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Knowing site metrics will help you stay competitive as industry changes

Drug industry should focus on efficiencies

The pharmaceutical research industry's productivity is declining and cost is rising, a dangerous combination that is the force behind changes in how drug company sponsors do research.

There has been a steady decline of new drug applications (NDAs) since the mid-1990s, says **Ken Getz**, MBA, MS, a senior research fellow at the Tufts Center for the Study of Drug Development at Tufts University in Boston, MA.

"At the same time [drug development] cost has been rising at 11.2% annually for the past five years," Getz says. "That's a dangerous combination."

Normally, if costs are rising then it might indicate that the industry is optimizing drug development activity, Getz explains.

"The expanding volume and scope of activity is a driver of higher cost, but there's no guarantee that the increased volume and scope will translate into higher success rates," he says.

As a result of these trends, pharmaceutical companies are conducting more clinical trials, and they've become much more global in scope, Getz says.

"About 50% of Food and Drug Administration-regulated trials are out of this country in the next couple of years," Getz says.

"One of the major factors that enticed companies to consider globalizing drug development activity was the cost saving and speed associated with conducting studies in ascending markets like Central and Eastern Europe, China, and India," Getz says. "Historically, those are places that offer cost benefits and, typically, more rapid enrollment speed."

However, there are drawbacks to globalizing drug development. "Over time, companies have come to realize that the more global you make your studies, the more complicated they are logistically, and it can add a layer of inefficiency or difficulty to optimizing your development program," Getz adds.

Clinical trial sites in the United States face the same challenge of rising costs, as well as increased competition. But they can make themselves more attractive to drug company sponsors through consistently

meeting enrollment deadlines and producing quality work, experts say.

"I believe clinical research organizations [CROs] and other organizations recognize quality," says **Nathan Segall**, MD, principal investigator and founder of Clinical Research Atlanta of Atlanta, GA.

The key is for both sponsors and clinical trial sites to capture metrics or data that show how well sites perform with regard to enrolling participants and meeting quality indicators and deadlines. **(See story on one research site's best practices, p. 124.)**

"The elements of quality have to do with the work and oversight of evaluating the clinical data captured in source documents and subsequently implementing them," Segall says. "Then [sponsors] are able to gather metrics and rate sites according to how well they've done and how they're doing now."

Since about one-third of sites enroll no participants, these metrics are an important way to improve efficiency and reduce drug development delays, Segall adds.

The Tufts Center for the Study of Drug Development identifies the top-performing drug developers over a five-year period.

"In every five-year period we looked at, the fastest companies have changed," Getz says. "That tells you a little about the volatility of the environment." But in the latest five-year period, the fastest companies enjoyed a 17-month speed advantage over their peers within a given therapeutic area, Getz says.

"Not only that, but they're getting faster relative to a median benchmark for the industry," Getz says. "So from 1995 to 2000, they enjoyed a 10-month speed advantage, versus a 17-month advantage they enjoy now."

Merck & Co. is one of the top performers for the most recent period of 2000 to 2005, Getz says.

Merck owes some of its recent drug development success to its relationships with investigators, regulatory agencies, and medical societies, says **Ernesto Aycardi**, MD, senior director of worldwide research operations at Merck in Rahway, NJ.

Research sites that are interested in conducting clinical trials for Merck should be objective and transparent on what they can deliver with regard to the number of patients and cycle times, Aycardi says. **(See Q&A with Aycardi, p. 125.)**

"Of the same importance, sites should have specific, well-documented site processes that are proven to be effective and consistent," Aycardi adds. "Having dedicated and experienced staff to support clinical research efforts is also critical."

Clinical research sites also need to stay informed about industry trends, especially while the industry is rapidly evolving.

For instance, although globalization is a current trend, there already are signs of fatigue.

While many sponsors claim they're seeing the

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benefit of moving trials overseas, they're also tempering the perceived benefit with some of the realities and challenges that global programs present, Getz notes.

"They're still doing it, and they want to increase the amount of activity going overseas, but they have a more realistic view at this point," Getz says. "There's not as much hype as it used to be."

While trials conducted globally have the short-term benefit of offering a lower cost and higher enrollment speed, there are potential problems over the long term, he adds.

"They may enroll patients who are not as representative as the American population, for example," Getz says. "And that could be a scientific problem later, and it could translate into marketing issues."

Getz provides this brief look at other current trends in the drug development industry:

• **Scope of drug development is expanding:** "Companies are chasing much more difficult chronic illnesses today that have endpoints that are more difficult to demonstrate," Getz says. The illnesses have longer time horizons for disease progression, he adds.

"We've also seen a huge shift from traditional small molecule candidates to biologics, and biologics by their nature tend to take longer to develop," he says. "So we've seen the influx of biotech companies and pharmaceutical companies getting into biologic-derived compounds from living compounds."

These factors add another layer of inefficiency to the drug development timeline, Getz says.

Since many of the biologics are targeted for specific uses, this requires a larger number of clinical trials that are spread out geographically. There will be fewer patients in each site, and the eligibility criteria are tighter, he adds.

• **Decline in success rates of new compounds:** "We're seeing a decline in the success rates of compounds moving through development … because these are much more difficult chronic illnesses," Getz explains.

"It's harder to demonstrate efficacy and safety," he says. "Part of the view is that we've entered a new realm where we're dealing with more complicated illnesses and more complex drugs."

Many experts think this signifies a major shift in the composition of the drug pipeline and the nature of drug development, Getz says.

• **Companies make slow decisions to kill less-promising candidates:** Pharmaceutical companies are making very slow decisions about killing the less-promising candidates in their pipelines, Getz notes.

"It may not be that different from before, but when you look at the high cost of delays today and look at the typical drug and performance in the marketplace, there's a real opportunity cost for companies," he says. "It costs an estimated $40,000 per day to manage a typical program, and it means $1.3 million in lost sales for every delay."

Sponsors could cut costs and more efficiently allocate their resources if they quickly abandon the less-promising drug candidates and focus more attention on those that likely will make it to market.

"What we've shown is it takes organizations so much time to terminate a candidate that it is often in the most expensive phase of research, the phase III trials, when they determine to terminate it," Getz explains. "There are a lot of resources that went into phase I and phase II."

Although it often takes a large patient population to determine whether a product is working, there are study designs that might provide signals in phase II studies about whether a new product is a "go" or "no go," Getz says.

