CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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IN THIS ISSUE

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Special Report: Compliance strategies for 21st Century research

[Editor's note: In this issue of Clinical Trials Administrator, *there is an in-depth look at how various research institutions have improved clinical trial research compliance and dealt with regulatory issues in an age of increasing scrutiny and high stakes, including the cover story about how tools can help with compliance efforts. Inside this issue are stories on self-auditing strategies, using a quality systems approach to research, and creating a consistent project memory for the purpose of improving compliance.]*

Expert advice to prevent regulatory audit findings and improve compliance

Use checklists and audit tools to assist with QA efforts

Clinical trial research teams can run into regulatory trouble when there are too few checks and balances established to catch the mistakes and omissions.

So one way to ensure a research site is complying with regulations and policies is through research tools, checklists, and templates, experts say.

Another strategy is to examine the Food and Drug Administration's (FDA's) research audit findings, which often will mirror an institution's own experiences.

"We took the FDA findings in 2004 and compared it to what we found in our institution, and we found they run mostly parallel," says **Susan Torok-Rood**, MSJ, BSN, CCRP, a senior compliance analyst with the University of Medicine and Dentistry in New Jersey (UMDNJ) in Newark, NJ.

For example, studies sometimes are not conducted according to the IRB-approved protocol, Torok-Rood notes.

"That is a problem, and it ends up a compliance issue," she says. "This is research without IRB approval."

Other common FDA findings are trials that have incomplete or inconsistent documentation, problems with informed consent, and under-reporting of protocol deviations or adverse events, Torok-Rood says.

"Another common mistake is inappropriate delegation of study-

related activities, including tasks or procedures," she says.

There might be a nurse who is performing a physical assessment when it's something the protocol states that the principal investigator should be doing, says **Tracie Witte-Saunders**, RN, MS, CCRC, director of nursing at the New Jersey Medical School (NJMS) University Hospital Cancer Center in Newark. Witte-Saunders and Torok-Rood were scheduled speakers on the topic of common audit findings at the Association of Clinical Research Professionals' Global Conference and Exhibition, held April 20-24, 2007, in Seattle, WA.

"Or a secretary might take trial subjects' blood pressure, which would be inappropriate delegation of tasks on a study," Torok-Rood says.

Research professionals sometimes forget that the IRB application asks investigators to list all of the people on the protocol who will be doing procedures, Witte-Saunders says.

Then the IRB reviews that list of names for credentials that would qualify the person to perform that procedure, Torok-Rood adds.

"At this site, the IRB requires each person working on the protocol to have some kind of IRB training," Witte-Saunders says. "We have a Web site that provides training for investigators and staff on how to do research, and they have to complete the Web site program before they can be listed on an IRB application."

When sites have problems with research without IRB approval, it's usually something subtle, Torok-Rood notes.

Perhaps the principal investigator decided to change a procedure in the study by adding an EKG or MRI procedure to the study, she says.

"They think of this as clinically necessary, so it's not a big deal," Torok-Rood explains. "But it changes the design of the study, and it may impact patient safety in a way that the IRB or any regulatory authority might not accept."

So any change, no matter how seemingly innocuous, requires IRB approval.

This is difficult for physician investigators to grasp because, as clinicians, they make decisions and changes many times in a day that are based on their own judgment, but in research there is a higher standard and so these changes need oversight, Torok-Rood adds.

"The problem with even adding a study procedure is that the design of the study may impact participant safety, and that's what the IRB is all about," she says. "So if you add procedures or subtract procedures they need to know ahead of time, so they can evaluate the safety protocol, risk-benefit ratio."

When investigators forget to inform the IRB of these changes, it's up to the study coordinator to recognize the change and have these submitted to the IRB.

Also, deviations from the protocol, however slight, must be documented and reported.

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For instance, an investigator might decide that a patient with hemoglobin of 9.9 can be enrolled in a protocol when the eligibility criteria say the minimum is hemoglobin of 10, Witte-Saunders notes. "This could impact the patient and study," she says.

