CLINICAL TRIALS
ADMINISTRATOR
An essential resource for managers of clinical trials

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IN THIS ISSUE

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Do you know what sponsors want from your site? Experts offer clues

Better education, transparency are key

With a rapid acceleration of changes in the clinical trial industry, including international outsourcing, even experienced clinical trial professionals might find it a little confusing trying to figure out what sponsors want from their sites.

And since sponsors are not uniform in their desires, with some seeming to value low cost above quality, the effort to position a particular clinical trial site as desirable becomes more challenging.

The problem is especially acute for new principal investigators (PIs) and clinical trial sites.

About one third of sites drop out of research trials because their inexperience led to their misunderstanding the difference between clinical research and clinical practice, says **Robin Newman**, RN, MSN, CPNP, RAC, CCRA, chief scientific officer of MedTrials Inc. of Dallas, TX. MedTrials is a clinical research consulting firm primarily working with the medical device and biotechnology industry.

For example, an orthopedic physician decides to conduct a clinical trial involving a marketed product for total knee replacement, Newman says.

"The first time around, the doctor will say this is just another total knee replacement, and he or she will not think about all of the end points necessary for the trial," Newman explains. "The doctor also doesn't think in terms of manpower expense."

The clinic's nurse is given the additional burden of managing the clinical trial, and unless the nurse is given training and the time needed to do the job correctly, the study will become a big headache for the office and possibly put subjects at risk, Newman says.

"Research is not just treating a patient in regular clinical practice; it's more complex," says **Eduardo Tschen**, MD, MBA, CPI, a clinical associate professor of dermatology at the University of New Mexico, who works with Academic Dermatology Associates in Albuquerque, NM.

"What happens is physicians think they can generate some revenue by just doing some clinical trials without putting in the effort up front,

including training a coordinator," Tschen says. "And the physicians also need to be trained, but they need to understand that a clinical trial is different from their regular practice, and they need to understand the regulations."

Chiefly, physicians need to think of clinical trials as running a practice with much tighter controls, Tschen says.

Pharmaceutical companies and other sponsors have been reactionary to problems, such as trial delays and slow subject accruals, and the proactive measures of improved investigator and clinical trial staff education have not been a big priority, says **Nadina C. Jose**, MD, CPI, MBA, president and chief executive officer of Research Strategies Inc. of Pasadena, CA.

"There should be a mutual investment between the sponsor, clinical research organization [CRO], and site to provide early training and a good infrastructure for training for every study that is initiated," Jose says. "These should be paid by both the pharmaceutical companies and the sites themselves."

Clinical trial outcomes show that sites that are well-trained and experienced in research are far better able to produce quality data for clinical trials than untrained and inexperienced sites, Jose adds.

As the research industry evolves, smaller clinical trial sites, such as clinics within communities, are becoming more important, Tschen notes.

And sponsors are beginning to spend more time with training these new sites, Tschen says.

"Clinicians are enjoying this opportunity very much, but it's like anything else in that it takes time," Tschen says.

Here are some basic steps sites can take to improve their competitive advantage and improve study quality, according to Jose and other experts in the clinical trial industry:

• **Invest in training and educating staff:** Although it would be ideal if sponsors would assist in educating clinical trial staff, the reality is they leave that to sites, Tschen says.

Nonetheless, this is not an area for cutting corners, he says.

When a sponsor visits a facility and sees that the investigator is not available, a computer system is lacking, and staff are untrained, they'll think this not a setting conducive to conducting clinical trials, Tschen says.

One way to self-train is to observe an experienced clinical trial site, Tschen suggests.

"Quite a few coordinators have come to our facility to observe and see how we operate," Tschen says. "We give those coordinators hands-on experience for a few days or a few weeks, and we hold a series of lectures each week for coordinators."

There's no standard educational background required for clinical trials coordinators, but it's important to find the right kind of dedicated staff, who are interested in research and are well organized, Newman suggests.

"As long as you have a small number of trials running, and they're not too complex, that will

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get you down the road," Newman says. "As the trials become more complex, and you take on more trials, then you need certified staff, which not only know the rules, but know how to apply them across multiple scenarios."

Hands-on training or training by professionals who can bring the reality of daily research to life in the lesson plans would be the optimal method of educating new clinical trial staff and investigators, Jose says.

Investigators and clinical trial staff need to be trained with real life scenarios of what they might expect during an informed consent process, for instance, Jose says.

"If everyone understands what the expectations are at the beginning, this is what makes you a site that sponsors and CROs are trying to use," Jose says.