• **There's no improvement in regulatory cycle time:** The regulatory cycle time is getting worse, if anything, he says. This particularly true of the FDA, Getz adds.

"The IRB cycle times have gotten faster, but the benchmark regulatory cycle time for the most part has risen by about 12 months," Getz says.

"There's a lot of speculation that it has to do with a more skittish regulatory agency," he adds. "This is a tough and critical climate of the FDA, and I think the FDA is quite nervous about how it is viewed and the kind of scrutiny that it's being put under right now."

The top-performing sponsors improve the regulatory cycle time by interacting proactively with regulatory agencies, Getz notes.

• **High prevalence of inefficiencies in study conduct arena:** "Sponsors are desperately looking for ways to optimize drug development," Getz says.

"Site selection and the study initiation process are two of the most inefficient activities today," Getz says. "It takes a long time to engage sites, and 30% will under-perform."

Lately, industry experts have criticized the pharmaceutical company practice of returning to under-performing sites, even if they never enrolled a single patient in the last trial.

It would be more efficient if sponsors used

metrics to help them predict how well a site will perform and to better manage the site's performance, Getz says.

Some of the top-performing sponsors are doing exactly that, and their success has shaved considerable speed off the drug development timeline, he adds.

"Their speed is not correlated with poor quality or higher costs," Getz says. "These companies maintain that standard of quality and contain costs, and they embrace speed practices at all levels of the organization." ■

Atlanta research company shares tips on promoting quality for growth

Recruitment database tops 8,000 names

Adhering to quality principles and building internal controls for compliance are key factors behind the growth of a successful Southeastern clinical research site.

Clinical Research Atlanta of Atlanta, GA, has grown since 2000 from having one investigator to a staff of 11, and its recruitment database includes more than 8,000 individuals who have agreed to participate in clinical trials.

"We've grown by starts and stops," says **Nathan Segall**, MD, principal investigator and founder.

"Clinical trials is an incredibly person-driven organization, and you can't rubberstamp anything, although you'd like to," Segall says. "We developed a great deal of oversight in our organization for that reason, and it goes into our improvement process."

Segall explains how the organization has grown successfully and maintained quality, using these strategies:

• **Recognize industry trends:** "We were primarily a respiratory and allergy site, and I recognized six or seven years ago that the robust pipeline in the field of allergy and asthma was beginning to wither," Segall says. "Because our practice is internal medicine, as well as allergy and respiratory, we had an opportunity to do clinical trials outside of my subspecialty."

Stricter regulatory oversight is another recent trend, and this is why the research organization needed to focus on compliance and oversight.

"We moved into a proactive modality as it related to good clinical practice," Segall says.

• **Learn from mistakes:** "We looked at issues of informed consent and issues of quality assurance," Segall says.

For example, the organization found that some prospective participants were misrepresenting who they were to collect the recruitment fee more than once, he notes. "We resolved that by requiring they present a picture ID with their name on it," he says.

To maintain quality in its recruitment process, the organization has incorporated informed consent into every step.

"We look upon informed consent as a process—not a signature and initial on the statement," Segall says. "So from the very beginning of the recruitment process, we inform the individual about the trial, and that information is given to our recruiter."

Also, the site sometimes sends the informed consent document out to prospective participants and asks them to read it and share it with their interested family members, he says.

"We ask them to make notes on the margins of any questions they might have, and when they come in, we can talk with them about informed consent and what the study will involve," Segall explains. "They are then asked to sign the informed consent prior to any procedures being performed, and we document that on the informed consent form.

"Also, there is an informed consent checklist which states that the subject or caregiver has received it and was given ample time to ask questions," he adds.

The study's risks and benefits are explained verbally, and all questions about the informed consent form are reviewed and answered.

If the informed consent form is changed for any reason, then the current version is kept in a clear plastic sleeve, and it's copied and placed in all subjects' charts for the next visit, Segall says.

• **Focus on quality improvement and training:** Quality improvement meetings are held quarterly, and everyone is expected to attend.

When there are changes that occur between meeting times, notices are sent out by e-mail, Segall says.

"We have a yearly training session on site, and we have the staff review the training and standard operating procedures, which are changed on

a yearly basis," he says. "Employees complete the training sheet, recertification and certificates, and we capture all of that, and we keep it on file."

Staff training sessions emphasize the organization's core values, which include integrity, culture of learning, and continuous improvement.

"The fourth value is fun," Segall says. "We want employees to think about the work they're doing, and we want them to see themselves developing in a profession."

The organization provides mentoring to new employees, and tasks are divided up so that no one individual has too much work, he says.

Everyone at the organization has human subjects protection certification, including investigators and coordinators, he says.

"If they're not certified, they're expected to certify after meeting the requirement of working two years for full-time, and we pay for them to take the certification test," Segall says.

Principal investigators provide ongoing education to coordinators about the disease processes of each trial, and coordinators are expected to read all adverse event and serious adverse event issues.

• **Learn from audits:** "The sponsor's audit is the best opportunity we have to look at ourselves with great scrutiny," Segall says. "Whenever that happens, we spend 45 minutes to an hour or an hour and a half after the audit with the quality assurance director, the chief coordinator, and the director of operations."

The group discusses what was found, and those involved ask questions and share suggestions. Segall learned from one of these sessions that the organization needed to look at its regulatory documentation in a different context.

"For example, if you have a page Z, which is under a folder in one section, then it could also be in another section, and you'd need to have an index in one of the sections so you could find it in the other one," Segall explains.

"We pay a lot of attention to our regulatory documents and how they are organized," he adds.

• **Develop better recruitment strategies:** "We have a very successful recruitment program that has allowed us to capture demographics on over 8,000 individuals, who are not patients in my practice," Segall says. "I do not use patients in my practice in study trials."

The organization has recruited these individuals through advertising and mailed fliers.

When people call in they are screened by telephone, and all of the advertising and screening process is IRB-approved, Segall says.

"We query people after they are screened for the initial study they called about, and we ask if they would like to be in our database," Segall says. "We inform them that our database is proprietary and it's not sold or used for any purpose except for clinical trials, and we'll inform them from time to time of upcoming trials."

The recruitment process is time-consuming, but it's an unrealized equity because everyone on the database list could potentially be in a clinical trial, he notes.

One employee manages the database, develops recruiting advertising, and seeks IRB approval.

