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Clinical Trials Administrator provides you with evidence-based information and best practices that help you make informed decisions concerning management, oversight, and regulatory compliance in clinical trials. Our intent is the same as yours — the best possible patient care.

The objectives of ***Clinical Trials Administrator*** are:

1. **Review** pertinent regulatory mandates.
2. **Develop** practical clinical trial oversight strategies.
3. **Review** best practices shared by facilities that successfully conduct clinical trials.

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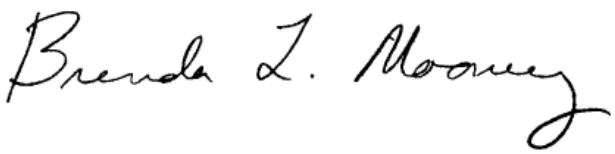

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IN THIS ISSUE

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Clinical trial drift can cause high PI turnover, low patient recruitment

Education assessment and interventions are the solutions

The clinical trial industry continues to experience problems with investigator and patient recruitment, and experts say the cause is trial drift, defined as the gradual reduction in study knowledge as a clinical trial ages.

The Tufts Center for the Study of Drug Development in Boston released a report in May showing that the number of principal investigators conducting industry-sponsored studies in the United States declined 11.4% between 2001 and 2003, while the same period had a 10.6% decline in clinical trials.[1]

This study highlights the ongoing trend of researchers abandoning clinical trial work due to frustration that is caused by trial drift, said **Al Oviedo Pacino** II, president of Hillicon Training and Assessment Campuses in Cedar Park, TX. Pacino spoke about trial drift at the 2005 Association of Clinical Research Professionals (ACRP) North American Annual Conference held April 2-6 in Orlando.

"More than half of investigators choose never to conduct another clinical trial," he noted. "Basically, the main problem in medical research is the lack of communication and assessments between sponsors, clinical research organizations [CROs], investigative sites, and vendors doing a clinical trial."

Trial drift typically occurs when clinical trial investigators and staff's interest in a clinical trial deteriorates over time and when the average knowledge base of all personnel involved in the clinical trial or study decreases as the trial extends its timeline, Pacino explained.

"What it simply means is the longer the trial is, the more the trial drifts, depending on the therapeutic area," he said.

Trial drift is a huge problem that contributes to the research industry's No. 1 problem and challenge of patient recruitment and enrollment, said **Ruth Ann Nylen**, PhD, lead consultant at the RAN Institute Inc. in Land O'Lakes, FL. Nylen also spoke about trial drift at the recent ACRP conference. "I've been in clinical research for 24 years, and I've rarely ever seen a clinical trial enroll all of the subjects at each of the centers for a multicenter trial," she added. "It's become a far greater

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Editorial Questions

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challenge for the pharmaceutical industry to enroll the number of subjects required within the time frame."

The cause of trial drift is inadequate investigator and clinical trial staff training about the protocol and good clinical practices, Pacino and Nylen said.

Recently, there has been a trend for regulatory agencies to require additional documentation and proof that all personnel involved in clinical trial research are informed, trained, and assessed properly, Pacino noted.

However, it's been left up to the clinical trial industry to decide how to do this, and so far, there are few who have solved the problem, which can cost the industry millions in money wasted on inefficient subject recruitment or on flawed studies, he said.

Typically, investigators will attend an investigative meeting that uses PowerPoint presentations and videos to explain the protocol but provides no tests to assess whether the attendees fully understand the exclusion/inclusion criteria and other features, Pacino explained.

The sponsors or CROs don't benchmark the investigators' knowledge because they're not assessing it, so investigators often walk away with an incomplete understanding of trials, he added.

"We don't know if any individual understood the specific areas of the clinical trial, safety regulations, and other topics," Pacino said. "There are no metrics or benchmarks collected."

Most of the time, investigators do not fully understand specifics of what's presented. That leads to frustration because their inadequate understanding of a clinical trial's inclusion/exclusion criteria often leads to problems in recruiting the right subjects and interest drifts, Pacino added.

In her more than two decades of working in the clinical trial industry, Nylen said she has never seen a multicenter protocol in which every subject enrolled was 100% compliant with the protocol and regulations. "There are some situations with protocol violations that are not in the control of the sponsor or investigator, such as the patient doesn't take his medication on schedule. That's a violation that the patient is responsible for."

However, that violation might be avoided if the subject is properly trained by a clinical trial team and investigator who also are properly trained, Nylen noted.