Research Strategies, which Jose founded 10 years ago, is a clinical trial support service company that provides comprehensive training for clinical trial professionals and investigators.

"The concept is not the traditional site management where you have a network of sites, but rather we're able to provide an a la carte menu of services to facilitate efficiency, provide administration services, conduct training and continuing education, and manage quality control," Jose explains.

The company provides basic training for all members of the research team at the outset, and then continuing education is provided through workshops, as needed, Jose says.

Before a site starts a study, the company will provide inservices about the protocol's specific information, she adds.

• **Be transparent**: Clinical trial sites that developed metrics or data showing their historical performance in certain therapeutic areas will go far in gaining the confidence of sponsors, Jose says.

These data may include the following:

- rates of enrollment;
- drop-out rates;
- completion rates;
- query response time;
- time frame to completion of study.

"Put these in a dossier and say, 'Here are our metrics, and here is our performance, and here's where we were deficient in the past,'" Jose says.

"A performance metrics is something I strongly advocate," she says. "So when a site submits it to the prospective sponsor, it will answer a lot of questions and will catch their eye."

Likewise, a site could develop a CD or even a video of what the site looks like, including the drug dispensary, lab, patient's room, where monitors will sit, etc., Jose suggests.

"It's like selling a house and showing your best features, making it a complete package," Jose says.

Another way to be transparent is to have a Web site and promote it potential sponsors, she says.

Also, sites could invite sponsors to visit their facilities, and when they do the staff should make them feel at home, Jose says.

• **Have the PI fully involved in the study:** The principal investigator is 100 percent responsible when a sponsor goes to the FDA to make a marketing submission, Newman says.

"Principal investigators have to be prepared to audit adequately, and they have to be engaged in the process because their lack of involvement jeopardizes the study," Newman says.

Sponsors and regulatory officials will think it's a problem if a PI has delegated too many of the tasks and now shows evidence of being involved in the data collection, Newman says.

"You can see in their charting that they're not doing the charting and following patients, and they have a lack of understanding about who is doing what on the trial, including for the informed consent process," Newman adds. "Investigators don't understand how vulnerable that makes them."

These types of investigators soon run into problems with warning letters or sanctions from federal agencies, and these are made public, causing damage to their reputations in the industry, Newman says.

"What I tell investigators is 'It may not be your fault, but it's your responsibility,'" Newman adds.

• **Learn from mistakes:** "You have to understand that your first clinical trial is a learning experience that won't make you wealthy or famous," Tschen says. "Investigators need to take it as a practice trial and learn what their shortcomings are and improve them."

For example, a first-time investigator typically will assign a staff nurse or another employee to take over the clinical trial work, and that usually fails, Tschen says.

Also, investigators quickly learn that there is less flexibility with patient visits during a clinical trial. So if a patient cannot come on a particular morning for a clinical trial site visit, then the investigator is left with the dilemma of either dropping the patient from the study or deviating from the protocol, Tschen says.

"Everyone needs to understand schedule conflicts and so forth, and that's what frustrates most physicians," Tschen says.

Also, the basic interactions and amount of time spent on interacting with patients changes within a clinical trial, he says.

"On average, a dermatologist will see 60 patients in one day, while in clinical trials we — two dermatologist/clinical researchers — probably see 25 patients in a day," Tschen says. "So we can spend much more time with our patients and take care of them much better."

Tschen's clinic has built up its research practice over 25 years, building up to a staff that includes six fulltime research coordinators and more than 1,200 clinical trials.

Clinical trials help physicians and their staffs learn how to improve the quality of the clinical practice, which in turn improves their clinical trial work, Tschen notes.

"More than anything else, you have a personal feeling of satisfaction from contributing to the development of new drugs or practices, and that's a benefit," Tschen says. "It also improves staff morale." ■

Tackle the beast of study delays following these principles

Know your own budget, chief solution

Study delays continue to accelerate costs of conducting clinical trial research and are a problem for clinical trial sites, as well as sponsors.

When studies are delayed for any of the common reasons, including a study population becoming unavailable or unrealistic inclusion/exclusion criteria, both clinical trial sites and sponsors are impacted financially, and the quality of research becomes an issue, says **Christopher T. Speh**, MA, MBA, an independent consultant to pharmaceutical companies. Speh founded a clinical research organization (CRO) Resources Solutions Inc. of Research Triangle Park, NC, in 1992, and sold it in 2003 to the Constella Group of Durham, NC. Speh has spoken at national conferences about reducing study delays.