"She is a former nurse and has an MBA in marketing, and we've learned where best to put advertising for certain trials," Segall says. "We're always learning because we tend to experiment with advertising."

When people return calls, the organization collects information about which piece of advertising encouraged them to make the call. ■

Merck director discusses company's strategies for clinical research success

Working with investigators is key

[Editor's note: ***Ernesto Aycardi****, MD, senior director of worldwide research operations for Merck & Co., is responsible for the Global Medical Organization, clinical research operations.* Clinical Trials Administrator *asked Aycardi by e-mail how the company has achieved its success as a fast drug developer in this question & answer story.]*

CTA: The Tufts Center for the Study of Drug Development has identified Merck as one of the five fastest drug developers for the most recent time period studied (2000-2005). As such, the Tufts analysis says that your company has more than a year time advantage over the majority of your peers. What are some of the benefits to a pharmaceutical company when a year or more can be shaved off the drug development process?

Aycardi: The drug development process is a very complex process that has a lot of variables

and interdependencies. Probably one of the most important issues in this process is to be able to be consistent. Reducing the time of the drug development process has significant benefits. First, we are able to bring new medications to patients faster, helping them to solve and/or alleviate significant health problems. It also gives us a great opportunity to focus our drug development efforts and facilitate investment decisions that bring significant value to our shareholders.

CTA: The Tufts Center says that one of the ways top-performing companies, such as Merck, have achieved success is through improving their sponsor-investigator relationship quality and collaborative effectiveness. Please discuss a few of the measures Merck has taken to improve its site selection process with regard to better study quality and faster product development?

Aycardi: Merck understands that the relationships we build with investigators, regulatory agencies, medical societies, etc., are critical to the drug development process. This is not just about individual efforts—we have to collaborate and work as real teams to be successful.

Selecting sites for clinical research is one of the most important decisions. As in any other process, the success requires having a simple, lean process with objective metrics, built on a well-structured control plan. Site selection decisions should be based on investigator qualifications and patient availability. We keep our focus on selecting investigators with high scientific qualifications and the appropriate training and background required by the protocol. The availability of patients is another critical factor to measure in order to facilitate our planning and anticipate potential difficulties. Understanding that all our processes should be primarily focused on quality is the key factor.

At Merck, we also always try to work closely with investigators in a collaborative way to achieve successful outcomes (i.e., full patient recruitment, within established timelines). For example, getting input from investigators in early phases of protocol design, engaging them in estimation of enrollment potential, and being responsive to their needs in how we run our clinical trials are some of the strategies that help us build this collaborative environment.

CTA: Some clinical trial experts say that pharmaceutical companies too often select sites that have low performance records, including returning to opinion leader investigators who often do not enroll patients in trials. Has Merck done anything to change this trend in hopes of improving site performance?

Aycardi: At Merck, site selection is a decision that is basically driven by the medical and scientific qualifications of the investigator and by placing a significant effort on estimating patient availability to predict enrollment success.

CTA: What are some other ways that Merck has improved collaboration with clinical trial sites?

Aycardi: Clinical research is not an individual effort. We have to build a collaborative environment that facilitates all the processes. Collaboration is based on two-way thinking. The expectations of all parties need to be clear upfront, and both parties must be totally transparent about capabilities and what they can offer to each other. It is not a matter of promises, it is a matter of responsibility and commitment. With this mindset, we develop our processes to facilitate this dialogue and have the appropriate discussion at the appropriate time, facilitating our decision-making processes. ■

Researchers and physicians have different obligations to patients

Investigators are not fiduciaries to subjects

Health care patients, the general public, and sometimes even physicians and researchers at times misconstrue the relationship investigators have to research participants, an ethics expert says.

Investigators have obligations to perform research according to ethical and legal guidelines regarding the protection of human subjects, but they are not fiduciaries of research subjects, says **E. Haavi Morreim**, PhD, a professor in the College of Medicine at the University of Tennessee Health Science Center in Memphis, TN. Morreim was the chair of the independent patient advocacy council (IPAC), established to represent study participants' interests in the first clinical trials of the AbioCor Implantable Replacement Heart, manufactured by ABIOMED of Danvers, MA.

"A fiduciary is someone whose No. 1 obligation, whose whole purpose of the relationship, is

for the fiduciary to promote the interests of the person who is beneficiary," Morreim says. "The classic example is a trustee who is overseeing assets on behalf of a beneficiary of a trust fund."

In this sense, a physician is a fiduciary of his or her patient because the physician's goal is to benefit the patient, Morreim explains. But this is not true of the relationship between investigators and research participants.

"By definition, the investigator's job is to do the research," Morreim says. "If you mistakenly think the researcher's No. 1 duty is to the research subject, then you'd have to modify the protocol anytime it would disservice the patient's interests."

Researchers' duties to subjects are as strong as those that fiduciaries have, but they aren't specifically fiduciary in character, Morreim says. Investigators have an obligation to follow the protocol and ensure scientific quality.[1]

However, medical care patients, the public, and even some physician investigators sometimes erroneously believe that a fiduciary type of relationship does exist between investigators and subjects.

Part of this myth is due to how physicians sometimes become investigators to their own patients. "A physician could be in conflict of interest in using patient trust to sign up patients for research," Morreim says.

This change in relationship can be appropriate when the patient has a disease for which there is no known cure or effective treatment, and the experimental treatment is all that is available, Morreim says.

"Then the physician might encourage the patient to sign up, but also to consider and look into the protocol," Morreim adds.

To prevent conflicts of interest, investigators generally should not recruit their own patients.

"Admittedly, in a community setting this becomes complicated, but I can envision some alternatives," Morreim says.

For instance, physician investigators could place information in their waiting rooms about research and provide a phone number to call if a patient is interested in participating.

"Normally, the treating physician doesn't have any business encouraging someone to sign up, but making this information available is not the same thing as recruiting," Morreim explains.

"We talk about therapeutic misconception and how patients/subjects may adopt the therapeutic misconception," Morreim says. "But frankly I think physician investigators are at least as susceptible to this."

Any physician who tells a patient that he or she thinks the patient should be in a particular clinical trial is quite possibly buying into therapeutic misconception, Morreim says.

Physicians might justify this type of interaction by thinking that they are doing what's best for the patient, but it's still a conflict of interest since the patient's participation in a clinical trial will benefit the physician investigator, Morreim adds.

