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IN THIS ISSUE

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Poorly done research can have big impact on public perception, policy

CT findings can be misrepresented

It's up to researchers and research journals to provide checks and balances to important investigative findings, but what happens when bad research seeps through the cracks and even becomes widely reported as the truth?

Several investigators say they've encountered situations where studies with poorly done methodology or other problems have captured the public's attention and had a broader impact than warranted.

For instance, an unpublished and statistically inaccurate dissertation that said grief counseling actually harms people seeking help was cited in a major journal article and led to public skepticism of grief counseling. Worse, some health care organizations used the faulty research as justification for cutting back on grief counseling services, says **Dale G. Larson**, PhD, a professor in the department of counseling psychology at Santa Clara University in Santa Clara, CA.

Larson recently published a paper refuting the flawed research, saying the negative characterization of grief counseling has no empirical grounding.[1]

The research process is supposed to catch flawed studies through peer-reviewed journals and follow-up research by other investigators. But the process doesn't always work as well as expected, and sometimes a flawed study can capture the public eye in a way that gives it a long life.

This happened with the negative reports on grief counseling. Even after Larson began to speak publicly about the flaws of the initial research and after he told a reporter from *Newsweek* that there really is no scientific evidence that grief counseling causes harm, the national news magazine published a major story that was critical of grief counseling, he says. **(See story on flawed grief counseling study, p. 112.)**

"The June 18 [*Newsweek*] article said that grief counseling was harmful, and it led with those [incorrect] statistics," Larson says.

Larson and other investigators have found that it's a lot more difficult to correct a public misconception based on flawed research than it is to gain attention for a study that says something provocative and new.

"The news media hypes interesting news on page one, and if it turns out to be wrong, the retraction is printed deep back in the first section of the paper," says **George Diamond**, MD, FACC, senior research scientist, emeritus, at Cedars-Sinai Medical Center in Los Angeles, CA.

Studies that show problems with a popular drug or technology or that refute a common therapy can lead to sensational headlines.

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"The media always loves a black and white headline, but the reality is always gray," says **Sanjay Kaul**, MD, director of the cardiology fellowship training program and director of the vascular physiology and thrombosis research laboratory at Burns and Allen Research Institute, Cedars-Sinai Medical Center in Los Angeles, CA. Kaul also is a professor at the David Geffen School of Medicine at the University of California, Los Angeles.

Diamond and Kaul testified on July 30, 2007, at an FDA advisory committee reviewing data on the safety of a Type 2 diabetes drug called rosiglitazone (Avandia®). They were among the three authors of a paper on the uncertain effects of rosiglitazone and myocardial infarction, which is slated for publication in the Oct. 16, 2007, issue of the *Annals of Internal Medicine*.[2]

The hearing was prompted by a May 21, 2007, article published in the *New England Journal of Medicine* that linked rosiglitazone to a significantly increased risk of heart attack.[3] The *NEJM* article was a meta-analysis of 42 trials on the drug, and it contended that the drug produced a statistically significant 43% increase in myocardial infarction, as well as a borderline significant increase in cardiovascular death, Diamond explains.

"The study received a huge amount of press the day the article came out," Diamond says. "I looked more carefully at the article as posted on the *New England Journal of Medicine's* web site, and I was struck by the paucity of the number of events in the trials that were analyzed."

Of 42 trials and 28,000 patients, there were fewer than 150 events, and there were many trials that had no events within either the treatment or control arms, he explains.

"So the study's conclusion was based upon a paucity of event data and that gave me pause," Diamond says. "I discussed it with Dr. Kaul and he was similarly impressed, and on that basis we redid an analysis of the data."

As cardiologists, Diamond and Kaul were interested in finding out the truth about this drug and did not do their analysis because of any financial incentives or ties to rosiglitazone's manufacturer GlaxoSmithKline.

Using a more sophisticated statistical methodology that could deal with zero-event trials, Diamond and Kaul determined that the odds ratio for cardiovascular death or myocardial infarction was substantially less than what was reported.

"The confidence analysis was very wide, and

there were no grounds for the national hysteria engendered by the publication of this report," Diamond says.

Diamond and Kaul presented their analysis before the FDA advisory board, which had some members who were intent on removing the diabetes drug from the market.

FDA statisticians had done a similar analysis and reached the same conclusion Diamond and Kaul had.