"The recovery from study delays is much more expensive than the anticipation," Speh says.

Sites, CROs, and sponsors all have a responsibility to conduct real time analyses, develop mapping plans, and maintain accurate budgets in order to improve the timeliness of clinical trial research, Speh says.

For example, sponsors and CROs need to make certain the specific study requirements written by the sponsor are both realistic and followed out, Speh says.

Clinical trial site professionals have the scientific and medical knowledge to review the protocol and make sure that what they're seeing with potential subjects and study accrual are reflecting the actual study needs of the sponsor, Speh explains.

"Also, it's incumbent on the CRO working with the sponsor to make sure the specification does reflect that requirement and reflects the protocol the site can undertake and be successful with," Speh says.

CROs might not have the medical expertise to challenge protocols in depth, but they can pay close attention to the mechanics of a study and note where expectations were realistic, Speh says.

"If we thought the sponsor was unrealistic about accrual or ramping up sites, we would bring that information back to the sponsor, whether we were asked to or not," Speh says.

"We would tell them what the study objective was and whether it was achievable, and our feedback was oriented at assuring that realism is built into these study plans," Speh says.

From the site's perspective, it's extremely important to have thorough knowledge of clinical trial costs, Speh says.

"Sites often have a general feeling, but they don't really know what the cost of research is for their site, so they're often not in a position to challenge a sponsor with solid data," Speh says. "Then they may take on a study that is unrealistic in terms of costs."

Naïve sites are particularly prone to taking on studies that may cost them more than what the sponsor has agreed to pay, he says.

While the ideal situation would be for sponsors to keep data and know who the better sites are and award contracts to the ones who are known to produce quality data, even if they do cost more, that's not the way it often works, Speh says.

Some sponsors focus more on the pricing issues than on the delivery of quality data, Speh says.

"We were fortunate as a small CRO," Speh notes. "We tended not to work with major production, cookie cutter clinical trials, and so we developed very solid relationships with our sponsors."

Speh's CRO had active interactions and conversations with sponsors about what would work and what wouldn't.

However, cost remains a chief driver of contracts for some sponsors, he says.

"Part of the reason why profitability is so difficult to obtain in the site business is because of modernization of service," Speh says. "We've increasingly seen site service as a commodity, and you basically bid it out to the lowest bidder."

For some sponsors, the contracting process is the primary means for selecting vendors, and cost is the predominant factor, Speh says.

"You do find that quality of the study goes down when cost is the main factor, because sponsors then are working with more naïve sites," Speh explains.

Naïve sites are the ones more likely to accept the first offered contract price because they want to build up their business or they don't have a realistic handle on their trial costs, he says.

On the other hand, if a site can demonstrate it can deliver subjects on time then the sponsor will pay for it, Speh says.

"Quality is good for business and it leads to profitability for the sponsor and the site," Speh says.

"The other issue is cash flow," Speh says. "The more naïve sites don't know their costs, and they don't project their cash flow, so they may struggle."

While sponsors have moved to more centralized contracting, this hasn't had the result of improving sponsors' knowledge about site performance, he notes.

"The pace often is driven by so much work going on that it's not just possible to gather all of the information and have it available to the next team putting together a study specification," Speh says. "However, sponsors recognize that the more information they have about potential vendors, the better off they'll be."

Alternately, sites are in a good position to know and market their own data to sponsors, he says.

Sites should know their own costs and, more specifically, how those costs are tied to milestones in the study, which would predict the cash flow situation, Speh suggests.

"For sites to protect themselves and to help the sponsor achieve a successful study, they should make sure there are very clear milestones in the contract, and this is where study mapping comes in," Speh says. "The milestones map back to the critical elements of study plan and design, so the site receives financial incentives to put its best efforts against the elements of the plan, and typically that will be the accrual rate."

Clinical trial professionals need to take a close look at the reimbursement methodology to make certain they know where the trigger points are, and then they need to map it out to learn whether the cash flow is something they can live with, Speh suggests.

"It doesn't do any good if six months into a trial you are profitable in principle, but you still don't have cash when you need it to pay the bills," Speh says.

Ideally, sites will learn to become differentiated and specialized in certain clinical trials that attract sponsors and make it more likely they will meet accrual goals, Speh says.

Once a site does this then it will be easier to find sponsors who know what it is that they do very well, he adds.

"Identify the niche areas where you have particular capabilities," Speh advises.

This is an increasingly important strategy as U.S. sites begin to compete with lower cost international sites, which often have faster subject accrual times, Speh notes.