When these deviations from the protocol are discovered, they should be logged and explained. For example, a typical deviations/violations log could be designed, with columns for the following:

- Event date
- Subject ID
- Event description (major/minor deviation)
- Reason/action taken to avoid recurrence
- Date IRB notified

The deviations/violations log assists clinical research professionals in assessing whether a specific incident needs to be reported, Torok-Rood says.

"You can sort it out based on this tool, which is basically an Excel spreadsheet," she adds.

Likewise, the adverse event tracking tool can be created on an Excel spreadsheet with columns for causality and other pertinent lab, physical exam data.

"Instead of having the adverse events in the progress notes, have the front of the chart with [the tool listing] each of these events, including when the adverse event happened and the worst grade," Torok-Rood says.

"This helps to capture the causality of the event," Witte-Saunders says. "Patients might be taking five different drugs on a study, and it's the doctor's responsibility to say it could possibly be, or probably not at all related, to the study drug."

It's the study nurse or research coordinator's role to make certain all the documentation is consistent, and the adverse event tracking form makes this easier, she adds.

Other tools also will assist clinical trial sites in improving compliance, Witte-Saunders says.

"We've developed different tools over time, so that when a protocol is submitted to the IRB, and we get approval, there are a lot of things we do behind the scenes," Witte-Saunders explains. "So, as soon as we get the IRB approval, we should be able to enroll patients the next day."

Among the tools is a clinical research organization pre-entry checklist, which includes a "yes" or "no" checklist for the complete initial work-up items, including these examples:

- Informed consent
- History and physical (including vital signs and performance status) within one week of first administration;
- Fiber Optic endoscopy;
- CT of head/neck and chest with contrast;
- Bone scan (if applicable);
- Quality of life questionnaire (within 2 weeks of first administration);
- Dental evaluation (if patient has own teeth — within six weeks of first administration);
- ECG;
- CBCD, CMP, LFTs, Creatinine clearance, pregnancy test (within 2 weeks of first administration); and
- Feeding tube placement.

Another important tool is the eligibility checklist, which clearly shows the inclusion and exclusion criteria, with each item in its own row.

For instance, under inclusion criteria there could be these detailed items, followed by "yes" and "no" responses, which are included in an example of an eligibility checklist used for educational purposes by Witte-Saunders:

- Previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, histologically or cytologically confirmed. The disease must be considered to be potentially curable by combined chemoradiation;
- Stage II or IV disease (excluding T1N1, T2N1 and metastatic disease;
- Age > 18;
- Signed written consent;
- Availability for follow-up for up to 4 years after treatment;
- The patient is infertile or is aware of the risk of becoming pregnant or fathering children and will use adequate contraception (oral contraception, intrauterine devices, diaphragm, and spermicide, or male condom and spermicide) throughout therapy and for at least 3 months after therapy; and
- Life expectancy greater than 6 months.

The beauty of using tools is how it makes the process consistent and accountable.

"We can have multiple hands on one patient's chart, but when everyone is using the same tool, the information is being captured consistently," Witte-Saunders says. "When you are taking care of patients, you are telling a story, and the story is only as good as the details you put in there."

Stories with gaps may result in questions or an audit by the FDA, she adds.

One of the best ways to ensure a site's documentation has no gaps and will meet regulatory standards is through the use of a clinical research audit checklist. This could be a tool with several

TABLE 1

Clinical Research Site Audit Form

REGULATORY REQUIREMENTS	Yes	No	N/A	Comments
Administration of Study Drug				
1. Were the correct drugs ordered?				
2. Were the dosages properly calculated?				
3. Were the correct doses given?				
4. Were the doses recorded on the Nursing Administration Form?				
5. Was there a dose modification?				
6. Was the dose modification per the protocol?				
7. Were there any delays in treatment?				
8. Was the treatment delay justified by the protocol?				
9. Is there documentation of the treatment delay in the patient's chart?				
10. PK's drawn as specified in the protocol and times recorded in the chart?				
11. Comments:				
Radiotherapy Administration				
1. Are the radiotherapy doses correct?				
2. Were there any delays in treatment?				
3. Was the treatment delay justified by the protocol?				
4. Is there documentation of the treatment delay in the patient's chart?				
5. Comments:				
Study Parameters During Treatment Period Performed as Outlined in the Protocol with Source Documentation Present				
1. Physical exams				
2. Breast/Gyn Exam				
3. Hematologies				
4. Chemistries				
5. LFT's				
6. U/A				
7. Radiologic evaluations				
EKG				
Special labs:				
Comments:				