There are alternative recruitment methods available. For instance, an investigator could place posters and other information in medical centers or at venues outside of his or her own clinic to describe a research trial and ask that volunteers call an information number if they're interested, Morreim suggests.

Or they can conduct advertising in the community through newspapers, television, and other media.

Having a physician's employee provide direct recruitment is not an ethically acceptable recruitment method in most cases because the employee is beholden to the doctor, Morreim says.

"You might describe the project and say, 'If you're interested I can set you up,' but that in itself carries the potential hazard of being weighted with encouragement by the physician," Morreim explains. "It's not an easy issue, and there can't be an absolute prohibition because there are times it's not feasible to have an independent entity."

Referrals made by physicians to another doctor investigator's trial are acceptable ethically so long as the referring physician is not entitled to a finder's fee, Morreim notes.

"If the physician is simply relaying information to the patient and saying, 'There is a study, and it's neither here nor there to me if you sign up, but you seem to be eligible, and if you're interested I can hook you up with people who give you information,' then it's okay," Morreim explains. "But if there's a finder's fee then that's a different situation than if someone is just paid to conduct extra tests to see if a patient is eligible for a trial."

Once participants are recruited, the physician investigator also might avoid ongoing issues with conflicts of interest and therapeutic misconception by having a neutral third party involved as a patient advocate.

In some cases, there are neutral persons on site who describe the proposed research project. This is what ABIOMED did with the AbioCor artificial heart transplant trials when they set up an independent group to work with trial participants,

providing extensive education and reinforcing informed consent.

For the artificial heart transplant trials, there was a patient advocate available to trial participants. This person typically was a medical doctor who could carefully explain the risks, including what might happen if the participant had a stroke.[2]

The AbioCor IPAC recommended that the informed consent document be changed to reflect some of the actual experiences of participants in the trial, once the trial had enrolled some heart patients and various side effects or outcomes had occurred.[2]

The IPAC also identified issues regarding whether certain nonmedical costs would be reasonable to provide to participants and their families without these becoming undue inducements.[2]

Whether it's feasible to use patient advocates, it's important for researchers and clinical trial professionals to consider the potential for therapeutic misconception and how they can avoid it.

"In the bioethics community you find a number of people who think the investigator is a fiduciary, but they don't understand what is packed into the word fiduciary," Morreim says.

Even IRBs are not fiduciaries to research participants, although they come closer to filling those criteria than do investigators, Morreim adds.

What investigators do have are constraints on how they can treat research subjects, and these are powerful constraints, both positive and negative, Morreim says. ■

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History of informed consent might predict trend of greater protection

Ethicist discusses current controversies

Investigators and clinical research professionals who have worked in the clinical trial industry for two or more decades may find themselves astonished by current controversies and debates over informed consent of human subjects.

Last year, Lynn Jansen published an article in *IRB*: *Ethics and Human Research*, which questions whether investigators should be sensitive to excessive optimism among potential study participants.[1]

"It's not a matter of people's cognitive understanding, but their emotional understanding," explains **Alan Wertheimer**, PhD, senior research scholar in the department of bioethics at the National Institutes of Health in Bethesda, MD. Wertheimer is a political philosopher who has published several books about ethical issues in nonmedical contexts.

"They might be too optimistic about the benefits to them of participating in research," Wertheimer says. "So we might ask whether a person can give valid consent if they're too optimistic."

This is a long distance from the days when informed consent was a novel concept in the research industry.

"There are a lot of moral issues where at the beginning a kind of core ethical position gets established, and then people begin pushing the boundaries out," Wertheimer says.

For instance, when the 20th century civil rights movement began, segregation was commonplace and discrimination based on race was institutionalized across the United States, he notes.

First the government and concerned citizens moved to end segregation and make discrimination illegal. This big push in a new direction was soon followed by further changes, such as the elimination of more subtle discrimination and the initiation of affirmative action, Wertheimer says.

The same journey can be seen with informed consent. "In the history of disasters in research, there was no consent whatsoever, so we had cases of Nazi researchers and the Tuskegee study," he says. Now the concept of informed consent is a core ethical idea that is well established, and so there are trends and ethical debates about activities that would provide even further human subjects protection and refine the consent process.

"What's happening over the last couple of decades is that bioethicists and others are saying that this core ethical idea isn't enough, so let's worry about other things that weren't previously on the agenda," Wertheimer says.

The idea of therapeutic misconception is one concept that pushes the envelope further.

"Now a person has been informed and has given consent, but maybe the person doesn't understand what he or she consented to,"

Wertheimer says. "Maybe they really don't get it and continue to think that what's going to happen to them is what the investigators believe is best for them."

Bioethicists question whether the person has provided true informed consent when that misconception is the case, he adds.

Another new controversy involves financial incentives to participants of research studies. "Some people think when you offer money to people who need the money that their consent is really not voluntary," Wertheimer says. "So there are worries about whether financial payments are coercive and whether people really do have a choice."

The language sometimes used to describe what bioethicists see as excessive financial payments is "undue inducements," he notes.

"In the classic cases in the history of research, these are not the issues," Wertheimer says. "But the key ethical points are settled, and now we can say it's not enough that there be consent and that people have been given information, but we also need to worry about their level of understanding and their level of voluntariness."

For example, there has been some debate recently about the amount of money that was offered to the participants of the recent English clinical trial in which six young and healthy men became terribly sick on March 13, 2006, after being given the study product.

The volunteers developed symptoms of inflammation, vomiting, swollen heads, and became unconscious after being injected with TGN1412, a humanized agonistic anti-CD28 monoclonal antibody, created by TeGenero AG of Wurzburg, Germany. Four of the men developed multiple organ dysfunctions.

The men participated in a phase I clinical trial conducted by Parexel International of Boston, MA. They were studied at Northwick Park Hospital in London, Great Britain, and their emergency and medical care occurred there, as well.

When recruited, the men had been offered 2,000 pounds if they completed the study. This inducement raised two ethical questions:

- First, was 2,000 pounds an undue inducement because it's a larger compensation than might be found in most other trials?
- Secondly, was the requirement that they had to complete the trial to receive the payment an undue inducement to stay enrolled even if they were worried about whether the trial was in their own best interest?

