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CLINICAL TRIAL ADMINISTRATOR

An essential resource for managers of clinical trials

AHC Media LLC

IN THIS ISSUE

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Drug safety has become an integral part of CT research from start to finish

More jobs, more focus on pharmacovigilance

Pharmaceutical companies and clinical research institutions have adhered to drug safety regulations and standards for decades. But in recent years there has been a trend of increasing attention paid to pharmacovigilance, with drug safety staffs increasing rapidly at research institutions and clinical research organizations (CROs).

Regulatory pressure has contributed to the trend.

For instance, the European Union now requires every drug submitted for marketing authorization to have a risk management plan, says **Edward A. Kelly**, MD, vice president of Global Pharmacovigilance at Quintiles Transnational Corp., in Durham, NC. Quintiles is a CRO and provides research support to the pharmaceutical industry.

Also, the FDA requires certain high-risk drugs to have a risk management action plan (Risk MAP). And the FDA has been granted by Congressional legislation new punitive power to force companies to conduct post-approval studies for the purpose of assessing drug safety, says **Axel K. Olsen**, PhD, MS, executive director of Global Pharmacovigilance at Quintiles Strategic Research and Safety, Quintiles Transnational Corp.

Quintiles' staff in Global Pharmacovigilance has doubled in size within the past 18 months due to growth in both marketed product safety programs and studies and pre-approval studies, Olsen says.

"A broader view is that companies are increasing the number and type of studies that they're doing on marketed products, and there is an increase in the epidemiologic investigations being conducted," Olsen adds.

Drug safety is big news

Another impetus to the heightened focus on drug safety is the media. Newspaper headlines regularly feature articles about drugs that are recalled or are relabeled because of drug safety issues.

In a recent example, a front page story in *The New York Times*, dated Oct. 20, 2007, discussed an FDA panel's recommendation to ban cold and cough medicine marketed to children younger than age 6.[1]

"The main difference now is that the issue of drug safety is much more

apparent because of the media," says **Esther King**, BS, a safety surveillance associate III at the Duke Clinical Research Institute (DCRI) of Duke University in Durham, NC.

"The question is whether there were enough studies conducted prior to getting the drug approved," King says. "We follow patients, but there's not that much long-term data—beyond 12 months—in most studies."

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Also, when drugs make it to the market they typically are used in a wider patient population than what they were indicated for, King notes.

"The physician can prescribe the drug for anybody, so you want to make sure the drug is truly safe," she adds.

The drug safety group at Duke also has doubled in size within the past couple of years, King says. **(See story about the drug safety group's work, p. 136.)**

Even small sponsors who previously handled all drug safety work on their own are now asking for assistance from DCRI, King notes.

"We have 12 people now and will hire again soon," she says. "Our workload has doubled in size."

The safety group has been available to researchers and clinical trial sites affiliated with Duke University for years, but people are paying more attention to its services now.

"Maybe with all of the black box warnings coming out and with the closer scrutiny, I think we would certainly err on the side of caution and perhaps consult with the safety surveillance group more frequently now than we have in the past," says **Peggy Arias**, project leader at the Duke Clinical Research Institute.

Increasingly complex therapies

As medications have become more complex, sponsors and research sites have had to be more diligent than they might have been in the past, Olsen notes.

"The complexity of trials also is increasing, and we have the added shift toward the biological compounds," Olsen explains. "We are dealing with a very different kind of situation because the biologic response is more of a systemic response and can be quite sudden."

For example, a research disaster occurred during the phase I clinical trial of a biological compound studied by TeGenero AG of Wurzburg, Germany, in March, 2006. Six healthy participants in London, England, simultaneously were given the study drug, a humanized agonistic anti-CD28 monoclonal antibody called TGN1412, and they became violently ill immediately. All six men were hospitalized, including one man who remained in critical care at Northwick Park Hospital for weeks.

Unpredictable events sometimes happen with biologic compounds, Kelly says. "The main thing you worry about with biologic and humanized antibody [drugs] is anaphylaxis," Kelly says.

