every documentation detail:** For example, a study on hypertension might say that subjects have to be sitting for five minutes prior to doing their blood pressure test, Mendenhall says.

"That needs to be documented," she says. "If the FDA auditor comes in and looks at the chart, how will the auditor know you've been doing it if it isn't written down?"

Everything that is done on the study needs to be documented, and so the source document needs a space for recording when these were done.

"This includes inclusion/exclusion criteria," Mendenhall says. "If the principal investigator (PI) says, 'Yes, this subject meets all inclusion/exclusion criteria,' then you have to write down the time the PI signs off on it and says the subject is okay to screen."

The signature with a date proves the inclusion/exclusion criteria was checked before study randomization occurred.

Other details include dating when the subject last took the study drug and what time the subject last ate, in the cases of fasting lab work.

• **Keep synchronized clocks:**"Time is a key factor when making FDA-friendly documents," Mendenhall says.

Clinical trial coordinators should jot down the time they perform each procedure or part of the protocol. To make certain their time is in synch, trial sites should have synchronized clocks, she adds.

"Use the same clock source you've been using throughout the entire day," she says. "We had a phone in our room and used the time on the phone."

Even if clocks are off by a few minutes, it can make a big difference in a clinical trial, Mendenhall notes.

"In our standard operating procedures (SOPs) it says the clock on the phone in every room must be used for every documentation, and all of the phones are synchronized," she says.

Mendenhall puts reminders on the phones in the form of bright orange Post-it® notes that say, "Document the time."

Staff will forget about this, so CR sites should train and remind employees to document time, using the synchronized clocks.

"Retrain and remind," Mendenhall says. "You hope you wouldn't have an FDA audit, but it's always a good idea to make sure people are trained properly."

• **Check protocol events table and lab manual:** One best practice in creating a source document is to use the protocol events table, which lists some of the procedural details.

"Get the general schematics and minor details, all of those nitpicking things out of the protocols," Mendenhall says. "Look at the lab manual and list the tubes used, capturing all lab draws."

It's best to go through the events table, examining each visit's procedures and then add these to the source document.

"The lab manual is self-explanatory," she says.

These items should be listed on the source document in the order in which the labs need to be drawn, so they'll be easy to document.

"I make a lot of check boxes as reminders," Mendenhall says. "So you don't need to know this one needs a cold centrifuge."

Having this information on the source document makes it easier for CR coordinators to remember what comes next and saves them time from having to go to the lab manual for the details, she adds.

While sponsors often did not provide that much detail on source documents for sites, it's a best practice idea for sites to add more details to the documents they create, she notes.

"It's a nice practice to make sure you've covered yourself and have not forgotten something," Mendenhall says.

• **Add reminders and use checklists:** "At each place where someone might forget something, add a reminder," Mendenhall says. "Put these in the order that you'll do things, so the informed consent should be prior to doing any procedures."

If a study has a questionnaire for subjects to complete before their vital signs are taken, then the questionnaire should be listed first, she adds.

Also, checklists can help with source documentation and completing case report forms.

CR coordinators should write progress notes, using checklists, and recording every subject visit and activity.

"It's a little time-consuming, but it's definitely worth the effort because it makes for faster and easier monitor visits," Mendenhall says.

The progress notes should be kept at the front of the source document binder, she adds.

"Show that you took extra time to initial items," Mendenhall advises. "Write things, such as the subject was given plenty of time to review informed consent and that the subject was given a copy of the informed consent document."

Mendenhall has a time-saving, informed consent discussion tool that includes lines to document the date and time of the IC discussion, as well as the names of people present and their relationship to the subject.

The tool also asks a number of "yes" or "no" questions, including these:

• Were questions from the subject and family, if present, encouraged and answered?

• Were all questions resolved?

• Were there any outstanding issues at the end of the discussion?

• Was the subject given adequate time to read, review, and consider the entire informed consent form?

• Did the subject agree to all protocol-required tests, procedures, and follow-ups?

• Was the subject given a copy of the signed informed consent form?

• Was the informed consent form signed by the subject prior to performing any study procedures?

• Did the subject agree to all protocol-required tests, procedures, and follow-ups?

• Does the subject understand possible risks and side effects of being in the study?

• Were alternative treatments (besides being in this study) discussed with the subject?

• **Keep source document material together:** "Buy gallon-sized plastic bags and put everything in that bag as they're needed for the next visit," Mendenhall suggests. "Include sticky pads, phlebotomy lab tubes, source documents, and even a binder."

This keeps the study visits running smoothly.

"If you do this for each patient on the day that you've made an appointment for the patient, then it's done and you don't have to think about it a month later," she adds. "You can store these on the shelf where the binders are kept."