Since the trial ended almost immediately after the men received the first study product, and the subsequent investigation found no evidence of wrongdoing on the part of the clinical trial organization and the study drug's sponsor, these questions were left unresolved. The investigators had no reason to think that the study product was dangerous or anything other than a low risk.

"It's not clear whether people acted unethically or whether it was a tragic case of things having gone wrong," Wertheimer says. "Even when people act in good faith things go wrong and people make mistakes."

However, there is controversy over whether it is ethical to have trial completion bonuses or to withhold all or some payment for participating in a trial until after the trial is completed, Wertheimer notes.

"Some have argued that it's only ethical to pay on a pro rata basis in proportion to the amount of time someone is in the study," he says. "Withholding payment until the end might coerce somebody into staying with the trial when it's in their best interest to withdraw."

Another area of controversy involving informed consent is the length and readability of informed consent forms, Wertheimer says.

"Some people have argued that consent forms are much too long and much too complicated and that they're designed more to protect the researchers than to give the subject information that they can really make sense of," he says.

While one solution is to design shorter consent forms and forms with less sophisticated language, there are concerns about how much information is necessary for subjects to know and how to impart that information, Wertheimer adds.

Informed consent issues and controversies will continue as the ethical debate over human participation in research continues to progress, he notes.

"Among the issues I see on the horizon involve contexts in which people cannot give consent," Wertheimer says. These might involve patients during a medical emergency situation in which there are no surrogate decision makers, he says.

"How do we justify research on people when they are in no position to give consent," Wertheimer says. "This is a context in which it's not a matter of how to improve informed consent, but whether it's permissible and under what conditions it is permissible to give consent." ■

Reference

1. Jansen LA. The problem with optimism in clinical trials. *IRB* 2006;28:13-19.

Build human subject protection education into research office practices

Education takes on many different forms

When the federal government suspended human subjects research at Virginia Commonwealth University of Richmond, VA, in 2000, the institution's leaders turned the bad news into an opportunity to create a new and improved human subjects research program.

"We built the human subjects protection program from scratch," says **Monika Markowitz**, PhD, director of the office of education and compliance oversight in the vice president's office for research at Virginia Commonwealth University.

And in the seven years since that research nadir, the institution has achieved the success of becoming fully accredited by AAHRPP. The institution is cosponsoring with the Office for Human Research Protection (OHRP) a regional conference about human subjects research protection in September, 2008.

The university's research shut-down was due to inadequate IRB processes, but there was no evidence of any serious adverse event involving a research participant, Markowitz notes.

The institution's new education and training about research protection for human subjects is provided to everyone who is involved in research, from the IRB staff and members to research coordinators and investigators, she says.

"The emphasis on education is on the ethical perspective of the regulations," Markowitz explains. "It's not just having IRB members and investigators understand the regulations, but it's understanding the ethical underpinnings."

Here are some of the educational forums provided to research staff and others:

• **Basic human subject research education:** There is a baseline requirement that all investigators and key personnel take a Collaborative Institutional Training Initiative (CITI) course on human subject research, and there are regular program series that focus on either biomedical research or social-behavioral research and working with the IRB.

"We offer those throughout the year, and we advertise them to the entire research community," she says. "We also have extensive communication on our web site with IRB news, and we've recently instituted a bulletin for human research protections, which is another venue for communication and education."

• **Fourth Friday featured program:** All research coordinators are invited to the fourth Friday programs each month. These target individuals involved in research, focusing on human subject protection and IRB updates.

A recent program featured the institution's HIPAA officer, who could answer questions about privacy, confidentiality, and the institution's HIPAA privacy board's work.

Markowitz selects topics for the program by looking at what's current in human subject research and repeating some of the more important topics. "We recently had the director of the investigational drug pharmacy speak," she says.

The talk included a description of the research drug cycle and procedures and explanations about what is changing and what research coordinators need to know as they do their work.

• **Fifth Thursday programs:** Several times a year there are five Thursdays in a month, and on these fifth Thursdays, the institution provides a special educational program for IRB members.

The program typically features new processes IRB members need to know or considerations they need when reviewing protocols. Research coordinators and investigators are invited to the second part of these sessions.

"For example, our last program in August was a conversation with one of our biostatisticians, and the title was, 'Do size and power matter in human subjects research?'" Markowitz recalls.

"So there was quite a bit of interest, and we had more than 35 people there, including coordinators and investigators," she says.

• **Post-approval monitoring:** "We have instituted a post-approval monitoring and education initiative which we call the IRB support visit," Markowitz says.

"This is a visit that is scheduled. It's a not-for-cause visit that targets protocols that are of high risk, that are very complex, or that involve vulnerable populations, and any combination of those," she explains. "They are conversationally based visits, and we try to include the IRB staff and reviewers in those visits, so they can associate a name with all of the communications they might have had with a particular investigator and research coordinator."

Markowitz, a research ethicist, and a nurse and two others within the office conduct the visits.

"Prior to the visit we have read the protocol and amendments and any reports of unanticipated problems and material submitted through continuing review," Markowitz says. "We start with the request that the investigator walk us through the process of what happens after a subject is referred to them or is identified as a potential participant."

Then the site visitors review the site's informed consent process and learn about the interactions between research staff and participants, she adds.

"We look for evidence of organization of regulatory and study documents," Markowitz says. "We're not looking directly at all the paperwork that might be of interest in an audit because it's more about determining whether or not the investigator is following the IRB-approved protocol."

They look at how data are protected and assess what happens when subjects begin to participate in a study. The monitoring visit takes about an hour, and the preparation time and post-monitoring visit time take longer than that, Markowitz says.

"We have a tool that is available on our web site, which is a post-approval, self-evaluation tool that we refer the investigator to when we set up the visit," she says. "They're not required to fill it out, but they can look to see the kinds of things we're interested in."

It's viewed as an educational tool for themselves and their coordinators, and it's a way to prepare for audits from sponsors or prepare for monitoring by clinical research organizations, Markowitz adds.

• **Update staff about policy changes:** Through e-mails and meetings, IRB and research staff are updated about any changes or revisions to the institution's written policies and procedures, which are referred to as WPPs, Markowitz says.

"Whenever we're introducing a new WPP or making revisions to a current one, we run those ideas past our IRB chairs," she says. "The IRB chairs meet every month and they can give their blessing and approve the revisions or new WPPs or suggest changes."