When subjects miss visits, those also are violations that sometimes could be avoided through

proper training and education, she said.

Better education and training is one part of the solution, but the hardest part will be to change the traditional mindset among sponsors, CROs, and clinical trial sites and convince all parties to become more invested in improved clinical trial quality from the moment a protocol is presented, Nylen and Pacino said. **(See story on solutions to trial drift, below.)**

"Historically, what has happened at the beginning of a multicenter trial is there's a review of the protocol, the study-specific issues, and invariably there's a good clinical practice component," Nylen explained. "For most investigators, when the GCP [good clinical practice] training and review comes, that's the time when they're in the hallway on their cell phone, and they miss it."

Nylen has taught these GCP portions of investigator meetings, and said she's convinced there is a better way to educate investigators on good clinical practice.

Reference

1. Number of Principal Investigators in the U.S. is Declining, According to Tufts CSDD [Press release]. Boston: Tufts Center for the Study of Drug Development; May 2005. Web site: http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=54. ■

Solving the problem of clinical trial drift

Planning, education, monitoring are key

Finding solutions to trial drift begins at the top with the sponsor, but also requires clinical trial staff to become more committed to good clinical practices and knowledge testing, experts say.

"No. 1, a sponsor needs to establish a strategic plan for every trial, on how they are going to communicate and train and maintain the knowledge level with every site before they ever start the trial," said **Ruth Ann Nylen**, PHD, lead consultant at the RAN Institute Inc. in Land O'Lakes, FL.

Nylen spoke about finding solutions to trial drift at the 2005 Association of Clinical Research Professionals (ACRP) North American Annual Conference held April 2-6 in Orlando. The written plan should outline when a sponsor or clinical research organization (CRO) will communicate with sites and how they will communicate, whether by newsletter, Internet training, etc., she said.

The next step is to provide training and education that can be measured to make certain investigators and clinical trial staff fully understand good clinical practices (GCP) and a particular protocol's details, added **Al Oviedo Pacino** II, president of Hillicon Training and Assessment Campuses in Cedar Park, TX. Pacino also spoke about solutions for trial drift at the recent ACRP conference.

Sponsors and CROs could hold educational sessions via the Internet and use Internet-based assessment tools to make certain investigators and clinical trial staff are meeting expectations for knowledge about research and protocols, he continued.

"If you want to do this in real time, then you could do it as a web-based program, setting up a trial campus on a virtual university and have sites involved in the clinical trial around the world do training and assessments at each participant's own convenience," Pacino said. "Then the system collects that information based on each specific module and measures those answers, and that gives the tools for the administration and managerial team to assess individuals who are involved in the clinical trial," he explained.

When test results show certain individuals performed poorly, then sponsors or CROs can target additional education to those individuals in an effort to improve their knowledge deficits, Pacino added.

Sometimes, an intervention could be as simple as a telephone call to clarify information; and sometimes, it might require a second test to ensure the individual has learned the material after the intervention, he said.

For clinical trials lasting 12 months or longer, which most of them are, there should be documented baseline training with a performance matrix that enables a sponsor or CRO to identify anyone who needs remedial training or whether there are any systemic weaknesses in the training program, Nylen said. "One huge solution is documenting what investigators know," she explained. "Train them up front and take the GCP out of the investigator meeting."

Instead, GCP should be taught as a 45-minute to one-hour training session on-line prior to the investigator meeting, and participants should be tested after they complete the session, Nylen added.

"Then when the investigator meeting happens, the sponsor can have face-to-face time with investigators to address any problems or areas of concern

because they have documentation to show where the investigator and staff were strong or weak," she said.

"We're doing that with some sponsors for protocol specific issues, so we can help the sponsor get the best quality knowledge in the hands of investigators, so they can conduct the trial accurately, efficiently, and properly," Nylen explained.

Another way to improve deficits is by sending research associates or coaches for additional training to sites that are having difficulty, Pacino said. "You can continuously do benchmarking and assessments in a clinical trial to better manage it, so if the trial starts drifting, you can figure out why."

An inadequately trained investigator might do a poor job planning, and this could have negative impact on a clinical trial.

For example, a trial protocol requires a subject to have a return visit 14 days ± two from the first visit. The clinical trial staff schedule the first visit two weeks before a holiday, which means that when the subject comes in for the visit, the second visit automatically is pushed back by four or five days during the scheduling process, Nylen pointed out.

Well-trained investigators and clinical trial staff will have planned visits in such a way that there's preparation for follow-up visits before the first visits are scheduled, so this problem, which would put the site in violation of the protocol, does not occur, she added.