Clinical trial sites that improve their source documents likely will find that monitor visits and even the day-to-day study operations become more efficient and faster, Mendenhall says.

Creating source documents will take some upfront time, but it will result in time saved over the long run, she adds.

"Everything you need is in one spot," Mendenhall adds. "I can do a moderately busy visit with EKGs and blood draws in 30 to 45 minutes versus 1.5 hours, so it cuts my time in half by being more efficient and creating source documents." ■

Avoid these common budget missteps with new studies

No upfront funds = a loss

Clinical trial (CT) sites and principal investigators can improve their budget cash flow by spending more upfront time on the budgeting process before signing contracts with sponsors.

"Sites sometimes forget the expenditure of resources it takes to get a study off the ground," says **Valera Bussell,** CCRC, CCRA, partner/senior clinical research associate at Clinical Research Trial Specialists (CRTS) in Parrish, FL.

This omission can be costly.

It's becoming a trend where sponsors will recruit CT sites to be add-ons to a study because the original sites have not met their enrollment goals, and the sponsor or clinical research organization (CRO) is worried the study won't meet deadlines, Bussell explains.

Then suddenly the original sites are threatened by this and they push harder to screen patients, ultimately meeting the enrollment goals. This leaves the last-on sites with no chance to participate in the study.

For instance, Bussell has worked with sites that put considerable time and energy into preparing to enroll subjects in a new protocol only to be told within a week of signing a contract with the sponsor that the trial was closed to enrollment. If they had failed to negotiate non-refundable start-up costs in the contract, then they would have lost considerable money.

"You can put all this time and energy into getting the documents, regulatory items, and confidentiality disclosure agreement (CDA), and if the sponsor shuts down the study right after giving you the study, then you're out of luck," Bussell says.

Or if a site has negotiated an upfront fee and then did not have the opportunity to enroll any subjects, the sponsor could come back and ask for a refund of the fee, she says.

"But we still expend these resources whether the study gets shuttered or not, so that doesn't work," she says.

So CT sites need to determine their own costs for start-up work and negotiate for non-refundable reimbursement, meaning it's paid regardless of whether the site enrolls subjects, Bussell advises.

Bussell offers this list of work that is done before a site can enroll subjects for a new study:

- Have the PI sign and return a CDA
- Review a protocol synopsis and complete a feasibility questionnaire before returning these to the sponsor or clinical research organization (CRO) to indicate interest in the study
- Compile and send in signed and dated curriculum vitae for site staff, as well as site questionnaire
- Participate in budget negotiation correspondence
- Submit an application to the IRB
- Attend an off-site investigator meeting
- Handle receipt, tracking, and storage of clinical study supplies, laboratory supplies, and study drug
- Complete sponsor-specific online training.

"These are all resource heavy tasks that are required before the site is ready to screen the first potential subject," Bussell says.

This is why sites need to request a non-refundable start-up fee, she adds.

"I usually ask for a non-refundable start-up fee of $3,500, and the typical approval is for $2,500, which does cover those expenses," Bussell says.

Another mistake CT sites can avoid involves advertising costs.

"A lot of sponsors are hesitant to give you much advertising money because they say if you are taking the study then you should have these patients in an internal database," Bussell says. "But you still will need someone to cold-call people on the list."

This is why sites should make certain an advertising budget is included as a line item that includes more than the actual cost of buying television, radio, or print media space, she explains.

"The ad line item should not be limited to an actual ad," she says. "It should include a recruitment cost too."

Sites also forget to calculate their overhead costs. These costs could be added to the budget in the form of a percentage of the total budget.

"I ask for 25% because it's in support of the whole operations, including copy machine, electricity, telephone, and rent," Bussell says. "Sites use these resources for the study; they're on the phone monthly with the sponsor, discussing enrollment; they have webcasts to discuss the study."

Also study coordinator and investigator training are becoming more important issues, and sponsors are asking coordinators to have compliance training and/or certification, and these all cost the site money, she adds.

CT sites can avoid these mistakes by taking a few proactive measures, including these steps:

• **Make your own budget:** "When you first receive a protocol synopsis and evaluation flow chart, create your own budget," Bussell suggests. "I use my own templates and compare it to the budget the sponsor sent me."

If the sponsor's budget is adequate, then this comparison will confirm it. If the sponsor's budget is too low, it gives investigators or research staff information to use in negotiations.

Either way, a site's own budget provides a good foundation for comparison, Bussell notes.

• **Save study cost data electronically:** Writing a quick budget for comparison should be a quick and efficient process, taking maybe 30 minutes, Bussell says.

The key is to save a template of typical costs electronically so these can be pulled up and plugged in as each new protocol is analyzed.

For instance, a CT site should know how much it costs to perform procedures like X-rays and ECGs, so if a new protocol lists these procedures for a particular study visit, the investigator could add those pre-determined costs to his or her budget.