"There is real potential in this country for sites that remain domestic, but they're going to have to work harder at differentiation," Speh says. "If you're just one of the pack, achieving profitability will be a challenge."

Another way to improve their success in subject accrual and to reduce study delays is for sites to know their own capabilities and limitations, Speh says.

"Sites go into research and see the potential revenue and there's a blinding effect of their own limitations," he says. "Sites should do assessments of their own potential subjects."

Sites are the best judge of whether a sponsor's accrual expectations are realistic, but this is true only if they know their own limitations, Speh says.

"I think most sites that engage in clinical research really don't have a comprehensive database of their subjects that can be screened in a very efficient way to determine how successful they can be in a study," Speh says.

While sites have the data available to make this assessment, they often fail to view the information from a business perspective, he notes.

"It's a terribly unforgiving world for a site that takes on a study and does not deliver it for whatever reasons," Speh says. "With as much competition as there is out there, being able to demonstrate you can deliver subjects can lead to profitability." ■

Compliance Corner

Complaints about FDA investigators are on rapid rise, raising concerns

Protocol deviation is biggest area of complaint

The Food and Drug Administration (FDA) has collected complaints about investigators for decades, but a look at the volume of complaints within the past eight years shows there are major compliance concerns at present.

"The rate of noncompliance continues to rise sharply," says **Ken Getz**, MBA, MS, a senior research fellow at Tufts Center for the Study of Drug Development, Tufts University in Boston, MA. Getz spoke about FDA compliance complaints at the 42nd Annual Meeting of the Drug Information Association, held June 18-22, 2006, in Philadelphia, PA.

Up until 1998, the FDA typically received about 10 complaints, annually, against investigators for noncompliance and fraud, Getz says.

Then in 1999, there was a 10-fold jump to 106 complaints. It's been uphill ever since, with the number of complaints reaching 266 in 2005, Getz says.

"It continues to rise every single year, so we have to think through what are some of the drivers of noncompliance and fraud," he says.

The rapid rise in complaints has changed the way the FDA investigates clinical trial sites, Getz notes.

"In the past, the FDA-conducted inspections primarily were driven by routine and unsolicited activity," he says. "But when the FDA receives a complaint, the agency takes it very seriously and treats these complaints as a priority."

So there's been a shift from inspections: prior to 2000, FDA inspections were mostly routine, and since 2000, they are mainly complaint-driven; this suggests the FDA's mindset also has shifted, Getz says.

"It's moved from a 'Let's see what we can uncover during a routine inspection,' to 'We're out here because they're guilty until proven innocent,'" Getz explains.

Another shift has been in who is making the complaints.

In early 2000, about one-third of all complaints were anonymous, and the largest portion of complaints came from site personnel, Getz says.

Now, only one in 10 complaints are anonymous, and 29 percent, which is the largest portion, come from IRB professionals, he says.

"The vast majority of the complaints are aimed at the investigator who signed the 1572 form, which is required by law for the investigator to complete before administering the study drug," Getz says.

Here are the other main sources of complaints to the FDA:

- 19 percent—site personnel, including study coordinators and administrative staff;
- 12 percent—sponsors or clinical research organizations;
- 9 percent—anonymous complaints, which might include disgruntled employees.

The shift from site personnel to IRB professionals in landing the top spot for filing complaints has occurred during an era of greater pressure being placed on IRBs, Getz notes.

"There is tremendous pressure on the IRB to demonstrate that it is being effective in monitoring compliance," Getz says. "So I think the IRBs have been sensitized to being even more careful to police human subject protections."

The industry buzz is that IRBs are overworked and overtaxed, working over capacity. IRB professionals take that criticism seriously and feel they have to be as careful as they can be, he says.

In 2005, the top complaint filed with the FDA was for protocol violations, which were cited on 34 percent of the complaints, Getz says.

Here are the other categories listed on FDA complaints:

- 27 percent — falsification of data;
- 12 percent — poor drug accountability;
- 10 percent — informed consent noncompliance;
- 8 percent — poor adverse event reporting.

"IRBs may be making the informed consent and adverse event reporting complaints," Getz says.

Similar complaint data from the Office of Human Research Protection (OHRP), covering complaints made between 1998 and 2002, finds that one-third of the complaints involved deficient IRB review, and 27 percent were about poor record keeping or reporting, Getz says.

"OHRP reports that one out of every five complaints they receive is for research conducted that has not yet received IRB approval," Getz says. "Some of these might be behavioral studies or studies where the investigator didn't think he or she needed approval."