"There are a lot of logistical problems that occur, and we can help investigators and investigative site staff better understand the logistics and help them with reminders on a regular basis, using the Internet," Nylen said.

(Editor's note: For more information about trial drift or to report trial drift problems or solutions, visit a newly formed trial drift solutions community at www.trialdrift.org.) ■

Don't overlook budgeting, billing quality initiatives

Experts offer strategies that work

One weak link for many research institutions in clinical research quality and best practices lies in the realm of financial affairs.

Too often the clinical research team charged with negotiating budgets consists of research professionals who don't have training in finance or compliance, explained **Harriett Singer**, MS, FACMPE, an instructor in the department of pediatrics at Baylor College of Medicine in Houston. Singer spoke about this topic at the 2005 Association of Clinical Research Professionals (ACRP) North American Annual Conference, held April 2-6 in Orlando.

"They often are trained in human subjects protection, but not in the sort of financial compliance areas where we feel there are significant risks to the investigators and also to the institutions," she said.

One of the chief financial issues that research institutions should address concerns creating budgets, noted **Angela Fornataro McMahill**, JD, CCP, CCRA, director of the University of California, San Diego (UCSD) Clinical Trials Administrative Services and Research Compliance Office. McMahill also spoke about financial compliance at the recent ACRP conference.

Research institutions need to ensure their final budget for a clinical trial has been drafted appropriately to make sure all costs are included so the institution is not subsidizing the research, she added. "Some institutions haven't developed initiated standardized research prices," McMahill said. "Four years ago, our institution put those in place, and most are moving in that direction."

Singer and McMahill offered these guidelines to improve the financial aspects of clinical trials:

1. Include all hidden costs in budgets.

"An industry sponsor might send out a complex or an even simple budget attached to a contract," Singer said. "That budget may not include all the line items and all the elements that go into the cost of doing clinical research."

For example, direct costs may include a lot of indirect or overhead costs, so if researchers are not experienced at teasing out those costs, then they may be undervaluing their research, she noted. "Even though there may be the appearance that there's excess revenue at the end of the study, I think it's more likely the costs are just not being outlined ahead of time and that a study is being underfunded," Singer explained.

"Another financial issue that occurs when investigators negotiate budgets is they may accept a proposed budget without discussing it because they think they have to and are uncomfortable with financial negotiations," she said. "Maybe they were in a hurry and didn't have the time and patience for it."

Singer recalled a study where the investigator

was willing to accept the sponsor's proposed budget, but wisely made the decision to receive Singer's input first.

"I said, 'I think we need to enhance the revenue in a variety of line items,' so we sat down and negotiated together with the sponsor, and this particular budget turned out to be greatly enhanced," Singer said. "After we successfully negotiated this study, the investigator turned out to be my biggest supporter, who now sends his contracts directly to me to negotiate."

When a study is underfunded, then it could run foul of regulatory rules that do not allow tax-exempt organizations to provide subsidies to for-profit sponsors, Singer explained.

"That might jeopardize the tax-exempt status of a nonprofit investigator site," she noted.

On the other hand, overfunding could represent a profit to an institution that might also jeopardize tax-exempt status, although this is far less likely because many more budgets are underfunded than overfunded, Singer said.

When an ending budget shows a profit, it's probably because the clinical trials office has not included line items for all of the costs, giving the illusory appearance of a profit when there actually is none, she added.

This problem of underfunding results from a lack of coordination between finance staff and clinical research staff, and it also represents a major compliance risk, Singer explained.

"The people invoicing a sponsor may not be responsible for day-to-day operations; and at a big institution, there may be a separation between finance and research staff," she continued.

A solution would be to have finance and research staff work together to determine all hidden and overhead costs prior to approving a sponsor's budget, Singer said.

2. Put in checks and balances for billing.

If an institution chooses to bill for clinical trial research, it should have specific policies and appropriate monitoring to ensure billing occurs appropriately.

"Our institution has a conservative policy that for commercially sponsored clinical trials, we don't feel it's appropriate to bill the participant or insurer for costs in the trial," McMahill said. "Instead, we bill the sponsor, and if there's an injury related to the trial, the injury costs cannot be billed as well."

The University of California has that policy despite the Medicare clinical trials coverage decision and a California law that permits some research billing to go to third parties for certain trials, she added.

Some sponsors will request research billing, but university policy does not permit this activity, McMahill noted.