"Calculate special testing based on the fee someone would have to pay cash for it," Bussell says. "Include your costs for giving informed consent, taking a medical history, dealing with concomitant medications, lab testing, drug dispensing, diaries, and all the standard components you'd have on visits."

When investigators compare their own line item costs to what the sponsor proposes and find that the sponsor's budget comes up short, they can return to the sponsor and say, "Your testing fees are a little low for this task."

Being armed with data helps, Bussell says.

"I haven't been denied a budget negotiation so far," she says. ■

Master documents, 'score cards' are latest trends in trial contracts

Negotiation process is faster now

Sponsor-initiated clinical trial agreements are well-worn pathways, so it makes sense that the latest trend of recent years is for research sponsors and research institutions to use master agreements.

"Why go through a line item negotiation over terms that are really well understood?" says **Jim Kiriakis**, director of industry contracts at the University of California, San Francisco (UCSF) in San Francisco, CA.

Research institutions typically have their own policy perspectives that are quite familiar to sponsors, and industry sponsors have been doing these types of agreements for 60-70 years, Kiriakis adds.

The contracting process has contributed to a very slow research pipeline in recent decades, and sponsors are beginning to realize this trend has to be reversed.

"You can't take a year negotiating a contract," Kiriakis says. "You have to do it in two weeks."

To make this process work, templates are necessary.

Both sponsors and clinical trial sites need greater consistency in the budget and contracting negotiations, Kiriakis notes.

"Uniformity and replicability are the main things from my perspective," he says. "Master contracts are the smart way to do business; why renegotiate individual contracts with sponsors?"

Master contracts save time and contribute to consistency.

"It can save hours," Kiriakis says. "Instead of having to read a 20-page contract and going back to fix stuff, you have legal items that are agreed upon in advance, and you just add the starting date, end date, dollars, who the principal investigator is, what the protocol is, and you're done."

From a clinical trial site perspective, master contracts bring predictability to the negotiation process. Investigators will know before the agreement meetings begin what a particular sponsor expects and provides in most of the negotiable terms.

"Sites have gotten more sophisticated about managing their operations financially; they understand they need to cover their costs," Kiriakis says.

It makes sense to have a contracting template agreement in place so that the time spent in negotiations can be directed to the most important points, including payment and timelines.

Another recent trend among sponsors is the use of scorecards, Kiriakis says.

"Recently, I meet a sponsor who had a list of all the trials we had conducted in the past three to four years," he notes. "The sponsor kept a scorecard, a report card that included accrual data, the number of patients on the study, and the actual number relative to the forecasted number."

The sponsor could easily identify how long it had taken a particular clinical trial site to accrue subjects and then compare its outcomes with what was expected.

Pharmaceutical and biotechnology companies, along with clinical research organizations (CRO) have begun to collect clinical trial site metrics because it's a survival tactic.

"They have to live up to investor expectations on Wall Street, and time is an asset," Kiriakis says. "You have to get the drug to market."

So sponsors want to know whether a particular clinical trial site can deliver quality on performance, timeliness, and subject accrual, he adds.

"Can you run the protocol accurately? Can you provide a deliverable, which is the whole purpose?" he says."People are measuring efficacy and performance and results as they should."

When the clinical trial industry's statistics suggest the entire industry has been slowed by inefficient site selection and time-consuming processes, including the budget negotiation process, it seems reasonable to wonder why these changes haven't occurred years or decades earlier.

"My guess is because this is such a relationship- and reputation-based industry," Kiriakis says. "If you're a sponsor, you want the investigator with the name and known track record."

Sponsors will say they've returned to do business with investigators they know can do the work, so they don't have to measure the CR site's performance, he adds.

"They're most interested in knowing their investigators extremely well," he says.

But as the CR industry has become more competitive, and the regulatory environment has made navigating new products to market a bigger challenge, this atmosphere has been evolving.

The industry is moving from an acceptance of long product cycles to a growing drive to move investigational products more quickly along the pipeline, Kiriakis says.

"With the dynamics of competition in the industry and the ebbing product portfolios, there's more pressure to do things quickly," he adds. ■

Subject injury program reduces claims costs at research institution

Office works as collaborator with PIs, others

Research institutions often lack policies and programs to deal with research participants' injuries. This neglected area of concern could prove problematic when injuries occur and result in litigation.

The University of California – San Francisco (UCSF) has handled this risk management issue by forming a subject injury group that has operated for the last six years under a system-wide subject injury policy.[1]

"When an event — usually an adverse event report by the principal investigator (PI) — is brought forward as a subject injury claim usually my office will do the initial investigation," says **Carroll Child**, RN, MSc, CCRP, clinical research risk manager, UCSF risk management/insurance services, and chair of the UCSF Subject Injury Group.