Source: Reprinted with permission from Tracie Witte-Saunders, RN, MS, CCRC, Director of Nursing, at New Jersey Medical School - University Hospital Cancer Center in Newark, NJ.

pages and detailed categories and items in which the site coordinator checks "yes," "no," or "not applicable." Also there could be a column for comments. **(See sample page from NJMS-UH Cancer Center's Clinical Research Audit Checklist, above.)**

For example, the audit checklist used by the NJMS University Hospital Cancer Center includes these six audit items under the category for "Informed Consent:"

- The entire original is in the chart?
- Are the 3 signatures present with the same date?
- Did the patient initial each page?
- Is there a note in the chart that the patient received a copy?

• Is it clear that it was signed prior to treatment being initiated?

• Additional comments

With the audit checklist, CR coordinators can conduct their own quality assurance process on the study and make certain that all of the time points have been completed, Witte-Saunders suggests.

The checklists should be seen as templates that are changed as needed.

"My staff modify the templates to each protocol," Witte-Saunders says.

With the proper tools, clinical research coordinators can handle every study more easily and more efficiently, Torok-Rood says. ■

Self-audits will help prevent major problems

PIs need to take full responsibility for site activity

Clinical trial sites and investigators should not rely on clinical research organization (CRO) monitors to find systemic problems. Instead, they should be proactive with their own in-depth audits, an expert suggests.

When investigators rely on the reports of superficial problems reported by monitors, they risk missing the systemic problems that cause the symptoms often reported by the monitors, says **Tamera Norton Smith**, PhD, MT (ASCP), president and senior consultant of Norton Audits Inc. of Lexington, SC. Smith has more than 17 years of clinical trial experience and, formerly, was a Food and Drug Administration (FDA) investigator. Smith was a scheduled speaker at the Association of Clinical Research Professionals (ACRP) Global Conference and Exhibition, held April 20-24, 2007, in Seattle, WA.

"To me, as an auditor, when I find things on the surface and observe the symptomology, the problem is really three times worse," Smith says.

Site monitors will send out a monitoring report, listing items identified, and investigators often do not take corrective actions based on the monitor's findings, she says. **(See chart on sample critical findings, p. 67.)**

"This is a huge risk because monitoring letters are available to the FDA to review," Smith explains. "If monitoring reports are sitting in files with all of these issues that haven't been corrected, then it's a major concern."

Even better, a principal investigator should be proactive and conduct thorough self-audits before problems draw the attention of regulatory officials and negative findings prompt a random audit occur.

For example, a physician investigator in Atlanta, GA, had worked with Norton Audits for several years to improve research compliance, Smith recalls.

"He'd had some bad experiences with sponsor organizations and knew enough to want his own external audit, so we did this audit three years ago," Smith says. "He has turned around his business and knows the regulations better than any physicians I know, and he knows enough to protect himself from making the same mistakes he made in the past."

Recently, the investigator was inspected for more than two months by FDA investigators, who looked at three different studies, and he came out of that intense scrutiny with only two findings for which he had already put corrective actions in place and the problems had been resolved, Smith explains.

"It was amazing that he came through this audit so well," Smith adds. "If he had not been conducting self-audits and made all the corrections and procedures, then he might have had problems."

While the fact that the audit occurred at all was a major inconvenience to the investigator, the good news is that a thorough look at his records turned up nothing of significance, she says.

In another case, Smith worked with an investigator in Florida who had had 27 monitoring visits over a four-year period, and not a single one identified the bigger issues, Smith says.

"The monitors did have some issues in their monitoring reports, but the PI didn't even sign off on his monitoring report that he'd seen these issues," Smith says.

For these reasons, self-auditing is necessary.

Smith offers these key guidelines for how to conduct and improve auditing and compliance at a research site:

1. Use good clinical practice (GCP) and the Corrective And Preventive Action (CAPA) system.

Staff need to be taught both GCP and CAPA, Smith says.