This is such a long-standing policy at the university that it hasn't been an issue with sponsors, she said.

Another checks and balance in place involves requiring investigators to open a bulk account number for a research trial prior to signing the clinical trial contract, McMahill noted.

"In order to register a patient here at UCSD and to make sure charges don't pass to the patient or insurance, we have a bulk account established," she explained. "There's a bulk account form on-line, and a number is assigned, so when they have a patient enrolled, the registration includes that bulk account number."

Institutions also could monitor clinical trial patients' accounts to make certain all billing goes to the research account and hasn't been mistakenly diverted to the patient or a private insurer, she added.

"We've set up a system where calls come in related to billing complaints, and we monitor those," McMahill said. "If there appears to be a systems problem, then we do a root cause analysis so we can correct it."

If there are errors related to research staff issues, then training is provided, she said.

Another good checks and balance tool is the institutional billing account, which should be sent to the person who oversees the research study to make certain the research staff are involved in deciding what is the standard of care vs. research care, Singer added.

"We work with the research staff from the very beginning of a study," Singer explained. "And we make sure the hospital is paid and the ancillary costs are paid from the appropriate source."

3. Provide adequate training of clinical trials and finance staff.

Training for clinical trial staff should include a financial compliance module, she suggested.

"This module might be anything from just raising sensitivity to the issues, lasting an hour or two, to a more extensive seminar training session," Singer said. "It's mostly to make people aware of the institution's resources that can help them and having them aware of compliance risks and how to mitigate them."

Likewise, finance staff should be educated about clinical trial work, she added. "If you're on the

business side of a large academic research center, you might not be aware of what clinical research is or how these studies work." Education for finance staff could take place with on-line courses and interactive tests, Singer added.

At UCSD the research compliance program is structured in a way that relies heavily on training and education, McMahill said.

The research compliance education activities include:

- bimonthly newsletter that focuses on research compliance policies and changes;
- monthly training sessions that provide basic information on conducting research, plus a recent session on effective budget preparation and negotiation;
- help line for staff who have questions;
- intranet that centralizes research information and forms necessary to conduct research at UCSD.

"Now we're working on mandatory competencies for research staff," McMahill said.

Compliance is woven into all of the clinical trials education, and educational sessions are taught by UCSD researchers, staff, and community members, who are considered experts, she noted. "We feel education is so important, and it's the basis for ensuring you have compliance."

4. Conduct a profit-and-loss analysis.

When research and finance staff have a working partnership, it's a good idea for the two groups to pair up and conduct a profit-and-loss analysis of research contracts after they've ended to see whether the contract budget was accurate, Singer said.

The first step of the analysis to look at what's included with regard to direct patient care costs, she explained.

Questions to consider during the analysis include these:

- What were the variable and indirect costs?
- Was the sponsor billed for all research-related costs?
- Has the sponsor paid everything agreed to in the contract or are there holdbacks?
- If it wasn't fully funded, why wasn't it?
- How was the investigator's effort extended, and was that effort covered by the clinical trials revenue?

Once the analysis is complete, the information should be used to help investigators and clinical staff understand more fully the true costs of research and the true revenue of research, Singer said.

When hidden costs are discovered through this analysis, then those will need to be researched, and this may include talking with clinical research professionals to find out what unusual or undocumented circumstances took place in the clinical trial, she noted.

"Were there visits that were unscheduled, and were they billed to the sponsor?" Singer added. "A lot of times the answer is, 'No.'"

A profit-and-loss analysis shows researchers the big picture of research costs, so they'll understand global costs the next time they negotiate a clinical trial contract, she said. ■

Compliance Corner

Deal with noncompliance before it reaches the FDA

Former FDA auditor offers insider tips

The main causes of research noncompliance result from investigators, research staff, and industry sponsor staff misunderstanding or having difficulty interpreting regulations, says a former FDA investigator.

While the average FDA investigator spends a year learning about the regulations and the law, the average clinical trial monitor receives maybe a three-day class, says **Tamera Norton Smith**, PHD, MT(ASCP), president and senior consultant of Norton Audits Inc. of Lexington, SC. Smith has spent 17 years in medical research compliance and began her career with the FDA as a federal investigator.

"I go inside of sponsor companies and find executive level managers who can't answer basic law questions," she says.

Clinical trial sites, sponsors, and site monitors could greatly improve their ability to audit a clinical trial site's compliance and prevent problems that may occur during an FDA audit by following a few important steps, Smith notes.