When the FDA board finally decided on rosiglitazone's future there was a 22 to 1 vote to keep the drug on the market, Diamond says.

"A number of physicians rely on this drug to maintain their patients' blood glucose," Diamond says.

Although future studies might suggest greater risk of cardiovascular problems with the use of the drug, the available literature is inconclusive, so the drug shouldn't be pulled from the market based on one flawed meta-analysis, Diamond and Kaul say.

Sometimes flawed studies are promoted by people who have a political agenda, Diamond notes.

In the case of the study questioning rosiglitazone's safety, there were members of Congress and others who wanted to use this as an example of why the FDA needs restructuring, he says.

And with so many different methodological techniques, research tools, and other strategies for analyzing data, it's easy to pull false alarms, Diamond says.

"Many eyes and many tools used can lead to a number of false alarms, but they can also lead to the early detection of a number of real fires that can be put out," he adds.

There are pros and cons, and the best strategy might be for the FDA to establish a proactive task force that looks at the problem in isolation of emotion and hysteria and come up with standards for monitoring safety before and after approval of drugs, Diamond suggests.

"Skepticism is a very useful tool for navigating through the labyrinth of hype and misinformation," Kaul says. "Be skeptical and try to verify a study, and if you cannot replicate it, then you have to dump it."

That's the beauty of the scientific process, Kaul notes.

"There's always a correction factor," he says. "The person who does an analysis has to be skeptical of his or her own analysis, and this has to be done in a dispassionate manner."

Not every study that contradicts previous perceptions or findings is wrong. In fact, often these studies that find flaws in accepted treatments or medications are part of the scientific process, filling in needed details within the existing body of research.

For example, Kaul also has investigated and testified before an FDA advisory panel on the topic of medicated stents, which quickly replaced the old uncoated stents in heart surgeries in the past few years, Kaul says.

"Typically the bare metal stents would be successful in 80 to 90 percent of cases, but in 10 to 20 percent of cases [the arteries] would reblock," Kaul says.

So cardiologist embraced the new coated stents, which greatly reduced the reblockage or restenosis. The problem was that the new stents caused more blood clotting, Kaul explains.

"Stent thrombosis, even if it's an infrequent occurrence, can cause a heart attack in up to 70 percent of cases," Kaul says. "So we raised questions of whether trading stent thrombosis for reblockage was a worthwhile trade-off."

Once a paper was published on the stent thrombosis link to coated stents, and the FDA convened on the issue, cardiologists stopped using coated stents as often, Kaul says.

"There are certain patients where the risk profile may favor the benefits of medicated stents," Kaul says. "And those are the types of patients where its use is beneficial."

Medical professionals sometimes embrace new technology too quickly and overuse it as enthusiasm exceeds evidence, Kaul notes.

"Whenever there's a technology trigger it quickly leads to a peak of inflated expectations, followed by a rapid fall, and trough of disillusionment and plateau of productivity," Kaul explains.

The key is to remain scientifically skeptical and to keep in mind that most new research is not replicated, meaning it doesn't prove to be fact over time, Kaul adds. ■

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Timeline: How results of a flawed study became embraced as new truth

One scientist's persistence may reverse course

For grief counselors, psychosocial investigators in psychology and loss, there has been a stunning turnaround in public perception of grief therapy due to one widely quoted study.

Due to one paper on the topic, grief counseling is viewed pessimistically as a possibly harmful therapy for people who have experienced a major loss. The truth is that there is no peer-reviewed, replicated research to support that pessimism, says **Dale G. Larson**, PhD, a professor in the department of psychology at Santa Clara University in Santa Clara, CA. Larson also is the interim dean in the school of education, counseling psychology, and pastoral ministries.

Larson and several colleagues who are experts in research methodology closely examined the original data and found it empirically flawed, Larson says.

No scientist who carefully reviews the data could conclude that anything is wrong with grief counseling, he says.

Even more amazing is the fact that despite solid evidence that the initial studies are inaccurate in their interpretation of the data, the misperception continues to make its way into national media reports about grief counseling.

The initial dissertation with inaccurate methodology is no longer cited in most of the scholarly publications that continue to cite the dissertation's findings, Larson says.

"People cite the later articles," Larson says. "It's like the children's phone game where one person says one thing and another one whispers it to someone else, and we get further and further from the actual data."