Once approved, the IRB staff and members are educated about the new WPPs, and the same

CE/CME *questions*

17. A clinical research expert notes which of the following current trends in the drug development industry?
    A. The scope of drug development is expanding.
    B. There's a decline in the success rates of new compounds.
    C. There has been no improvement in regulatory cycle time.
    D. All of the above
18. Successful clinical research sites should focus on which of the following?
    A. Cutting costs to make the site more competitive for private industry studies
    B. Improve quality through training, education, self-audits, and adhering to core values
    C. Use patient database as much as possible when seeking study participants
    D. None of the above
19. Which of the following is a recent controversy involving informed consent in research?
    A. Should informed consent be required for all conscious human subjects in research?
    B. Are signed consent forms necessary?
    C. Should prospective study participants be enrolled if they are overly optimistic about what they might gain from a trial?
    D. All of the above
20. The 2007 job market for clinical trials professionals could be characterized which way?
    A. It's a little difficult to find a job unless one has a PhD or at least 10 years of clinical research experience.
    B. It's a great market for both salary and finding work in a variety of different types of research settings and positions.
    C. Clinical research professionals are primarily young and inexperienced.
    D. None of the above

Answers: 17. (d); 18. (b); 19. (c); 20. (b)

COMING IN FUTURE MONTHS

- Research institution's prospective monitoring provides education, QA
- Follow these tips to better manage the close-out process
- Medical students lack some education essential for clinical research, study finds
- Research group will focus on new model for drug study to expedite research

educational information is given to clinical research investigators and staff.

"We announce on our IRB's web site that there are new WPPs out there, and we have a tutorial PowerPoint presentation that describes any changes and anything new in the WPPs," Markowitz says. "We send out broadcast e-mails to IRB staff and IRB members, and we try to give inservices within the IRB meetings." ■

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CLINICAL TRIALS ADMINISTRATOR
An essential resource for managers of clinical trials

New jobs are opening up and existing ones compete for workers in clinical research industry

Experts say more education is latest trend

It's a very good time to be an experienced clinical trials professional, according to experts and the 2007 *Clinical Trials Administrator's* salary survey.

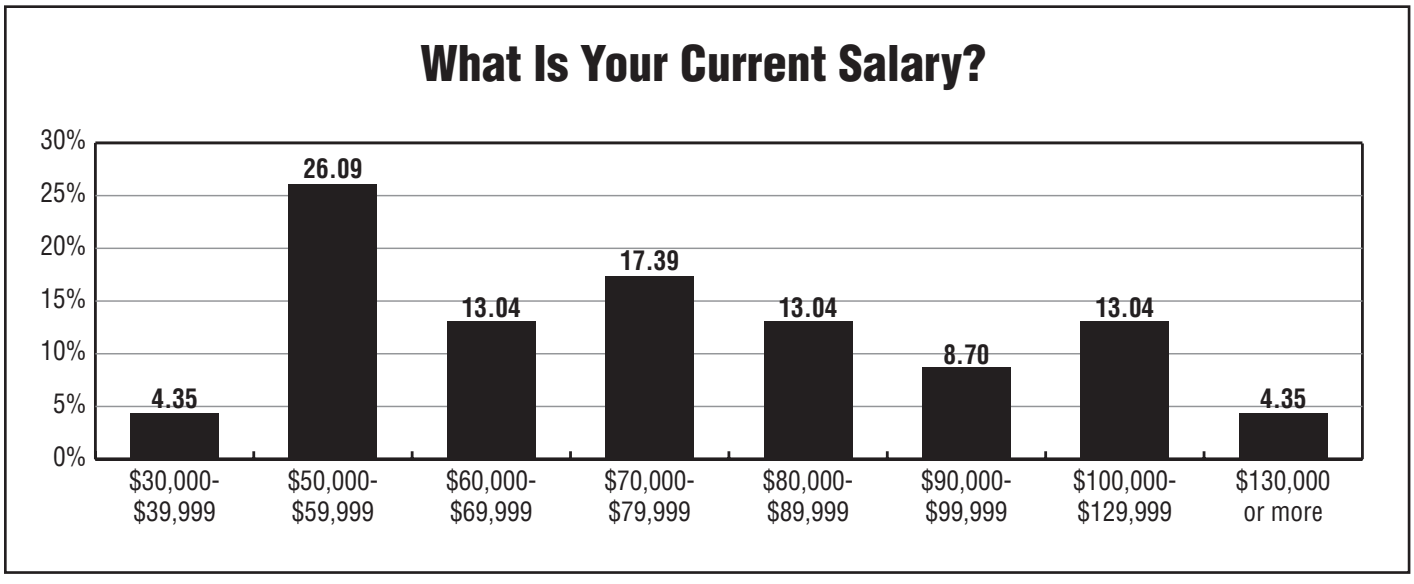
"I definitely think this is a wonderful industry to be in," says **Tamara Dowd Owens**, RN, MSN, MBA, director of clinical trials for Pinehurst Medical Center in Pinehurst, NC. Owens also is an editorial advisory board member for *Clinical Trials Administrator*.

"I have had several friends and colleagues in the industry tell me they are getting calls left and right from job recruiters, and it sounds like there are numerous jobs in the field," Owens says. "And the pay sounds good too."

The *CTA* salary survey has found that nearly all respondents to the survey report having annual salaries of greater than $50,000 per year, with close to 70% reporting salaries greater than $60,000. **(See gross income chart, below.)**

The survey's 23 respondents hold a variety of positions within the clinical research world including these: senior director of clinical research operations, IRB administrator, clinical research specialist, director of clinical trials protocol management office, medical director, certified clinical research coordinator, quality assurance/site trainer, and research manager.

Clinical research professionals, whether they



come from nursing or other medical backgrounds, have a wider variety of career options in the current clinical research environment than they have had in the past.

For example, while many have gained experience working for clinical research sites, there are new jobs opening up at clinical research organizations (CROs), particularly in the relatively new field of working in site start-up groups, Owens says.

New job trends

CROs are creating lists of preferred CR sites, offering pharmaceutical companies value by saying they can provide a group of sites that are able to recruit X number of trial participants, Owens explains.

Once a CRO receives a trial contract, the organization goes to the site start-up group and tries to identify sites that may fit well with the protocol's recruitment needs. The site start-up group facilitates the recruitment and start-up process by having a site start-up specialist assist research sites with contract work, regulatory work, and other tasks, Owens says.