Here are her suggestions:

1. Develop a corrective and preventive action (CAPA) plan.

CAPAs are necessary for conducting and documenting internal activities for constant compliance assessment of clinical trial research. Norton

Issue Completion Tracking Log

Assessment Date: _____ Reviewer(s): _____

Investigator: _____ Prepared by: _____ Date: _____

Protocol Number(s): _____ Number: _____

Corrective Action Review:

Clinic Director: _____ Date: _____

Clinical Investigator: _____ Date: _____

No.	Observation	Recommendation	Corrective Action	Completion Target Date	Responsible Person(s)	Completion Date
1.						
2.						
3.						

Source: Reprinted with permission.Tamera Norton Smith, PhD, MT(ASCP), President, Senior Consultant, Norton Audits Inc., Lexington, SC. Web site: www.nortonaudits.com.

Audits has a mock CAPA program's standard operations procedure (SOP) for clinical investigators available for a free download on its web site at www.nortonaudits.com.

Norton Audits also has created a clinical investigator's corrective action resolution form, a CAPA assessment plan, an issue completion tracking log, and a CAPA assessment tracking log. **(See sample compliance tools, above and inserted in this issue.)**

"We find during the auditing process that the average monitor is pretty good at identifying errors within a monitoring process, but not very good at making sure their researcher can correct those errors," Smith says. "So when the agency comes in and inspects that position, we often find that those errors have stayed for the duration of the trial, which could impact data or patient safety and reflect poorly on the sponsor."

Sponsors typically use a memo or note to file when errors are found; and while that's a red flag, it doesn't correct the problem, Smith notes. There has to be a system to find problems and to teach compliance monitoring to staff, she adds.

2. Write SOPs.

Norton Audits provides training services to the FDA's Center for Devices and Radiological Health's Division of Scientific Investigations, as well as to research sponsors and clinical trial sites, and part of its efforts have included developing SOPs to improve compliance quality, Smith says.

The research industry is handling compliance incorrectly, she notes.

"We put a lot of money into education, and we're not really getting the results," Smith says. "In fact, noncompliance is worse than it has been, which is why we're trying to get these skills out there and are teaching people how to read the regulations."

For example, the SOPs developed for CAPA includes 15 procedure steps that must be followed, including these examples:

- All clinic research team members can be delegated to in various aspects in concert with their experience, training, and qualifications to achieve ultimate compliance outcomes.
- All monitoring letters received from sponsors or contract research organizations, which identify issue(s) that need to have corrective actions, will need to have a CAPA form completed and issues resolved prior to the next monitoring visit. When issues are ongoing or potentially incorrectly reported in the monitoring letter, the CAPA form should reflect that the issues(s) continues to be open and still is being resolved.
- All CAPA forms are reviewed, signed, and

dated by the individual preparing the form and approved by the clinical investigator.

3. Educate and train staff about regulations.

The first step in training staff is to go over the regulations and provide realistic interpretations for what is expected of clinical trial sites with regard to compliance, Smith continues.

"Secondly, we teach skills for setting up a proper infrastructure in a company to be based on quality systems," she explains.

For instance, the infrastructure should include a definition of noncompliance because if it's not defined in the procedures, how will staff know whether something is in compliance, Smith points out.

"You want them to break apart the procedures and say, 'In this process where we do informed consent, what are all noncompliance issues that happen in this area?'" she says.

This process may require regulatory changes so the research industry could see regulations that more clearly define and describe noncompliance, Smith notes.

"We're working with the Center for Devices on this issue," she says.

4. Teach staff how to audit.

"From what we see in the industry, the problem is the average auditor and monitor are doing what I call the practice of inventorying," Smith says. "They look at the case report form and medical chart and compare the two."

That's not a true audit or an adequate way to monitor compliance, she notes.

"That's not challenging a record," Smith says.

Sites should train staff to conduct true audits, which include multiple cross-checking of records, she explains.

"They need to know the difference between what is a true source record vs. a transcribed record, which is the anchoring of knowledge," Smith says.

Calling it the Norton method, she says there are a set of skills that need to be developed before a true audit can be performed.

For example, a site has a source medical record that is missing certain entries, Smith adds.

"You have the master drug record, and you can tell it was filled out after the fact; and you have the actual drug product that was returned from the patient," she explains. "And you have to figure out which is the most accurate representation of fact — the medical chart or what came back from the patient?"

The answer likely would be the actual drug that came back from the patient, and that's what is called anchoring, because it's the most accurate representation of facts, she says.