"We discuss the situation with PI and/or subject," he adds. "We try to bring together both sides of the equation."

The Subject Injury Group (SIG) works as a collaborator with PIs and subjects and serves as a liaison between the PI and the institution, Child says.

The SIG makes certain all parties agree with the facts and circumstances of the case, including the fact that what happened to the subject is indeed an injury related to the study.

When the case is adequately vetted by the SIG, the case is forwarded to the UC system-wide subject injury program for another assessment and determination.

"They work through a third-party administrator who also can investigate the claim if they choose

to, looking at the past medical history," Child says. "The system-wide — or university-wide — Subject Injury Program makes the final determination."

Having a subject injury policy and program can help reduce costs, according to an analysis performed by Child and Bruce G. Flynn, MS.

Their study found that 57% of subject injury claims filed between Jan. 2006, and Jan. 2010, resulted in no direct costs to the subject injury program. Of the 43% that required payment costs to bring them to settlement, half were litigated outside of the subject injury program, and half were managed within the program.[1]

The litigated claims had settlement costs that were about 20-times higher than the non-litigated claims settled within the subject injury program, suggesting that such programs can result in significant cost benefits.[1]

Subject injury programs might not be a quick or easy answer, however.

"It's not a fast process," Child says. "It involves investigating the billings to vet them and determine which costs would be questioned in terms of treatment costs for an injury versus all the costs that are ongoing for someone with a complicated disease process."

This distinction is particularly an issue for studies involving treatments for complex diseases, such as for cancer patients or people with neurologic diseases like Parkinson's, he notes.

"Another thing my office gets involved in is managing the financial aspects of the case," Child says. "We work with patient financial services and other departments to secure holds on billings so the injured subjects don't get billed for the cost of treatment until there's a final determination."

The subject injury group meets six times a year. It consists of members who are concerned about subject injury, including Child and representatives from sponsor projects through industry, medical center risk management, legal affairs, and the IRB.

"Our subject injury program at the campus level is a close collaboration between the risk management office and the IRB here," Child says. "The IRB carries a lot of responsibility for subject injuries in terms of assessing the risks and benefits of the study."

The subject injury office works with the PI and subject on determining the facts of the case, including looking at these issues:

- Is the injury directly related to the study?
- How well does the claim fit into the definition of a subject injury and the University's Subject Injury Policy?
- Is there a sponsor who has contracted to assume the cost liability for medical treatment?

"Our policy states that we will provide treatment for study-related injuries, including injuries from procedures as well as from the study intervention itself," Child says. "But payment of the costs of such treatment may be covered by the University of California or by the study sponsor, depending on a number of factors."

REFERENCE

1. Child C, Flynn BG. Analysis of an institutionally-based subject injury compensation program. Poster presented at the 2010 Advancing Ethical Research Conference by the Public Responsibility In Medicine & Research, held Dec. 6-8, 2010 in San Diego, CA. ■

CNE/CME OBJECTIVES / INSTRUCTIONS

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

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

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

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

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

COMING IN FUTURE MONTHS

■ Educational groups provide teaching moments

■ Compliance tool and checklist assist with informed consent

■ Plain language in IC forms gains momentum

■ Data safety monitoring tool assists with remote monitoring

CNE/CME QUESTIONS

13. Which of the following is the purpose for creating a corrective action plan (CAP) template?
A. IRBs use the CAP template to inform the continuing review process
B. OHRP and the FDA require a CAP template
C. A CAP template provides a structure for dealing with any kind of research compliance issue
D. The template gives investigators precise language to use when submitting a report on unanticipated problems

14. The federal government now can fine health care and human subjects research organizations for HIPAA privacy breaches. Which law added these penalties?
A. The HIPAA Reauthorization Bill of 2010
B. The American Recovery and Reinvestment Act of 2009 and its Title XIII, the Health Information Technology for Economic and Clinical Health (HITECH)Act
C. The 2010 Health Care Reform Act
D. None of the above

15. In a growing trend, sponsors and clinical research sites increasingly are using master contracts during study negotiations. Which of the following is the reason why they are moving in this direction?
A. Master contracts provide greater consistency, uniformity, and replicability
B. Master contracts save time and expedite the study process
C. Master contracts bring predictability to the negotiation process
D. All of the above

16. An informed consent discussion tool that is used to document the IC discussion probably would need to include all of the following except which question?
A. Were questions from the subject and family, if present, encouraged and answered?
B. Was the subject given adequate time to read, review, and consider the entire informed consent form?
C. Was the informed consent form signed by the subject at the first study visit?
D. Did the subject agree to all protocol-required tests, procedures, and follow-ups?

Answers: 13. C; 14. B; 15. D; 16. C