The peer-review process was broken down to the point where researchers weren't checking to see whether authors were citing original research, he adds.

Here's the timeline of how one paper reshaped public perception and policy with regard to grief counseling:

1999: A dissertation, which is never peer-reviewed, called "The effectiveness of grief counseling and therapy: A quantitative review," claimed that 38% of grief counseling clients deteriorated due to treatment and 50% of clients experiencing normal grief are likely to be harmed by counseling.[1,2]

2000: Robert Neimeyer publishes a paper about grief counseling in *Death Studies*, which captures national media attention. It cites the 1999 dissertation's data and refers to a technique called treatment-induced deterioration effects (TIDE).[1,3]

2001-2006: More studies that are pessimistic about grief counseling are published; some cite the *Death Studies* paper and some cite the 1999 dissertation.[1]

2003: The 2003 *Report on Bereavement and Grief Research*, published by the Center for Advancement of Health, concludes that grief intervention studies challenge the effectiveness of these interventions.[1]

June 18, 2007: *Newsweek* magazine published an article by Sharon Begley, titled, "Begley: Get shrunk at your own risk," that quotes from the inaccurate studies about grief counseling and paints a pessimistic view of the intervention. The news magazine article states, "A 2000 study found that four in 10 people who lost a loved one would have been better off without grief counseling (based on a comparison with people who were randomly assigned to a no-therapy group)."[4]

August 2007: Larson and William T. Hoyt publish a paper on the inaccuracies of previous studies on grief counseling, disproving the original data from the 1999 dissertation.[1] ■

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Give staff comprehensive training in good clinical practice and ethics

Begin by defining GCP

Here's a good question for stumping clinical trial staff and investigators: How do you define GCP?

Everyone knows it stands for good clinical practice, and everyone says it's what they practice at their research sites. But beyond that, true descriptions are hard to come by from the people directly involved in clinical research, an expert says.

Protect subjects and produce accurate data

"GCP is a set of standards that exist to do two things: One is to protect the rights, safety, and welfare of subjects participating in research, and, two, is to ensure the accuracy of data coming out of the trial," explains **Brian Bennett**, BA, CCRA, CCRT, senior director of corporate communications and knowledge management at i3 of Little Rock, AR. A global Ingenix company, i3 provides support for drug development, including research, drug safety, data services, staffing, and science. Bennett is a speaker and instructor about research ethics, GCP, and other topics.

True understanding of GCP requires in-depth knowledge about the history of research ethics. In other words, the first place to start is with answering the "why" questions, Bennett says.

Clinical trial investigators and staff often receive GCP training through industry-sponsored sessions or professional advancement courses or investigator meetings, he notes.

Large research institutions dedicate infrastructure to training staff on GCP, often through computer-based education programs, he says.

"You're told very often what you're supposed to do and what can be done in the course of the standard operating procedures (SOPs)," Bennett says. "But in none of this did I find that anyone told me why we do what we do."

Certainly, there are regulations to follow, and there are industry standards, but these do not answer the "why" question, Bennett says.

Here is how Bennett answers the ''why' question and teaches clinical trial coordinators and others about GCP:

- **Everything goes back to the big three: The Nuremberg Code of 1948, the Declaration of Helsinki in 1964, and the Belmont Report.**

Everyone has heard of these, but they typically can't tell you very much about them or why they even exist," Bennett says.

For example, the informed consent form was developed as a result of these three ethical doctrines.

From an ethical standpoint, a lot of what we do is rooted in those three doctrines," Bennett says. "We're all working to bring better medicines to market."

To do so requires relying on volunteer participants, he adds.

The Nuremberg Code was the result of a 1946 American military tribunal that heard of war crimes by German physicians who had conducted lethal and crippling experiments on concentration camp prisoners. The Nuremberg Code declares that the voluntary consent of human subjects is essential.

The Declaration of Helsinki has recommendations by the World Medical Association, guiding medical doctors in human subjects research, including the guideline that research with humans should be based on results from laboratory and animal experimentation and that informed consent from research subjects is necessary and that risks should not exceed benefits.

The Belmont Report was prepared in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research as a way to summarize the basic ethical principles regarding human subjects research and establishing GCP.

The Belmont Report came after the medical and research community was made aware of the ethical violations that occurred in the Tuskegee Syphilis Study, Bennett says.