"An antibody can have a target that no one understands," he adds.

In studies of riskier or more unpredictable drugs, a pharmacovigilance best practice would be to start the pharmacovigilance plan in the pre-clinical phase, Kelly suggests.

"One of the critiques of the TeGenero situation is there were enough signals out there that there could be problems with the drug in humans," Kelly says.

No one suggested that when human subject trials began that the process begin slowly with even smaller doses and, perhaps, one person taking the drug and having his health monitored before the next person is given the drug, Kelly explains.

"Now, our best practices is to have a pharmacovigilance plan that pulls all safety information together at any stage of development and say, 'What are we looking at in risks, and what can we do to mitigate those risks?'" Kelly adds.

Quintiles has had preliminary discussions with pharmaceutical companies about providing a pre-clinical drug safety plan, but this practice has not yet caught on, Kelly says.

"I think we will over time see more and more of that," he says.

Ideally, a pharmacovigilance plan would be put in place from the pre-clinical research to the post-approval stage, Olsen says.

"You should broadly apply the same principals in pre-approval to post-approval," he adds.

Risk MAPs for high-risk products

Risk MAPs already are being used to save lives among consumers of high-risk products.

For example, the medication natalizumab (Tysabri®) has a risk MAP that is required by the FDA, Kelly says.

The drug is used to treat patients with Crohn's disease and multiple sclerosis.

"Data came in after the drug was on the market that it was associated with three cases of potentially fatal brain infection," Kelly says.

The opportunistic viral infection of the brain called progressive multifocal leukoencephalopathy (PML) was observed in two patients with multiple sclerosis and one patient with Crohn's disease, according to the "Dear Healthcare Professional" letter, dated in July, 2006, by Biogen Idec Inc. and Elan Pharmaceuticals Inc.

The risk MAP enabled the sponsors to quickly learn of the three cases and determine that PML is a true risk of taking the medication, Kelly says.

They also found that what placed patients at greater risk was being prescribed a second immune modulator in addition to natalizumab, he says.

The risk MAP also came up with these precautions, as outlined in the "Dear Healthcare Professional" letter:

- Natalizumab is available only through a special restricted distribution program that includes distribution of the drug solely by authorized sites;
- Health care professionals are advised to monitor patients on the drug for any new sign or symptom that could be suggestive of PML and dosing should be withheld immediately at the first sign or symptom;
- The manufacturer provided education to health care providers about how concurrent use of natalizumab with antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML;
- All physicians prescribing the drug and their patients are enrolled in a Tysabri registry.

The risk MAP for natalizumab has been a success story, Kelly says.

Since putting the drug back on the market 18 months ago there have been no additional cases of PML, he says.

"The good news is that, through expert drug safety management, a drug of great therapeutic value for patients with a potentially devastating disease was kept in the market," Kelly says.

Although the FDA doesn't require risk MAPs for all drugs, global pharmaceutical companies create risk management plans similar to risk MAPs because every drug marketed in Europe now needs one as part of the marketing application, Kelly notes.

These risk management plans require sponsors to identify the product's risks and explain what will be done about those risks, Kelly said.

"The risk might be a headache, and you won't have to do that much about it other than routine pharmacovigilance monitoring," Kelly explains. "But some risks may be more substantial, and you're obligated to say what the risks are and what the safety profile is and what you'll do about it."

What clinical trial site professionals and investigators need to keep in mind is that the research industry is focused on safety concerns, Olsen says.

"We need to engage the entire segment of the life sciences sector into this process," Olsen says. "That's a theme we're seeing from the pharmacovigilance and pharmaceutical industry, and we're broadly promoting it to the life sciences sector."

All clinical trial staff should understand what their own responsibilities are with regard to

patient involvement in clinical trials, he adds.

"I would encourage investigators to see themselves as members of a team that has an important mission to bring helpful medicine to the public and to protect the public safety," Kelly says. ■

Reference

1. Harris G. FDA panel urges ban on medicine for child colds. *New York Times* Oct. 20, 2007:page 1.

Here are examples of best practices in drug safety

Drug safety group can be helpful

Clinical trial sites and research institutions could save time and improve reporting efficiency by working with a drug safety group, experts say.