"Sponsors have investigator meetings where they train them on the protocol and, most of the time, the GCP training is maybe 15 minutes long," Smith says.

Instead, investigators and clinical trial staff need thorough training and education in GCP, all research regulations, and how to conduct informed consent, as well as document properly, she says.

Under the CAPA system, a site will first identify what the problem is, analyze the root cause of why it happened, come up with a corrective and preventive plan, and monitor/audit the process.

Also, it's important to have a buddy system put in place where one study coordinator is looking over the shoulders of another one, she adds.

"They need to learn how to audit themselves and not rely on monitors," Smith explains. "If you are depending on monitors to tell you how you're doing, then they're only finding surface issues and not looking at the root causes that will help them improve their organization."

For example, during the informed consent process, there should be another person, who was not involved with the informed consent, checking all of the signatures on the informed consent form and making sure everything is dated properly and that all of the pages are there, she says.

This could be accomplished with a checklist, Smith adds.

"Be proactive rather than reactive," Smith says

"Most principal investigators will have more than one study coordinator," she explains. "If one is assigned to a study, then a different one will look behind her and do quality control checks, looking at the other coordinator's informed consent or regulatory binder."

2. Create standard operating procedures (SOPs) individualized for the organization.

"Many investigators think they can buy SOPs from any company and be compliant," Smith says. "But they need to know how to follow them, organize the site, and conduct a self-audit."

SOP development and training should be thorough so that investigators have greater skills in this area than do monitors, she says.

"We make SOPs for investigators, but we won't give them to them without the online training," Smith says. "They need the online training to know how to do the procedures."

3. Emphasize investigator duties and responsibilities.

Another goal is to make certain the investigator clearly understands his or her responsibilities, Smith says.

"Most investigators turn over their responsibilities to the clinical research coordinator, but they can't turn over all of the responsibility because they're responsible for the trial," Smith says.

Those who delegate too much of their duties and responsibilities run the risk of having negative findings during an FDA audit, she notes.

For example, the FDA had these comments for an investigator whose site was investigated in 2004, according to a letter written, Oct. 21, 2005, by the director of the FDA's Office of Compliance, Center for Devices and Radiological Health:

• "You failed to adequately supervise the conduct of the study. [21 CFR 812.100, 812.110].

"When you signed the Investigator's Agreements for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation [21 CFR 812.100]. The Investigator's Agreements that you signed required that you or your sub-investigators personally supervise all testing of the device involving human subjects. In addition, regulations provide that an investigator will permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized to receive it, in accordance with 21 CFR Part 812 [21 CFR 812.110(c)]. Although you may delegate study tasks to individuals qualified to perform them, you may not delegate your general responsibilities as a clinical investigator.

"You failed to supervise the study, so as to ensure that your general responsibilities were fulfilled. As detailed in charges 2-6 below, there were numerous violations such as ones involving informed consent, including the falsification of your signature on informed consent documents; protocol violations, including enrollment of patients not meeting eligibility criteria and problems with follow-up visits; and record keeping violations, including the failure to maintain device accountability records. Despite the widespread nature of these problems, in most cases, you made no effort at correction until action was requested by study monitors or your IRB.

"In your responses to the two Form FDA 483s issued to you, you admitted generally that the

Sample chart on critical findings categories and observations

Here are problems in nutshell

Here are some examples of critical findings categories and observations, reprinted with permission from **Tamera Norton Smith**, PhD, MT (ASCP), President and Senior Consultant, Norton Audits Inc. of Lexington, SC:

A. Administrative

1. Inappropriate and/or frequent staff changes;
2. Missing signed agreements;
3. Missing or inconsistent signatures/handwriting;
4. Conflict or discrepancy between sponsor/CRO and Site SOPs; and
5. Discrepancy between sponsor/CRO study files and site records.