Nonetheless, when pharmaceutical and clinical trial industry professionals hear the FDA and OHRP statistics, they typically are surprised, Getz says.

If they want to reduce noncompliance and reverse the FDA's complaint trend, then both clinical trial sites and sponsors should focus on investigator and trial staff training and education, Getz suggests.

"What the statistics tell me is we have to choose places to invest resources to reduce noncompliance, and we have a pretty clear roadmap," he says. "GCP and study management training need to be more effective."

Although sites might say their training and regulatory requirements are quite onerous, perhaps one of the problems is that the training is not tailored to the experience level of investigators, Getz says.

Instead of having experienced sites repeat the same training program annually, why not give them the option of undergoing training every three years, while giving novice investigators and sites additional training, he suggests.

"We need to re-evaluate the training and move inefficiency and redundancy out of it so it will be practical for investigators," Getz says. "We also need to simplify some of the guidelines to make those that relate to current compliance issues as effective as possible." ■

Data mining, data warehousing may be relatively new, but here to stay

Here's how clinical trials will improve with them

The use of data mining in the pharmaceutical clinical trial industry might still be in the Triassic era, but that is changing, as industry leaders learn more about how new methods of using research and medical data can improve clinical trial efficiency and patient care, according to an expert.

"People talk about individualized medicine, and data mining is the right tool for the delivery of individualized medicine," says **Andrew Kusiak**, PhD, a professor of industrial engineering at the University of Iowa in Iowa City, IA.

The pharmaceutical industry and clinical trial industry have only touched the surface of data mining, often mistaking data analyses for true data mining, Kusiak notes.

For historical reasons, true data mining has not yet caught on in the industry, he says.

"There are many statisticians who do data analysis, and as this new science of data mining emerges, it's up to them to either accept it and recognize it as something that's different or they could just basically stay with what they already know and try to reject it as a tool," Kusiak says.

Each time an established industry is presented with a new tool or advancement, it takes some time for the field's practitioners to accept it, Kusiak says.

Kusiak often speaks at clinical trial and pharmaceutical industry conferences, offering attendees a tutorial in how the new data tools work.

Here are some basic data mining concepts and their definitions:

- **Data mining:** "It's an emerging science that deals with the discovery of patterns in data, and those patterns can be presented or interpreted in different ways," Kusiak says. "One way to interpret those patterns is think of them as new knowledge."

The new knowledge, which is drawn from the historical data, can be used for various purposes, including decision making, Kusiak says.

"For example, one could extract knowledge, and that knowledge could be used to prescribe the right medication in the right quantity for minimal side effects for a patient," Kusiak says. (See story with example of data mining, p. 106.)

"The knowledge also could be used to select the most appropriate patients for a particular clinical study," Kusiak adds. "So, not only the effectiveness of the study and the outcomes could be maximized, but also the cost of the study could be minimized."

While some people might view data mining as a subset of statistics, that's not a proper definition, Kusiak says.

"It's essentially its own discipline that has different shades and other theories," he explains.

While statistics is a population-based science in which its goal is to discover the truth about populations, data mining looks at individual information and tries to analyze individuals in

the context of a subset of other individuals, Kusiak says.

"Data mining delivers what's good for individuals, rather than what works for the population, and it's a very distinct science," he adds.

So people who use data mining from the statistical perspective, haven't taken the effort to look at algorithms and theories that come with true data mining, using it in an individualized or patient-based perspective, rather than a population-based perspective, Kusiak says.

Data mining was created around computer science, using some statistics and mathematical logic, and that's one reason why it hasn't caught on in the clinical trials business, Kusiak notes.

"There's a huge gap now between computer scientists and clinical application, and so that's where the problem comes in," he says.

The solution is to educate more people in the industry about data mining, but this strategy sometimes encounters the barrier posed by patient confidentiality, Kusiak says.

"In my classes, people ask me for case studies, so I always tell them to give me their data, and then I'll show them case studies," Kusiak says. "The data we use with algorithms requires us to sign many disclosure forms, so that's one of the barriers."

While it would be nice to have benchmarked data sets available, and people could present the value of data mining based on those data sets, it has not yet happened because of the confidentiality barrier, Kusiak adds.

• **Data flow modeling:** Before data mining can begin, it's important to know the location of the data and how to manage better data, Kusiak says.

Data flow modeling identifies where the data are, helps to improve the data flow, and defines appropriate data, Kusiak says.