The U.S. Public Health Service began studying black men with untreated syphilis in 1932 and

then continued to follow the men, observing illness progression and deaths, until 1972, decades after antibiotic treatment was available and consistently denied to the study's participants.

• Regulatory requirements are both necessary and not as onerous as often feared.

Bennett typically explains to clinical trials professionals the history of the current research regulations and the FDA's power, including a number of research tragedies that have led to oversight laws.

For example, more than 100 people died in 1937 due to a cough syrup that included a compound that had been shown by basic science to be toxic, but was nonetheless included in a prescription bottle for human consumption. **(See story about FDA's and GCP's roots, p. 115.)**

Although it's part of GCP to follow national and international regulations, clinical trials professionals often confuse laws with industry standards, Bennett notes.

"One of the most shocking things in delivering GCP training is when you do an in-depth analysis of the FDA regulations, and you look at what's out there, you often find that people believe the FDA requires a lot more than it actually does," Bennett says.

There are many examples of incidents where clinical trial professionals believed some practice or deadline was required by the FDA, when it actually was not, he adds.

"They're sometimes told by a colleague or a monitor or quality assurance person that the FDA requires this to be done, but when you look at the regulations, you'll find there's nothing point blank or specifically requiring that," Bennett says.

"I try to empower people by saying, 'If somebody tells you something needs to be done on your study, and they say it's because the FDA requires it, then challenge it," Bennett says. "I say, 'Ask the person where in the regulations it says I have 30 days to submit a final report to the sponsor or IRB?'"

What actually happens is many clinical trial practices are done because of industry standards, he says.

Everyone has done it this way or met a certain deadline, and many of them assume it's because of regulations, Bennett explains.

Overall, industry standards are a positive force because these fill in the blanks between the lines of regulations and guidelines, he says.

"Anytime you have consistency or standardization in the process, whether its standard operating procedures (SOPs), or meeting a timeline, then it eliminates guess work," Bennett says.

• Clinical trial data must be credible and accurate.

"So if any authority around the world looks at the data about a product, the product can be put on the market based on accurate and credible data," Bennett says. "As many people that are exposed to a product in a clinical trial setting, it is a small number compared with those who will be exposed once it's approved for marketing."

It's essential to protect both the study participant and the accuracy of the data because one day the medicine being studied will be on a pharmacy shelf and have someone's name on it, Bennett says.

"It could have the name of you, your mother, your father, your friends," he says. "At the end of the day, I want to sleep well at night."

Once clinical trial professionals know the background and why they need to follow GCP, they'll have a greater appreciation and openness to learning how to improve their trial activities, Bennett says.

• Teach GCP at the clinical trial site for most pointed impact.

Good clinical practice might best be taught at a clinical trial site, Bennett suggests.

"One of the best approaches to GCP training for research professionals, in my opinion, is to bring GCP training on site when there is no dedicated internal training capability," Bennett says. "I really like and prefer this approach over sending personnel to generally available GCP training courses because it presents the perfect opportunity to assemble not only a class of research professionals to learn about GCP, but a class of research professionals who work together at a site as a study team conducting a protocol."

Also, when clinical trial sites bring GCP training to their locations, they can instruct staff about GCP in the context of their own research operation, providing details on how the site's research team approaches and complies with GCP in a day-to-day manner, Bennett says.

"In other words, it's a great opportunity to, one, ensure the collective understanding of an immediate team of research professionals at a particular location," Bennett explains.

Secondly, this approach identifies areas of inconsistency in how staff conducts site business, and, third, it helps to identify any gaps in the current processes, Bennett adds.

These can lead to action plans and a more standardized and consistent approach to research, he notes.

"Again, it's that standardization and consistency that are critical to quality in the clinical trial process," Bennett says. ■

FDA's and GCP's roots extend back 100 years

Good clinical practice (GCP) may be a catchphrase of the 21st century, but the concept's roots date back to the shortly after the 20th century began.

"In the context of the evolution of good clinical practice, I try to set up a regulatory framework," says **Brian Bennett**, BA, CCRA, CCRT, senior director of corporate communications and knowledge management at i3 of Little Rock, AR.

"It dates back to the 1906 Pure Food and Drug Act," Bennett says.