B. Regulatory

1. Missing protocol, amendment or administrative documents;
2. Missing protocol, amendment, and/or administrative signature pages;
3. Missing investigator's brochure and/or updates;
4. Inadequate or missing Form FDA 1572/ Investigator's agreement;
5. Inadequate or missing credentials of research staff;
6. Inadequate or missing financial disclosure form;
7. Failure to obtain IRB approvals;
8. Failure to submit progress/annual/final reports to IRB/IEC;
9. Inadequate or missing relevant IRB/IEC;
10. Inadequate or missing IRB/IEC composition or compliance documents;
11. Inadequate or missing delegation of authority documents and/or site signature log sheet.

C. Clinical Laboratory

1. Missing current laboratory license, certification, and/or accreditation;
2. Missing Lab Director credentials; and
3. Inadequate or missing laboratory reference ranges (normal values).

D. Informed Consent

1. Missing IRB approved subject consent form;
2. Inadequate subject consent form;
3. Inadequate consenting process; and
4. Missing or illegible signatures, dates, and/or times on the subject consent form.

E. Study Execution and Monitoring

1. Failure to comply with protocol;
2. Inadequate or missing documentation of protocol exemptions/deviations and/or violations;
3. Inadequate or missing subject screening enrollment log;
4. Inadequate or missing phone contact log, reports, notes, and/or documentation of phone conversations;
5. Inadequate monitoring of site;
6. Inadequate or missing documentation of monitoring activity;
7. Inadequate investigator involvement/oversight;
8. Randomization errors;
9. Inadequate or missing patient compensation;
10. Protocol inconsistencies;
11. Inadequate or missing documentation of site personnel training; and
12. Inappropriate delegation of authority. ■

noted deficiencies did occur, but in those responses, as well as in your statements to the FDA investigator and in your correspondence with your IRB, you repeatedly attributed them to poor performance and lack of experience by research staff, including your former study coordinator, and in some cases, to poor oversight by the study monitor. While your 483 responses also indicate that those staff have been replaced, that you yourself are no longer the principal investigator for these studies, and that new procedures have been implemented, these responses do not excuse your failure to adequately supervise the conduct of the studies during the period in which you were the principal investigator……"

When the FDA has findings, such as in the above case, it means the site will be suspended from conducting that type of research, and the

principal investigator could lose his or her medical license, Smith notes.

"The PI blames the study coordinator for most of the noncompliance, but the law says he's the most responsible person, so you can't delegate your responsibility for the trial," Smith says.

Smith was teaching a compliance course when a number of study coordinators told her that it was okay that they handled many of the details of a clinical trial.

"I said, 'It's okay for you to do them, but not without being supervised,'" Smith recalls. "If you have a coordinator who does bad things, then the PI has no one to blame but himself."

4. Look at critical observations on audit report.

When sites conduct self-audits, or when monitors write reports, the most efficient way to document problems is to use the FDA's deficiency codes, Smith says.

For instance, a monitor might say that the informed consent is missing, but what they should report is that there is a violation of code 01, and there are no records of informed consent available, Smith explains.

"It sounds like an administrative issue, but it means the patient wasn't properly provided informed consent, which should be documented, also, as a violation of deficiency code 02 — 'Failure to obtain and/or document subject consent,'" Smith says.

It would also be very helpful if these audits and monitoring reports referred to CFR codes when problems are noted, she adds.

"Monitors right now are so far away from being able to do that, but hopefully, in the next three to five years, we can get most of the industry to do that," Smith says.

Here are some examples of deficiency codes and the federal regulations reference numbers:

- Code 05: Inadequate drug accountability — 21 CFR 312.60, 312.62
- Code 07: Unapproved concomitant therapy — 21 CFR 312.62
- Code 10: Inappropriate delegation of authority — 21 CFR 312.7, 312.61
- Code 16: Failure to report adverse drug reactions — 21 CFR 312.64, 312.66

"Most of the time, I learn from investigators that there's not a lot of intent to do research the wrong way," Smith says. "It's about education, because very few of them are deliberately or repeatedly trying to be noncompliant." ■

CR site problems may mean inadequate monitoring

Expert offers quality systems approach tips

Compliance problems at clinical trial (CT) sites can result in FDA warning letters to sponsors for their lack of adequate follow-up after finding compliance problems, an expert says.

The FDA is particularly concerned about CT sites that have no clear documentation and have failed to correct problems, says **Paul Below**, CCRA, clinical research consultant and trainer of P. Below Consulting Inc. of Burnsville, MN.