"In many applications, there are plenty of data that are very useless essentially," Kusiak explains. "There have been some processes in place or someone was overzealous, and people don't pay attention to it, so over the years you might have been collecting data that nobody is using."

This is why a first step is to establish processes for good data collection and assessing data quality, he says.

A data flow model would follow the organization and flow of data within an organization, improving and optimizing the flow in terms of quality and flow cycle, Kusiak says.

"Some data may take too long to get from one place to another place," he offers as an example of a data flow problem.

The model could help improve efficiency and reduce the cost of data collection, Kusiak adds.

"This is a business framework we're bringing to data flow," Kusiak says. "It's a known method that has been used since the 1990s in the main industries, but is new to the pharmaceutical companies."

The clinical trial and pharmaceutical industries have given little thought to optimizing data flow, he notes.

"Looking at this from a wide perspective, you have data flow within an organization; data flow between organizations, like pharmaceutical companies and clinical research organizations [CROs] or pharmaceutical companies and the FDA, so this applies to everyone," Kusiak says. "We can use other terms like streamlining data flow or reducing bureaucracy within organizations, and those goals could be accomplished with data flow modeling."

• **Data warehousing:** "Between data flow modeling and data mining is warehousing," Kusiak says.

"We typically mine transactional databases, which are databases and files stored at CROs or pharmaceutical companies, or even at the FDA," he explains.

"In recent years, the warehousing technology has been introduced," Kusiak says. "It's a collection of different databases that has been transformed, and the data quality has been improved and is designed for effective usage."

For instance, if there is a clinical question of any type, then the person posing the question could obtain the answer within a fraction of a second rather than having to dig through six different data bases, Kusiak says.

Data mining is another application.

Suppose a warehouse had genetic data that linked with patient data, and the entire database could be mined, Kusiak proposes.

Or, another potential use of warehousing would be to merge data from different clinical areas, in one centralized repository, and then mine them, he adds.

Data warehousing has a great deal of potential, but also can be costly, so companies carefully investigate its potential use, Kusiak says.

Computer software can handle all of the security issues arising from data warehousing, he notes.

"If you have someone's patient or genetic data, you cannot find out who this person is if you don't have the patient identifier or address because the data doesn't reveal this information,"

Kusiak explains. "So what needs to be protected is the personal identifier."

Also, the personal identifiers do not have to be stored in the data warehouse. These can remain with the doctor and facility providing medical care, Kusiak says.

The other advantage to a data warehouse is it provides additional protection of data by permitting storage off site. For instance, this could be helpful in the event of a natural disaster.

• **Knowledge management:** "Knowledge is important, so companies are always concerned with managing knowledge assets," Kusiak says.

"Some knowledge stays with people, so we have to take good care of people so they won't take their knowledge and disappear," he adds.

Another part of knowledge management is to prevent knowledge degradation by taking better care of the data, Kusiak says.

"If I have good quality data, then I could have the best knowledge and won't be using knowledge that's out of date," he explains.

The goal is to store good quality data for long periods of time and use data mining when it's necessary to extract information that can be put to good purposes, Kusiak says.

This could include textual information, interviews, and discussions, he says.

"Within data mining, we could have text mining algorithms, so we can extract knowledge from both data and the test at the same time," he says. "So I could go through emails in a corporation and minutes of meetings and extract knowledge from these."

In the past, knowledge was stored in repositories and was cumbersome to extract.

"Things are changing quite fast today, so by trying to protect a process that doesn't work today doesn't make sense," Kusiak says. "Knowledge that's five years old is not applicable now."

The goal is to extract new knowledge as needed, and this can force controversial changes within an organization, he notes.

For example, a company's department that manages knowledge will have to solve the problem of deciding what to store and what not to store, Kusiak adds.

"But for clinical trials, especially, and the pharmaceutical industry, the main thing is data which dictates everything else," Kusiak says. "Drug creation is about data, and so it's a data-driven business, and there's value in the data." ■

Discussion of microdosing with Xceleron CEO

Pharma industry chiefs predict microdosing will soon be ubiquitous in clinical trial industry

[Editor's note: In this question-and-answer article, ***R. Colin Garner, BPharm****, PhD, DSc, FRCPath, chief executive officer of Xceleron, Ltd. of York, England, discusses with Clinical Trials Administrator how microdosing, which has been called the Phase 0 clinical trial, works, and why it is useful for reducing cost and time in clinical trial work. For more information about microdosing, you may view Xceleron's Web site at www.xceleron.com.]*

CTA: What is the basic premise behind microdosing, and how was the technology developed?