5. Work on improving staff's interviewing skills.

If you have ever wondered how an auditor with the FDA was able to find out so much more than what a research organization volunteers, then the answer is here: It's because they're taught interviewing techniques that include paying strong attention to nonverbal cues.

"The average FDA investigator receives training in interviewing, interrogation, and body language," Smith notes. "The paperwork trail tells you one story, and how a person operates tells you another story.

"For example, say I'm doing an interview for a sponsor of a contract research organization involved in the training process, and I ask them how they train monitors, what their important selection criteria are. The training manager tells me how they have a good training process for monitors, but I looked at the records and wasn't too impressed by the paperwork," she adds.

So the decision boils down to the one-on-one interview.

"This is a good time for the CRO [clinical research organization] to convince me how good their training is, and I want it to be very strong," Smith says.

Instead, the CRO representative sits at the conference table with folded arms. She's leaning back as far away as she can from the interviewer.

"She's almost underneath the table, and her crossed arms are telling me she's not engaged," Smith says. "Her body language tells me a lot: She doesn't want to be in that room and was trying to get as far away as possible, feeling very closed-in and taking a defensive posture."

Smith sees this body language and concludes the representative is very uncomfortable about sharing information about training because an honest and open person would have the arms open and be frontally aligned with expressive body language as the person discusses how great the program is and how committed the organization is to it. The representative's body language confirms her suspicions from the paperwork that the training program isn't adequate, and so the CRO loses that contract.

Research sponsors and even research institutions should train staff engaged in auditing and monitoring how to conduct thorough and useful interviews, Smith suggests. ■

Do you know what should be included in a CTD?

Learn what sponsors need to understand

Clinical trial staff might have little knowledge or interest in the common technical document (CTD), although this document often is what drives some requests for additional information that come from sponsors and clinical research organizations (CROs).

"Knowing about the CTD and what goes into it gives people in clinical trials a better expectation and understanding of what data and what information are going to be collected in a trial," said **Robert Pearsall**, MS, president and principal consultant with AXON Research in Potomac, MD. Pearsall is active in software development, project management, and process improvement. He spoke about CTDs at the 2005 Association of Clinical Research Professionals (ACRP) North American Annual Conference, held April 2-6 in Orlando, FL.

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals is a cooperative effort to harmonize the laws, regulations, and procedures of the United States, the European Union, and Japan.

The CTD for Registration of Pharmaceuticals for Human Use is the form sponsors use to market their therapy according to standards developed by the ICH, Pearsall said.

"The fundamental point is that at some point, an independent organization was formed to harmonize the submissions so the same documentations and material could be used in all three jurisdictions," he explained. "What you want to call it is a universal outline for the documentation for having a drug approved."

There are five modules involved in the submission, and they collect quality data, manufacturing data, toxicity information, nonclinical and clinical trial data, and regional administrative information, Pearsall added.

"In the real world, what people are trying to do is have a plan at the outset that includes goals for the submission, whether it's a specific therapy or specific treatment," he said.

During the planning stage, they'll fill in the outline and plan the clinical or nonclinical studies, looking at how the data will support the main goal, Pearsall explained.

"For the site running the study, that may not be a huge issue," he noted.

But eventually, there will be questions for the principal investigator about specific patients, and if the clinical trial staff have some idea about the goal, then they can address the right issues more efficiently and have fewer cycles of questions and answers between the site and the sponsor, Pearsall said.

"The more range of services you offer to the sponsor, the more it's helpful to understand what the goal is for the sponsor in terms of this kind of information," he continued. "Some physicians will write study reports and be one of the authors of a study report, knowing the primary issues being addressed, and it just makes it easier to get down to the specific pieces the study has to address."

The other advantage to sites understanding the CTD submission process and the sponsor's chief goals is this will keep the clinical trial staff tuned into thinking about research issues in the same way the sponsor and regulators think about them, he said.

Ideally, sponsors would make the CTD submission a transparent process, but it typically doesn't work that way, Pearsall noted.

Usually the sponsor will collect information for the CTD and submit it directly after asking sites for specific information, he said.

"Sites may wonder why they get a specific set of questions," Pearsall explained. "They are asked to write a certain type of summary, and the reason for the question is it's fitting into a massive document structure for the sponsor."

For example, one question that might be asked of a site involves a request for additional information on patients who had safety issues, he said.

"The sponsor will want more background on the patient because what they're trying to do is put together a big picture of the variety of factors that would be relevant," Pearsall said. "They want to know what subpopulations this treatment is good for and what the exclusion/inclusion criteria is for therapy."