With years of project management and clinical research association supervision experience, Below says it's frustrating to see the types of mistakes found by the FDA.

"Compliance problems seen again and again at the site level could have been prevented by monitoring," Below says.

"My colleagues and I at the Association of Clinical Research Professionals (ACRP) review the compliance problems that are identified at the site level by the FDA, as evidenced in their warning letters," Below says. "In 2006, there were 33 warning letters to investigators."

The key is for sponsors and CT sites to use a quality systems approach to research, Below says.

"The quality systems approach has been used in the pharmaceutical industry for a long time," Below explains. "It includes good lab practices and good manufacturing processes."

Some CR experts are proposing that the industry move toward a quality systems approach, including consistency and standardization in dealing with problems, because regulatory audit findings suggest that CR sites are not learning from the mistakes of their peers, Below says.

"The number of issues seen in warning letters is not going down," Below says. "Each year, there are multiple examples from FDA audits of failures in monitoring; they're not preventing deficiencies, and they're not being corrected."

Some of the problems are widespread. For example, some warning letters indicate there are informed consent problems with not just a few subjects, but with the majority of subjects, Below says.

"That's a problem that should have been picked up by the monitor initially, but obviously was not," he adds. "And if you look at FDA

warning letters to sponsors, there were a number of citations of sponsors who didn't adequately follow-up on those deficiencies."

The sponsors didn't do anything to correct problems found at sites, and they passed on the findings to their management, with no plan for correction and follow-up, Below says.

"So the problems happened again and again," he says.

Whenever there's a failure in the manufacturing system, the quality systems approach requires the organization to analyze it, find the root cause, and come up with corrective action, as well as a plan to prevent it from happening again, Below says.

Called CAPA for Corrective And Preventive Action, the approach was designed to fix manufacturing problems, Below says.

"But I've had a number of clients who've started to adopt it in the good clinical practice arena, he notes.

"When a quality assurance auditor investigates a site and finds deficiencies, he or she puts in the report that a site should write a CAPA plan, so clinical sites are becoming accustomed to designing CAPA responses and audits, Below says.

"But we don't look at it as something to do on an ongoing basis for a clinical trial," he adds.

The quality systems approach would look for deficiencies or failures in the CT process, including protocol violations, safety problems for trial participants, data integrity, and other issues that could result in a FDA warning letter or deficiency issues raised by CT monitors, Below says.

Here's how the quality systems approach could be pursued by CR organizations, including CR monitoring companies:

1. Identify deficiencies.

"In the good manufacturing practice (GMP) world, they call them failures," Below says. "In the GCP world, it's not the same."

When a clinical trial site first identifies a deficiency, it could be a violation of the protocol, a violation of good clinical practice, or an informed consent violation, he explains.

"The first step is to identify the root cause of the problem; find out why it happened," Below says. "This requires a clinical research associate (CRA) to ask a lot of questions and interview the staff to try to figure out the real root causes, because there can be a couple of root causes to a deficiency."

For example, suppose a CRA was to note in the monitoring report that a serious adverse event (SAE) occurred to a subject at the site and the SAE was not reported to the sponsor or IRB, Below says.

"This is not a rare finding, and probably all CRAs have come across it at one time or another," Below says. "The issue for the CRA would be why it happened, what was the cause."

"It could have been a simple inadvertent oversight by the staff, and if that's the case, then you have to dig a little deeper to find out why there was that oversight," Below explains. "Was something else going on with the staff to prevent them from doing a thorough review? Were they not documenting study subjects like they should?"

In the audit world, questions relating to what caused a failure are referred to as the Five Why's, as in, "Why did this happen and why did I miss it?" Below notes.

Those questions should reveal the root cause.

"Another explanation might be that the study coordinator didn't report the event and didn't think it met the criteria for a serious adverse event," Below says. "So the root cause in that case is going to be a lack of training issue."

The bottom line is that the CRA needs to get down to what caused the problem, and it needs to be the first step, he adds.

"Most good CRAs will find the cause intuitively, but they don't think of it as a first step," Below explains. "Most are trained to correct a problem, and their initial activities revolve around what do we do to fix this now — instead of finding out what the root cause is."