Garner: The basic premise behind microdosing is it enables drug developers to get human data much earlier than they could historically. The reason I say that is because, primarily, man is the best model for man. So this is really a method to obtain specific human metabolism and PK [pharmacokinetics] information on development drug candidates without going to the great expense of manufacturing large quantities of API [active pharmaceutical ingredient] and having to conduct reasonably expensive toxicology studies.

The reason that microdosing exists was really through the introduction of ultrasensitive analytical techniques, such as accelerated mass spectrometry (AMS), which is what our company is focused on. The main role of microdosing is as a way of selecting drug candidates early in order to take them forward or, more importantly, to kill drug candidates early before you spend large amounts of money on development. That's perhaps a rather negative view. But it's the potential of a fast kill earlier that is one of the things people talk about.

CTA: How long has this technology been available that has made microdosing possible?

Garner: The actual AMS instrumentation was developed in both the U.S. and Canada in the mid-70s. So it's been around for a long time. But it's mainly been used by archeologists. It's the main way that archeologists date artifacts through a process called radiocarbon dating. So that's the technique people have been using. And it's really only been used for biomedical research probably since the early 1990s.

Here's a look at a study of data mining's use in patient care

Data mining provided an ideal approach for predicting survival time for kidney dialysis patients, according to one study.

"We are able to predict the survival time of patients who have undergone kidney dialysis," says Andrew Kusiak, PhD, professor of industrial engineering at the University of Iowa in Iowa City, IA.

This information is useful to both clinicians and researchers, the latter because they could use the data to determine which patients would be suitable for enrollment in long-term clinical trials, Kusiak notes.

The data collected included historical information and machine-collected information, he says.

Hospitals were motivated to assist in data collection because the data analyses could help them improve patient care, but it was the data mining approach that answered a question that would have been difficult to answer otherwise, Kusiak says.

For instance, patients on dialysis machines could be impacted by multiple factors, and their survival rates may depend on relationships between demographic and clinical parameters, as well as medications, interventions, and dialysis regimen.[1]

Investigators collected data from known and unknown parameters at four locations of The University of Iowa Hosptials and Clinics. Then dialysis machine data was organized to summarize each of 188 patients' information.[1]

The patients' age, total time on dialysis, age when dialysis was started, and age at death — when applicable, also were collected. Then investigators created three decision categories of above-median, below-median, and undetermined for data mining purposes.[1]

The initial data mining used a rough-set algorithm with two types of decision rules, including certain and approximate. A decision-tree algorithm also was used to analyze the dialysis set, and after classifications were made, a decision-making algorithm was developed to predict outcomes of dialysis patients.[1]

As a result of the data mining study, investigators were able to predict survival for patients who had at least 15-20 dialysis visits. They found an enormous potential for making accurate decisions for individual patients and a classification accuracy of greater than 75 percent.[1]

Reference:

1. Kusiak A, et al. Predicting Survival Time for Kidney Dialysis Patients: A Data Mining Approach. *Computn Biol Med*. 2005;35:311-327.

We really pioneered the commercial application of AMS in biomedical research.

CTA: How extensively is it being used now? Have some of the major U.S. pharmaceutical companies adopted this in some form or another?

Garner: We have worked for 16 of the world's top 20 pharma companies since we were created in 1997. We've been around for a bit of time. We've worked with all the major pharmaceutical companies really, in the U.S., Europe and Japan.

CTA: Tell us about the technology for a "fast kill."

Garner: If you're developing a novel drug you need to know it has some pharmacological activity, which usually is established using in vitro systems or animal models. Then perhaps the next important property you need to know is its pharmacokinetics and metabolism, because without appropriate human pharmacokinetics, you might have a very nice molecule, but you will never make a drug. So you either administer the molecule orally and none of it gets absorbed, or that's the end of the molecule. So that's the information that microdosing, in particular, provides. The pharma companies we've worked with have used our technology for many different applications, not only microdosing.

We can use this technology for combined phase 1 mass balance; so that's where you want to know the rates and routes of excretion of a drug. We've used it for human metabolic profiling, and we've used it for absolute viability studies. There's quite a broad range of information, but all within the drug metabolism, pharmacokinetic area.

What microdosing does is give you pharmacokinetic information, and on the basis of that information you can determine if your molecule will have suitable properties to make the drug. And that's why if it doesn't you would kill the molecule at that stage, and if it does, then you would probably take it forward.

CTA: If you take a drug forward, in the phase I clinical trial, would the fact that microdosing occurred provide any assurance of less risk to subjects?