The Pure Food and Drug Act of 1906 and the Harrison Act of 1914 banned the sale of some narcotic drugs and established the first version of the FDA.

But it was the 1938 Food, Drug, and Cosmetic (FDC) Act that gave the FDA broad regulatory powers in approving pharmaceutical products before they could be marketed to the public.

The 1938 FDC Act was a response to a nationwide tragedy in 1937 in which 107 people died after ingesting a cold and cough syrup called Elixir Sulfanilamide, Bennett says.

The product existed in pill form, and there was a rush to dissolve it and put it in liquid form, Bennett explains.

A pharmaceutical company succeeded in creating the syrup after using a solvent called diethylene glycol, which is a clear, odorless liquid that is similar to antifreeze.

Once the manufacturer mixed the solution with a strong enough raspberry flavoring and put it on the market, it was quickly purchased by parents who wanted a cold and sore throat remedy for their children, Bennett says.

"It killed 107 people in the United States, and these were primarily children," Bennett says. "The tragedy got a lot of public attention and led to the 1938 establishment of the FDA."

S. E. Massengill Co. of Bristol, TN, which had distributed the lethal cough syrup, had not conducted any studies, even on animals, according to an FDA report of the event.[1]

The drug had been shipped early in September, and the first deaths were reported in early October by physicians who had prescribed the syrup.[1]

The children who took the drug were ill for 1-3 weeks, finally dying of kidney failure after suffering intense pain and experiencing severe nausea, vomiting, and convulsions.[1]

At that time, the law did not prohibit the sale of toxic or untested drugs, and the manufacturer's statement after the tragedy indicated that the company's owners did not feel the problem was their fault since they could not "have foreseen the unlooked-for results."[1]

There had been similar tragedies due to toxic drugs prior to the Elixir Sulfanilamide poisoning. These included people going blind after ingesting a new drug called dinitrophenol and liver poisoning and deaths from ingestion of cinchophen, a drug used to treat rheumatism.[1]

Ironically, although the use of diethylene glycol in products consumed by humans is prohibited in the United States, the deadly compound continues to show up in cough syrups, toothpaste, and other products—both sold in the United States and abroad. According to various news reports, dozens of children in Haiti died in 1996 after being given glycerine contaminated with diethylene glycol in a syrup that was traced back to China. Likewise, in May, June, and July, 2007, there were media reports of similarly contaminated toothpaste sold in Costa Rica, Spain, England, the United States, and elsewhere. These also were traced back to Chinese manufacturers who used diethylene glycol rather than a more expensive and safe compound.[2-6] ■

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Expert develops successful start-up strategy for sites

Cutting costs and time is goal

Research industry sponsors increasingly are looking for ways to cut drug development costs, particularly during the site selection and initiation process.

A strategy developed by a clinical trials advisor showed significant improvements on the product development timeline over control sites that followed conventional practices.

"The timeline and everything else was better than the control set of sites that didn't use these strategies," says **Rita Viegas**, BSc, MA, a clinical trials advisor for IRX Therapeutics of Brighton, MA. Viegas has spoken about her site start-up support strategy at national research conferences, and she plans to publish her study.

"Basically what I did was create a set of strategies and comparison in a small biotech company based in New York," Viegas says. "I compared metrics on how much time was saved."

Here is how the strategies work:

• **Hold a prequalification teleconference:** The goal is for sponsors to develop a relationship with investigators and get investigators on the telephone with study coordinators to assess how knowledgeable they are about their own sites, Viegas says.

Investigators and site coordinators were asked these questions:

—Do you have any specific review committees in addition to the IRB?

—Which documents will need to be approved?

—What processes of the start-up structure will have to be carried out in a sequential manner and which have to be carried out in a parallel manner?

—What is the typical interval for budget negotiations at your site?

—How long does your IRB take to make a decision?

—Can the contract be negotiated while submitting to the IRB?

"Then with that information, I created a timeline specific for each particular site," Viegas says.

For example, the timeline might include verbal qualifications, visit to sites, contract/budget negotiation, IRB approval, and approval by any other committee, including biosafety or oncology committees. The timeline might also include time for drug shipment and time for initiation visit, Viegas says.

Viegas would estimate how long this timeline would take, based on a typical site start-up scenario.

No sites kept precisely to their estimated timelines, Viegas notes.