2. Show what needs to be done to correct the problem.

In the above example of an overlooked SAE, there were two potential root causes described. If the CRA determines the root cause was staff oversight, then the correction would be to revise the study coordinators' medical record review process, Below says.

"In the second scenario of the study coordinator not thinking the SAE met criteria for SAEs, then the site will need to retrain staff on the definition of serious adverse events," Below says.

If the root cause is a workflow issue in which research professionals are not reviewing the medical charts the way they need to in order to identify the SAEs, then the corrective action is to counsel them to make sure they are doing so, Below says.

"Investigate the way they are reviewing charts, and make sure the study coordinator and principal investigator are doing independent reviews of each other, so that if one is missing something then the other one can catch it," Below adds.

Also, there are immediate actions that need to be taken, Below says.

"You have to make sure it's reported right away and that it's reported to the sponsor," he adds.

3. Review corrective and preventive plan for problems.

"An obvious failure of the plan is if you go back to the site and things still are missed," Below says.

"The major responsibility or implementation [of a CAPA] is with the principal investigator at the site," Below says. "But the project manager's responsibility also is to do ongoing monitoring to make sure preventive plans are working."

Project managers should be able to assess problems from all sites in a study and note any trends, he adds.

"They need to look at how sites are implementing corrective plans and determine whether the corrective and preventive action plan is sufficient, Below says.

"If it's not sufficient, they need to step in with a more robust plan, and good project managers do this intuitively," he says.

CR monitors also need to keep better documentation about CAPA plans.

"Monitors are good at describing deficiencies, but they're not so good at describing corrective and preventive actions they've taken," Below says.

4. Find workable strategies for ongoing monitoring.

The mechanics of monitoring needs some adjustment, Below suggests.

"A number of sponsors have gone to an approach now where they're not monitoring all of the source documents, not 100 percent," he says. "They're only choosing a number of randomly-selected patients and doing monitoring based on those patients."

This is a cost-saving strategy, but it poses risks, Below adds.

"When you take an approach like that and decide that monitors are only going to look at a selected set of data, then the project manager needs to define, in advance, what the error rate will be before you automatically have the monitor look at more documents," Below says. "This requires you to have a plan in advance."

The error rate might be the number of data queries generated by the site, which would include monitoring deficiencies noted on every visit, Below says.

"When those exceed a certain level, then you'd have the monitor stay on the site, look at more data, and monitor more frequently," Below says.

"A lot of companies that do the random sample monitoring approach do have policies where, if needed, the monitor can look at more records," Below notes. "But they don't define when they will implement that."

Another strategy for improving monitoring is to have it occur early during a trial's enrollment and to make this a best practice, Below suggests.

"Many sponsors, but not all, have adopted this approach, but a lot I've worked with have not," he says.

"After the first one or two people have enrolled, that's when the CRA has to get out there and monitor the study," Below says. "They need to look at the documentation, and if there are going to be problems, then you'll typically see them early on."

Lastly, CRAs need to do a better job of documenting and communicating the issues they've found. This is so sponsors really understand what's going on, Below says. ■

Approaching research administration: Risk?

Key is creating consistent project memory

Universities in North America face risks in the way they execute research administration, an expert says.

Typically, research universities take the project approach to studies, which results in a lack of consistent project memory, says **Carl Weatherell**, chief project officer, research and international, Carleton University in Ottawa, Ontario, Canada.

"A lot of risks universities are faced with now are financially-based," Weatherell says. "In Canada, a lot of projects are complex, with multiple funders."

So if someone at the beginning of the study process doesn't understand study budgets and cycles when negotiating a study budget with sponsors, investigators and a research team could be stuck with a project they are unable to deliver, Weatherell explains.

For example, Weatherell was on the board of a large consortium project, and the people writing the budget allotted 1 percent of the total budget for managing the project.

"The industry metrics are a minimum of 10 percent, so right there you have a problem and can't deliver that project," he adds. "We have a $45 million consortium project, and we'll give you $450,000 to deliver management across the university over a number of years — it's impossible."

This approach to federally-funded projects is unmanageable, Weatherell says.