This relatively new position of start-up specialist is a great career move for clinical research professionals, Owens adds.

"This is absolutely creating new jobs," she says.

Another new job trend is in the area of pharmacovigilence, which was off the radar screen for nurses looking at career changes until recently.

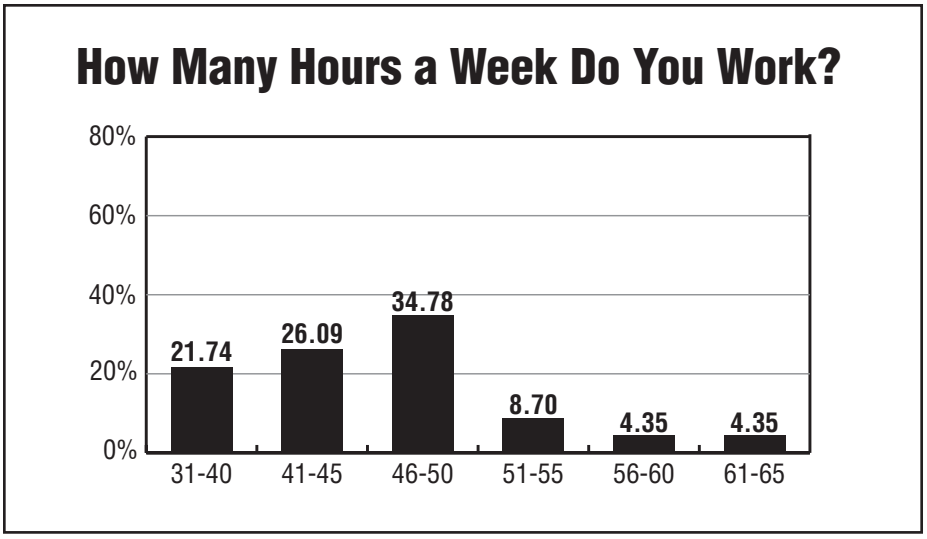
"Pharmacovigilence is booming," Owens says. Nurses who decide to switch from hospital and clinical work are moving into this field where they become drug safety associates, she explains.

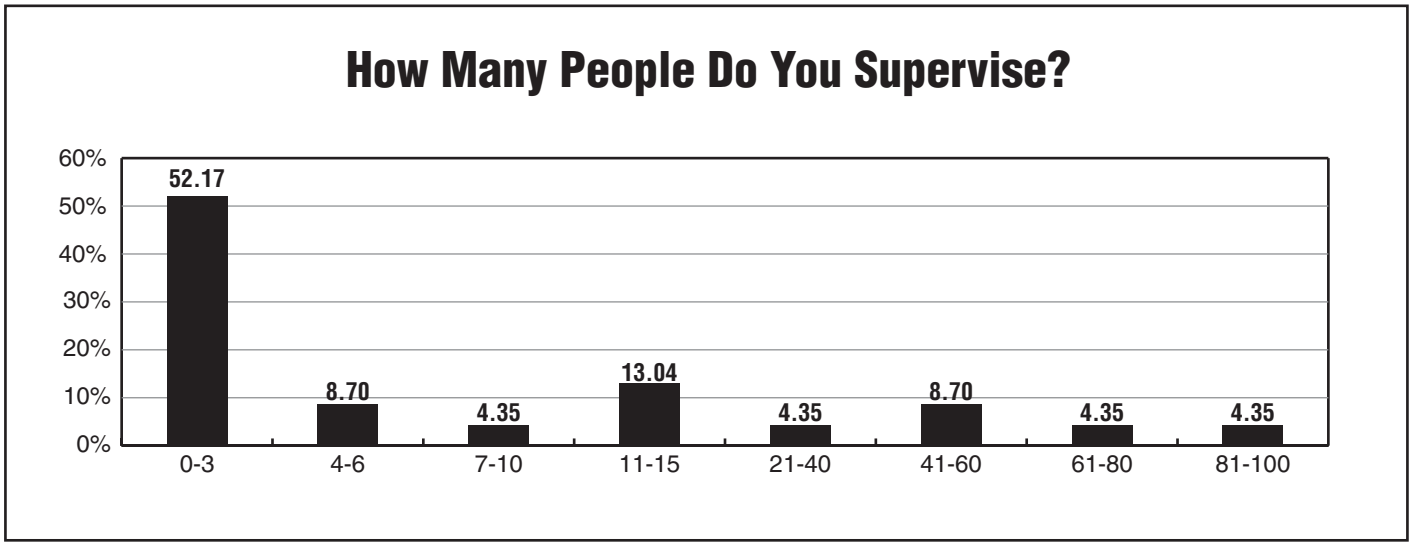
"If a clinical trial site has a serious adverse event occur, and it's sent to the CRO, then the event is reviewed by the site safety associate," Owens says. "The site safety associate makes sure all information in the initial report is done and puts the information into the FDA's MedWatch form."

The site safety associate is a separate career path than clinical research organization, but both types of jobs are drawing from the nursing pool of applicants, which has helped to make the clinical research job market challenging from an employer's perspective.

It's hard to find good people to work in clinical trials research, notes **Barbara J. LoDico**, BS, CIP, director of the human subjects research at The Children's Hospital of Philadelphia in Philadelphia, PA. LoDico is on the editorial advisory board of *Clinical Trials Administrator*.

The pay and work are rewarding, so the field is continuing to attract new candidates, but many





are coming from fields other than nursing, LoDico says.

"They used to recruit just nurses, but now they're recruiting PhDs, MDs, clinical and advanced practice nurse practitioners, so I think what they're looking for has changed a little bit," LoDico says.