"But only one site was delayed in a way that affected the overall timeline," she says. "For all other sites, the timeline would shift, but the overall timeline didn't change."

For instance, a site might predict it would take two weeks to sign the contract, and the actual time is three weeks. But the site still would be open for enrollment at the time predicted, Viegas explains.

• **Encourage competitiveness among sites under consideration for study:** This part of the strategy wasn't part of Viegas' study, but she would advise sponsors to use it as a strategy in site selection.

"So investigators would be aware that this was a competitive start-up, the same way you're normally aware that enrollment is competitive," Viegas says. "So if the sponsor thought 50 sites would be necessary to enroll the amount of patients needed, I'd enroll 60 sites and the last 10 would be shut down."

The process would be called the selection initiation of excess number of sites, she says.

"During budget negotiations, it's proposed that they're performing for the sponsor," Viegas explains. "All beginning activities would be paid for."

This way sites wouldn't have to fear devoting chunks of time to the project and then not be reimbursed, she notes.

"The rationale for making it competitive is to make sure you're getting the best enrollers on your team," Viegas says. "It's well known that there are sites that start up faster and enroll better."

• **Create a country-specific regulatory documentation tracking tool:** All countries have different requirements, so Viegas has created a tool that can be used to track all of the documents needed by sites in particular countries.

"It's amazing how many situations people find themselves in where they did everything they thought they had to and at the last minute, they stopped enrollment because something was missing that nobody knew about," Viegas says.

Viegas solved this problem with her tracking

tool. As part of the process, she spoke with regulatory consultants within the countries where sites were located.

"I had one-hour teleconferences with regulatory consultants to make sure we had the regulatory document requirements for each country and nothing fell through the tracks," Viegas says.

Viegas found the right people through experience and contacts. She recommends that sponsors hire consultants within the countries to do the research about documentation requirements when necessary.

The documentation tracking tool is a one-page Excel spreadsheet that is kept in house and not shared with clinical trial sites, Viegas says.

"I would tell sites what documentation they were missing," she says. "This tool could be adapted and used in many different sizes of studies and companies and situations."

• **Keep in close phone contact with site staff:** Viegas kept phone numbers for all site staff, following her philosophy that a phone call is more effective than e-mail or a letter because it adds a personal approach.

"If you're on the phone with them it's way easier for them to ask a question, rather than letting them write you an e-mail to ask that question," Viegas says. "It's a way to keep the line of communication open with the site staff, and I'm pretty sure it solves a lot of problems down the road."

Snafus can be averted by a simple off-hand comment on the part of the site staff, such as this one: "By the way, can I ask you something?" Viegas says.

When Viegas called sites she would try to reach the research nurse or study coordinator.

"If there were any issues with the IRB, I'd try to reach the investigator," Viegas says. "By that time, I'd have a relationship with the site staff and know their personalities."

For instance, some investigators are happy to have someone on the phone to talk with them, and some others don't like to be bothered with a call, she says.

"I'd keep notes on all investigator personality traits," Viegas says. "If an investigator doesn't like to be bothered, then I'd drop him an e-mail."

• **Provide additional training as needed:** Investigators and some site staff had been trained collectively, but some individual training is necessary, Viegas says.

"I'd conduct training at the site according to the site's standards, so they wouldn't have to adapt or interpret anything I was saying," Viegas says.

It only takes about 30 minutes during the training program to adapt a few things to the specific site, she notes.

For instance, each clinical trial site had different pharmacy logistics, so Viegas would try to find out who received the investigational drugs.

She'd find out the answers to these questions:

—Are there any additional drugs that go into the regimen?

—Are the drugs bought locally?

—Does the sponsor have to supply the drugs?

—What is the line of communication to have the drug available to the principal investigator?

"Those logistics vary a lot at every site," Viegas says. "That's the kind of information I'd collect during the site qualification visits."

Then she'd outline the information on training slides, adding names of actual people and their roles within the process.

"That was particularly important for the study," Viegas says. "I was preparing them."

For example, if the investigational drug was frozen and had to be prepared for shipping and then sent back to a local lab to make sure the temperature was stable, it would require extra staff logistics, and Viegas would train the clinical trial site staff about who would be responsible for unpacking the drug and sending it back, etc., Viegas explains.

The training is also people-specific with separate training meetings for study coordinators and research nurses, Viegas notes.