This is just one example why there is risk in the way universities typically conduct research, he says.

Universities follow an administrative approach to research. This means that different offices handle various parts of the research study cycle, and there is no project memory as the study moves from one stage to the next, Weatherell explains.

For example, a university will have a pre-award office help an investigator write a grant proposal to a government agency, Weatherell says.

Then a post-award office will assist with what happens when the study is executed, and this might include research accounting, risk management, and health and safety issues, he says.

"This is a silo approach to research administration," Weatherell says.

The better approach would be a project management approach, in which one office manages the project from start to finish, relying on project memory to avoid common obstacles and mistakes, he says.

"For example, if a faculty member is working on a proposal, the typical administrator looks at the budget and says, 'You need 10 students and some equipment, and this is a good budget,'" Weatherell says.

"I would look at it and say, 'How will you phase this? What is the contingency in each area? Are rates going up?'" he says. "And I would let faculty members know that it will not be done in five days."

At Carleton University, the risk manager is required to review every contract over $300,000, Weatherell says.

"So if investigators want $1 million for research and they give us a contract to review, the risk manager will review it and be a part of the negotiations," he explains.

The risk manager is part of a team that deals with every research project, which creates the necessary consistency and project memory.

"We put teams together with broad or specific knowledge," Weatherell says. "For contracts, the risk manager will look at clauses; the information technology person will look at everything, but focus on IT things, the financial experts look at the funding and note what we can meet and what we can't meet, and I will look at everything and ask questions and learn from the other experts."

From the investigator's perspective, this means there now is a team in the room when they discuss a research contract, Weatherell says.

For instance, in one research project review, the team told an investigator that her budget cycle was unrealistic and should be adjusted, he recalls.

"I had a comment from a faculty member who said this was the first time anyone ever helped

CE/CME Objectives / Instructions

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

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

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

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

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

COMING IN FUTURE MONTHS

- ■ Institution starts a clinical trial monitoring service
- ■ Check protocol for feasibility before signing
- ■ Foster team-building at CR site
- ■ Strategies for making profit from CR investment

her with a budget, and it was really good," Weatherell says.

The project team's goals are to keep the project managed and make sure everyone is fully engaged, he says.

It's important to make sure all partners are on equal footing, and good communication with funders is a risk reduction strategy as well, Weatherell notes.

"We had a project that had some challenges with it, so I went to one of the funders and said, 'We have a challenge, so how can we work together to work this out?'" Weatherell says. "He was stunned and said, 'I've never done this before.'"

The way to approach the sponsor is to say, "We both have a problem — you gave us the money, and we're trying to do a project, but if it doesn't work out, then we both look bad," Weatherell suggests.

Through this type of communication, the sponsor might provide additional funds to help complete the project.

In this case, there was greater risk if the research team didn't do anything about the looming problem.

They key is to look at risk from the flip side of, "What would happen if I didn't do something?" Weatherell says. ■

CE/CME *questions*

19. A typical deviations/violations log should be designed with columns for which of the following?
A. Event date, subject ID, event description, reason/action taken, date IRB notified.
B. Event date, subject ID, regulatory report code, date FDA notified.
C. Event date, subject's name, event description.
D. None of the above

20. The deficiency code and federal regulatory section pertaining to a problem of "Inappropriate Delegation of Authority" is which of the following:
A. Code 05 - 21 CFR 312.60, 312.62
B. Code 07 - 21 CFR 312.62.
C. Code 10 - 21 CFR 312.7, 312.61
D. Code 16 - 21 CFR 312.64, 312.66

21. The corrective and preventive action (CAPA) process involves which of the following activities?
A. Identify the root cause of the problem.
B. Correct the problem.
C. Put processes in place to monitor and prevent the problem from recurring.
D. All of the above

22. Which of the following is not a good example of a regulatory critical findings category and observation?
A. Discrepancy between sponsor/CRO study files and site records.
B. Missing protocol, amendment or administrative documents.
C. Missing protocol, amendment, and/or administrative signature pages.
D. Missing investigator's brochure and/or updates.

Answers: 19. (a); 20. (c); 21. (d); 22. (a)