Garner: What can you use microdosing data for? Well, you can use it to help set the first dose in the phase I study back up, and you might be able to reduce the number of doses you might give in a phase I study, having got microdose data.

Also, clearly you will have to question the ethics as it were of a phase I study where you have taken a drug in a concentration that may be significant and then you find in a human study that pharmacokinetics are inappropriate. Well, haven't you unnecessarily exposed someone to a drug when you could have found out that information at a much lower dose, i.e., a microdose. So there will be a trend, I believe, of being more cautious when going into humans, particularly after the incident in London. Therefore, microdosing could provide a safer way of getting dosing into humans for the first time.

CTA: I was going to ask you about the London phase I clinical trial of TGN1412, a humanized agonistic anti-CD28 monoclonal antibody, created by TeGenero AG of Wurzburg, Germany. This was the disaster in which six participants were hospitalized after suffering severe reactions to the study substance. Could microdosing have helped to prevent that problem?

Garner: We've obviously been asked that quite a lot. In that particular circumstance I suspect that microdosing could not have been useful. This is simply because the questions being asked in that study were safety and tolerability questions, rather than metabolism questions. For biologicals, metabolisms, certainly historically, has not been regarded as an important parameter, whereas with small molecules it has. So I think that all that the London incident demonstrates really is that we need to be more cautious when we go into humans for the first time, and microdosing does that.

The other thing is when you're thinking about the ethics aspects, when you go into humans in phase I and you end up killing the compound, you've exposed a lot of animals to a drug to get the preclinical information to allow you to go into a phase I study. So, again, using microdosing allows you to use much fewer animals as part of pre-clinical testing. Then if you kill the compound as a result of a microdosing study, then you've exposed many fewer animals.

CTA: That would seem to be very important for studies that require use of chimpanzees and other primates?

Garner: I think there's a lot of discussion going on at the moment about whether one should consider using microdosing in humans rather than in primates.

If you're using primates to predict human metabolism, then I would argue, why not do a microdosing study and get human metabolism rather than try to predict it.

You won't get direct safety and efficacy information out of a microdose study; you primarily get metabolism information.

CTA: Is this simply another tool that allows pharmaceutical companies and others in the clinical trial industry to maximize efficiencies in their work?

Garner: I think it's helpful to a variety of buyers. Clearly for the pharmaceutical industry it ultimately should be of benefit to patients because the aim would be to improve the efficiency of the industry and, therefore, the price of drugs as a result should also be reduced because the development times and, ultimately, the development costs would be reduced. The other thing microdosing does is it allows academic groups and non-governmental organizations (NGOS) to do human studies at a much lower cost than using conventional phase I approaches. For an academic lab to get some limited human data could be quite beneficial when they try to develop a molecule themselves for some orphan disease or if they try to sell the molecule to a big pharma company. So the academic groups have quite a big interest in microdosing.

CTA: Where do you see microdosing going in the next decade?

Garner: There has been a recent report which has been published by Cambridge Healthteck Associates, and they asked a question of vice presidents of research and development in the pharma industry and in CROs. They asked, 'Looking at microdosing today, do you use it?' And only 3 percent of people said they use it currently. Then they asked, 'What about in two years time, in 2008?' Then 41 percent of them said they consider it would be used routinely, and by 2010, another 46 percent said they thought it would be used routinely. So about 90 percent said that by 2010 it would be used routinely. ■

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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. ■

CE/CME *questions*

9. Clinical trial sites might gain greater trust with sponsors if they develop metrics or data showing their historical performance. Which of the following could be included in the data collected?

A. Rates of enrollment
B. Drop-out rates
C. Completion rates
D. All of the above

10. Complaints filed with the FDA about clinical trials and investigators has increased in recent years. Until 1998, the number of annual complaints averaged 10, and then in 1999 the number of complaints jumped to 106. What was the number of complaints made to the FDA in 2005?

A. 158
B. 203
C. 249
D. 266

11. While statistics is a population-based science, what is data mining?

A. Data mining looks at individual information and tries to analyze individuals in the context of a subset of other individuals.
B. Data mining analyzes subsets of a population.
C. Data mining is a science based on demographical cohorts
D. None of the above

12. What is microdosing?

A. It's a method to obtain animal metabolism and pharmacokinetics information on drug development candidates.
B. It's a method to obtain specific human metabolism and pharmacokinetics information on development drug candidates.
C. It's a new form of phase I trials
D. All of the above

Answers: 9. (d); 10. (d); 11. (a); 12. (b)