"The goal was to explain the drug mechanism of action and all the background knowledge of the drug in a language that the audience would understand," Viegas says. "So we would have our medical advisory people in the sponsor company deliver training to the principal investigators so they would speak the same language."

The training was provided MD to MD, she says.

"Our project managers and clinical team leads would conduct training for research nurses and study coordinators, so it was clinical operations people speaking to clinical operations people," Viegas adds.

"We understand that they will only enroll patients if they believe in the drug, so we wanted them to understand the mechanism of action and how it works," Viegas explains. "We did not want to hear, 'I heard it works, but I don't understand how.'" ■

Cost containment is on everyone's agenda these days

Here's what the big companies are doing

One of the biggest issues facing the research industry these days is revising long-time habits and practices and instituting efficient new ways of doing business, an expert says.

"There's a natural tendency on the part of individuals to do things their own way," says **Laurie Halloran**, MS, CCRA, president and chief executive officer of the Halloran Consulting Group in Brighton, MA.

"What happens at both sites and sponsors is people do it the way they did it the last time, and this creates an individual process for every single person in the organization," Halloran says.

Reports analyzing the current state of the research industry discuss the inefficient research and development processes, Halloran says.

"So what I see sponsors doing, and sites can learn from this, is trying to create a more efficient process where they don't have a thousand steps that people do," she says.

For example, if a research team has to review documentation to start a study and if there are too many people involved in the review, then it ends up slowing down the process, Halloran says.

"There's a lot of critical thinking that has to go into how companies work," she says. "And critical thinking is something sorely missing in this industry."

Research professionals have lost touch with the basics and tend not to interpret regulations in a way that works for them, Halloran says.

Instead of grasping the big picture and interpreting the regulations with the flexibility that is built into the regulations, research professionals will increase documentation and create lengthy internal processes to take the place of thinking through what is really important and needed, she explains.

Another factor that plays into this problem of over-interpreting regulations is a predominant mindset among clinical trial staff.

"A lot of people who do clinical research have a rule-following mindset," Halloran says. "They follow the procedure."

What is needed is a framework in which the research organization dictates some of the process, but which allows for the process to be modified to suit any particular situation, she explains.

Another way sponsors and others in the research industry are trying to contain costs is by looking critically at how well their resources are used, Halloran says.

They need to assess who the people are on their team and look at what each person is capable of doing, she suggests.

"Then you maximize their ability to be busy, but not too busy, which is extremely difficult," Halloran says. "Clinical research organizations (CROs) do this really well because they work in a consulting environment where their only source of revenue is people time."

CROs have the mentality that they are only valuable when they are billing for staff time, and the pharmaceutical industry has never had that mentality, she notes.

So in the past, pharmaceutical companies tended to put too many resources on projects, and they didn't have any managers for whom the top concern was the efficient use of resources, Halloran says.

"That was a limited concern," she adds. "What pharmaceutical companies are starting to realize is that their resources and down time are some of the most expensive areas of their organization."

If an organization uses an employee efficiently and at the right skill level, then they've saved a lot of money, Halloran says.

"The challenge is to quantify how much you've saved," she says. "There has always been a lot of fat in pharmaceutical companies, and that fat is being sliced now."

Once an industry catches on that its old practices have created resource waste, there might be a tendency to swing the pendulum too far in the other direction.

"In the past, pharmaceutical companies have had more people than they needed, but they didn't know it," Halloran says. "Now there's a much higher level of awareness that they can't sustain that staffing level, so a lot of pharmaceutical companies are cutting costs by cutting people and outsourcing the work to CROs and contractors."

This staffing shift is fine so long as the companies cutting jobs have defined processes to follow, she notes. "If there's no definition for how you do the work, then that's a recipe for disaster," Halloran says.

Clinical trial sites have been lean all along, so there issues are different, she says.

"They take longer to do things because they also don't have a systematic way of doing their tasks, and this varies by site," Halloran says.

Some research sites are all about trying to define and communicate the most efficient way of doing things, especially when research is their top priority, she says.

"In research sites where research is tolerated by the administration, but not necessarily supported, they don't get the attention and support they need, and this slows them down," Halloran adds.

This is where the sponsors' new focus on efficiency and saving time can clash with what happens at the site level.

Sponsors and sites have a symbiotic relationship, Halloran says.