Research may suggest a treatment is not as effective for women or people with diabetes, for instance, he added.

A sponsors' questions to a site may be structured differently than expected because they're driven by a centralized goal, Pearsall said.

"There are analyses that are expected across

studies, and it may turn out you get questions about patients having some condition that none of your patients have had, but it came up in some other study," he continued.

"They try to present as clear a picture as possible and create and consolidate summaries, so they might ask all sites if they had allergy symptoms," Pearsall explained. "It might not be something that was on the main clinical protocol, but it could turn out another study had people who had pollen allergies who were having some reaction to the medication."

So when the sponsor's doing these summaries, the goal is to address all of these issues, he said.

The next phase in the CTD is the electronic CTD, Pearsall noted.

"The electronic CTD is one of the technical standards coming along, and you don't want to be caught by surprise by all the acronyms and advancements in the industry," he said.

"I think most people, if they understand why things are happening, they're more motivated, and the net result is everything will be entered electronically," Pearsall explained. "And it will go through the submission process, and they'll be able to access the information electronically with a seamless on-line work flow from the site all the way to the regulatory agency." ■

PHRP launches public education campaign

Info is available free to trial sites

A new campaign aimed at improving public trust and knowledge of clinical trial research was launched in May by the Partnership for Human Research Protection Inc. (PHRP) based in Washington, DC.

Called "What You Should Know About Research Studies," the campaign includes a brochure that can be distributed to patients at hospitals, clinics, clinical trial sites, and other places across the country. PHRP is sending the brochures to more than 5,000 hospitals and other organizations and has made them available for a free download from its web site at www.phrp.org.

"Every year, thousands of people volunteer for clinical trials that help to advance medical science and contribute to breakthroughs," said **Karen Timmons**, president of PHRP, who spoke at a media conference about the new campaign.

"As we conduct important clinical trials, we must be sensitive to the needs of volunteers participating in this research, and that's why we launched the educational campaign," she added.

PHRP's brochure tells the public, including potential research subjects, what questions they should ask their physicians or the research conducting a study.

Among the questions the brochure suggested are these:

- Why is this experiment being conducted?
- Will I be able to continue to see my own doctor?
- Is there any cost to me, or will I be paid to participate in this study?
- What other options or choices do I have if I decide not to take part in this study?
- Could my condition get worse during the study? What will happen if it does? If my condition worsens, will I be notified? How?
- Who pays for my care if I'm injured during the study?
- What will happen to me at the end of the study? Will I be told the results of the study?
- Who stands to benefit financially from the results of this study? Is there a conflict of interest with the researcher? If so, how is it managed?

These are the kinds of questions **Paul Gelsinger**, father of Jesse Gelsinger, who died in 1999 four days after participating in a clinical trial involving gene therapy work, said he wishes he'd known to ask six years ago. Gelsinger, who has worked with PHRP for several years as they developed their human research accreditation program, also spoke at the media conference about the patient education initiative.

"When we got involved in this clinical trial, we trusted that the system was impeccable, that there were no problems with it," he pointed out. "I didn't know the questions to ask; I asked what I thought were appropriate questions, but I didn't delve into conflict of interest with the researchers."

For example, Gelsinger said he had no idea the head researcher of his son's clinical trial had a 30% ownership of a biotech company that held the patent rights to the researcher's work.

"I had no understanding of how that could impact his impartiality in the research," he added. "Unfortunately, in our experiences, the system is not trustworthy. There are too many influences that are unseen from the patient perspective, and they just have to be revealed; and

this brochure gets into a lot of those questions."

Potential subjects who read the brochure and use it to guide their questions during the informed consent process or prior to becoming involved in a clinical trial will be better informed and prepared than the typical research subject, Gelsinger and Timmons said.

"It will put investigators on the spot and make them have to answer them and give people the courage to ask the questions," Gelsinger noted.

Clinical research professionals have the obligation of informing the public and potential subjects about human subjects protection in research, and the PHRP campaign will assist them with this task, said **Lori Roesch**, CIM, CIP, manager of the research subject protection program at Aurora Health Care in Milwaukee. Roesch also spoke at the media conference.

"The more information a person has, the better equipped he can be to ask questions and make decisions," she said.

"I often hear people refer to themselves as guinea pigs when they participate in research," Roesch added. "It's our goal at Aurora to dispel that myth."

Aurora Health Care will make the brochure available to research staff for their trial volunteers, and they'll pass them out at community education events, she explained.