Research-specific curriculum

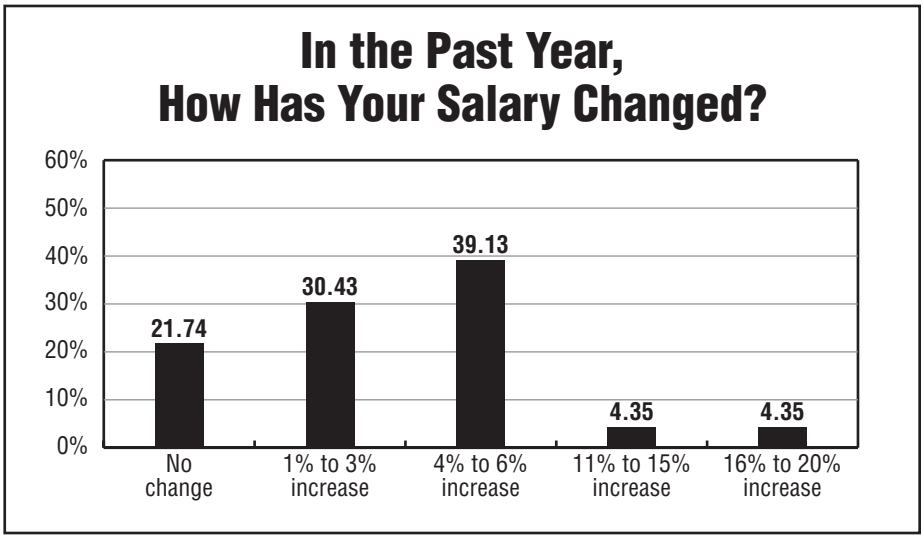
Also, some universities have begun to offer specific courses in clinical research with the goal of providing new graduates with backgrounds in either nursing or other fields who can find a job in clinical research and have training that replaces experience, LoDico says.

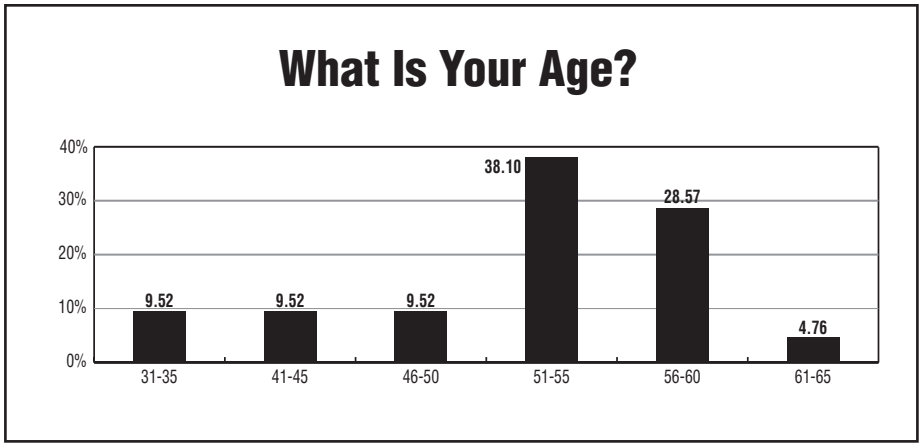
For example, Duke University has clinical research management programs for both nurses and professionals with other college degrees, says **Elizabeth E. Hill**, RN, DNSc, an assistant professor, nurse planner, and director of the Clinical Research Management program at the Duke University School of Nursing in Durham, NC. Hill also is on the editorial advisory board of *Clinical Trials Administrator*.

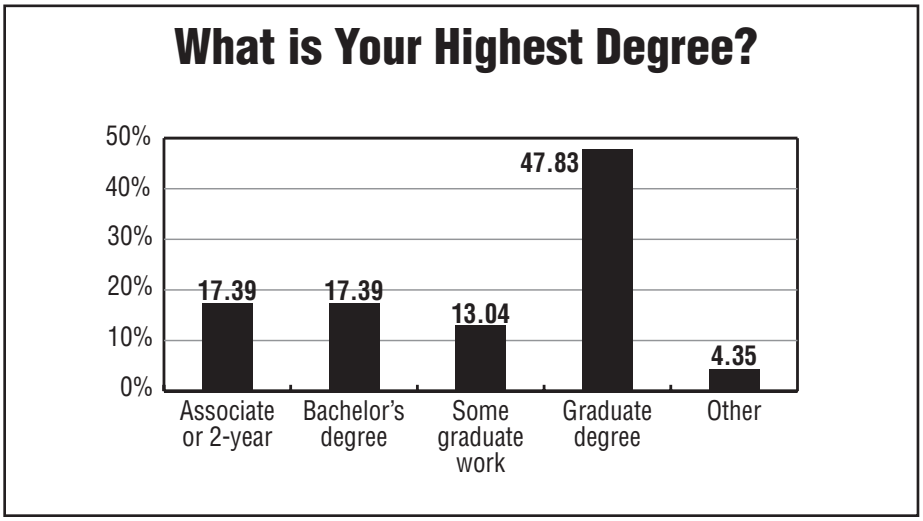
The clinical research management program includes courses in regulatory affairs and how to make an IRB submission, Hill says.

Traditionally, nurses might apply to work at a research site at their medical institution, and they acquire on-the-job training and experience, Hill says.

But the latest trend is for nurses and other professionals to acquire coordinated education about how to perform study coordinator tasks, she says.







The master's degree program in clinical research management at Duke is more for an advanced position in the research industry, but the principle serves the same goal of giving people with experience in other fields—mostly medical fields—education and training in clinical research for the purpose of helping them make a career change.

"We're the only group in the school of nursing that has something to offer people who are not nurses," Hill says. "You can apply if you have a graduate degree of some sort."

For example, some of the recent students have been Chinese physicians who are unable to practice medicine here, but who want to be involved in some aspect of science and medicine, Hill says.

Others are professionals who have earned a PhD in another field.

"We have a lot of people who have been in the industry for a while, and they feel they need a graduate degree to advance," Hill adds.

Since clinical research work often draws people who have started out in other fields first, it's a field that has mostly middle-aged and older workers, according to the experts and the salary survey.

More than 90% of those surveyed are age 41 or older, and more than 70% are age 51 and older.

"Really young nurses just coming out of school are not aware of clinical research and are not interested in it," Hill says. "It's better if they have a little experience anyway."

People don't start their career thinking they'd like to be a study coordinator, LoDico says.

What typically has happened is that a physician sees someone who is very bright and recruits that nurse, or a nurse decides he or she doesn't want to do floor duty anymore, LoDico says.

Clinical research is a good field for a second career, Owens says.

Salary-wise it's comparable to nursing, but the benefit is that the hours are more regular and it's a salaried position so there's more potential for advancement, Owens says.

Salaries likely will remain high due to the growth in jobs for people with research experience, the experts say.

"Everything is on the upswing," Owens says. "Small biotech companies and start-up companies and spin-offs from universities are doing clinical research and need staffs."

Also, more research is moving into the community where physician offices need experienced people to assist with clinical research, Owens adds. ■