"There's an enormous amount of attention paid by sponsors on investigator site metrics, and a lot of sponsors are saying, 'Sites have X number of weeks to get started, or we won't use them,'" Halloran says. "And they'll say, 'Sites have X number of weeks to enroll patients, or we'll shut them down,' because the sponsors literally cannot afford site inefficiencies."

Site performance is going to be a heavily scrutinized area by sponsors from now on. She adds, "Merck is doing something interesting: The company has an extensive prequalification process with research sites, where they pay for time to evaluate whether the site really can deliver on its promise."

Then Merck will manage the site, and if the site promises to enroll five patients in three months, and the site fails to do so, it will receive first a warning letter and then they're closed, she says.

"What that translates into for sites is they need to manage those expectations and meet them, or they won't be used by Merck," Halloran says. "And it's only a matter of time before other sponsors start doing it."

The priority is on how quickly patients are enrolled, which is also the real reason why sponsors are starting trials overseas, Halloran says.

"So if research sites want to be ahead of the curve, then they need to think about the sponsor as a customer as much as they think of themselves as a customer," she says. "I get the sense that a lot of sites feel that working for the sponsor is something that's lucky for the sponsor because the sponsor is fortunate to have them."

It's an elitist attitude that will cost sites business, she adds.

"There are plenty of hungry young doctors overseas who are willing to make a sponsor's study their top priority," Halloran says. "Cost is secondary; time is more important."

From the perspective of pharmaceutical companies, it makes sense that there's so much emphasis placed on time. For example, if a company expects a new drug will bring in $500 million a year, then it only makes sense to spend $50 million to bring that drug to market a year

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

- ■ Follow these tips to manage the close-out process
- ■ Pharmaceutical company offers suggestions for improving CR efficiency, quality
- ■ CR industry's top performers have these best practices
- ■ Get the sponsor's perspective on contract negotiation

sooner, because they've netted $450 million, Halloran explains.

"Sites still don't recognize that equation," she says. However, the top performing sites are learning that time is most important, and they're the ones working not to be the cast aside in favor of overseas trials.

"Only in the most well-established research sites where research is the primary business line are there recruitment specialists," Halloran says. "Most institutions don't have that position." Yet they need it to help expedite subject enrollment.

"I get the sense that a lot of physicians and research personnel are fairly uncomfortable with the whole topic of approaching patients and recruiting them," Halloran says. "They don't want to be seen as coercive, so they're very measured in approaching subjects, and that's a difficult paradigm for a sponsor to live with."

The solution is for all research sites to assign one person on the clinical research team to the role of patient recruitment, she suggests.

"Sites could write that salary into their budget and get the position covered by sponsors," Halloran says. "That could evolve into a really active function and set the site apart from others."

While sponsors have been slow to recognize how important it is to pay for these types of start-up costs, that will change as they begin to see the return on their investment, Halloran says.

"For sponsors to expect people to put their studies as a top priority and spend their time on it, there has to be some compensation," Halloran says. "And it'd be worth trying to get someone to pay for the salary of a recruiter." ■

CE/CME *questions*

13. When clinical research has flawed methodology, which of the following could be a consequence?
    A. The inaccurate study's findings are reported as truth widely in popular media
    B. The flawed research guides public policy
    C. More studies cite the flawed research and base analyses on its inaccurate findings
    D. All of the above

14. Good clinical practice is a set of standards that does which of the following:
    A. It ensures that research subjects have give voluntary informed consent
    B. It protects the rights, safety, and welfare of subjects participating in research, and it ensures the accuracy of data coming out of the trial
    C. It ensures that research sites meet all regulatory requirements and industry standards
    D. None of the above

15. Which of the following would not be a good question to ask investigators and sites during a site pre-qualification process?
    A. Do you have any specific review committees in addition to the IRB?
    B. Which documents will need to be approved?
    C. What processes of the start-up structure will have to be carried out in a sequential manner and which have to be carried out in a parallel manner?
    D. All of the above would be good questions to ask

16. What is one of the major reasons pharmaceutical companies are outsourcing clinical research these days?
    A. To cut time in the CR process
    B. To find more talented investigators
    C. To save money on subject recruitment and incentives
    D. To bypass U.S. research regulatory bureaucracy

Answers: 13. (d); 14. (b); 15. (d); 16. (a)