"I think it will help to raise people's awareness of research, much like the Terri Schiavo case raised awareness of advanced directives," Roesch added.

The brochure has a section titled, "What you need to know about participating in a clinical research study," and in that section, there are 10 main points, including the following:

• At the time you sign up for the study, it will not be known if the experimental drug, medical device, or treatment will help you more than the standard treatment.

• Ask for a copy of the study protocol. Look for a description of potential side effects of the treatment.

• The costs of participating in a research study are not always covered or paid for by health insurance. Talk to the doctor conducting the research and your insurance provider to determine if there will be any extra expense to you.

• You will be asked to sign an informed consent form, which explains the nature of the study, the risks involved, and what may happen to participants. Take the informed consent document home, read it thoroughly, and review it with your family.

• For help in understanding the informed consent or study protocol, seek out expert advice from a family physician, a patient advocate, or a specialist who treats your disorder.

PHRP also explained in the brochure how some IRBs and human subject research programs are accredited and where research volunteers can find out more information about accreditation.

While the accreditation process doesn't alter the regulatory framework, it does build in safeguards by providing a prospective independent review of an organization's performance, says **Jessica Briefer French**, an assistant vice president of PHRP.

For example, the regulations are limited in their guidance for conflict of interest management, French said. "Conflict of interest was not a major issue 30 years ago when the Common Rule was written," she added. "But as more and more research is funded by industry, conflict of interest has become a much more important issue."

PHRP requires accredited organizations to have specific requirements or policies for the management of conflicts of interest, including the collection of data about potential conflicts of interest and policies for taking actions to mitigate or eliminate the conflicts, French explained.

The main purpose of the education campaign and brochure is for these to serve as a vehicle that involves potential research participants more in the process, Timmons said.

"They can take the brochure home to their families and discuss its potential implication before making the decision," he added. "This really is a nice way for an individual to understand the implications and ask the right questions prior to signing the informed consent." ■

COMING IN FUTURE MONTHS

- ■ Clinical trial site selection is changing: Here's how
- ■ Research ethics experts provide suggestions for building public trust
- ■ Improve data management of international clinical trials
- ■ Use new tools to improve trial management
- ■ Refine methods for targeting recruitment messages

CE/CME instructions/objectives

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

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

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

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

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

CE/CME *questions*

For more information about the CE/CME program, please contact customer service at (800) 688-2421.

1. How is trial drift defined when used to describe what happens after a clinical trial has continued over time?
   A. Trial drift is the escalation of costs above the contract budget in a clinical trial.
   B. Trial drift occurs when clinical trial investigators and staff's interest in a clinical trial deteriorates over time and when the average knowledge base of all personnel involved in the clinical trial or study decreases as the trial extends its timeline.
   C. Trial drift is the phenomenon of high staff and volunteer turnover in clinical trials.
   D. All of the above

2. As a part of good billing and budgeting practice, it's a good idea to conduct a profit and loss analysis. Which of the following is a good question to ask as a part of this analysis?
   A. What were the variable and indirect costs?
   B. Was the sponsor billed for all research-related costs?
   C. Has the sponsor paid everything agreed to in the contract or are there holdbacks?
   D. All of the above

3. Which of the following is a good tool for conducting and documenting internal activities for constant compliance assessment of clinical trial research?
   A. Auditing log book
   B. Corrective and preventive action plan
   C. Standard operating procedure guidelines
   D. None of the above

4. Common technical documents are designed to collect what kind of data?
   A. Manufacturing
   B. Toxicity
   C. Quality
   D. All of the above

Answers: 1. B; 2. D; 3. B; 4. D

CLINICAL INVESTIGATOR'S CORRECTIVE ACTION RESOLUTION FORM

Section I

Identified Issue:

Section II

Casual Analysis:

Section III

Proposed Resolution(s):

Section IV

Final Root Causal Analysis:

Issue Resolved on: _____

Continuing to be Reviewed: _____

Next Planned Assessment: _____

Section V

Documentation of Staff Retraining:

Members Required to Attend Retraining:
Attach attendance sheet with minutes.

Section VI

Continual Process Improvement:

Event Reoccurrence:
Address reoccurrences and further preventive measures and retraining and process improvements.

Section VII

Clinical Investigator's Review or Corrective Action Plan and Acknowledgement of Continual Improvement:

_____ _____

Clinical Investigator's Signature Date of Review

_____ _____

Corrective Action Plan Preparer's Signature Date of Signature

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