In the past, clinical trial teams often would handle their own drug safety work, and clinical research organizations would process such reports, notes **Esther King**, safety surveillance associate III of the Duke Clinical Research Institute (DCRI) at Duke University in Durham, NC.

Now Duke University studies have the benefit of an on-site drug safety group's assistance, King adds.

"We try to get involved at the stage where the protocol is being written," King says. "If our input is not needed, then we at least review the protocol and make sure there's a solid safety section in there."

DCRI studies make drug safety a major priority in other ways, as well.

"One thing we do here at DCRI with our larger trials is we have adverse event and serious adverse event (SAE) reporting through an electronic data capture mechanism," says **Peggy Arias**, project leader at the DCRI.

"That gets the information out immediately," Arias adds. "And that's been one of our safety surveillance focuses over the last couple of years."

This change was the result of greater vigilance paid to drug safety issues and to the need for real-time information on drug safety, Arias says.

"We always have a safety surveillance component in the trials that we manage here, when it's appropriate," Arias says. "We're always working with Esther's group, and her group is always available to us."

King elaborated on four advantages sites and sponsors have when working with a drug safety group.

1. Evaluate safety issues of study.

Study protocols include definitions of the anticipated adverse events and SAEs. It's a good idea to evaluate the SAE form for drug safety issues, King says.

"We have a medical monitor who is a licensed medical doctor do the review," King explains.

These questions should be asked:

- Has the site investigator reported the causality and documented it on the form?
- Is the causality associated or not associated; related or not related?
- Has anyone died who was on the study, and was the death due to this event?

"If the principal investigator thinks it's possibly related, then that's one criterion we're looking for," King says. "We say that's something we have to send to the Food and Drug Administration (FDA) quickly."

Next the medical monitor reviews the event for expectedness.

"We use the investigator's brochure to see whether the event was expected or not," King says. "If it's not listed in the investigator's brochure then it's considered unexpected."

If the event is listed and if it occurred at the severity listed in the brochure, then it's an expected event, she adds.

2. Follow regulatory reporting requirements.

If the event is unexpected and related to the study drug, then the next step is to follow standard reporting regulations under 21CFR 312.32 for the investigational new drug (IND) safety report, King says.

After the medical monitor makes his or her assessment, then the information is faxed to the sponsor.

"If the sponsor disagrees and maybe interprets the event differently, then they provide their documentation," King says. "It's their final call."

Whoever holds the IND is responsible for the reporting.

"The only time the site would do IND safety reporting is if the site has a single trial, and the PI holds the IND," King says. "Usually sponsors are holding the IND, and we have had studies where the National Institutes of Health (NIH) is the sponsor and holds the IND."

If the sponsor has contracted with the drug

safety group to handle regulatory reporting, then the drug safety group will take care of the reporting, she notes.

The key is having an expert decide whether the event was both associated with the study drug and unexpected, she explains.

"You could have an event that is related, but expected, or we have lots of events that are unrelated," King says. "The site principal investigator will say the patient has metastatic cancer and they expected him to die due to disease progression, but that's unrelated to the study drug."

Typically only a small percentage of events that occur in the study are reported to the FDA quickly, King adds.

3. Work with a data safety monitoring board and trial team.

The data safety monitoring board (DSMB) looks at study information at least monthly, and it helps to have a drug safety group assist with providing information to the DSMB.

"We work out a process with the trial statistician to provide information to the DSMB," King says. "The DSMB is not part of our group, but we collect information and clean it so it's there for them to review at scheduled points in the study."

The safety board also works closely with the clinical trial team, including clinical research associates and research monitors, King notes.

The board answers their questions about whether a particular event is an adverse event and needs to be reported, she says.

"We base every decision on the IND safety regulations and on being compliant with what's in the protocol," King says.

"And sometimes for larger or late-phase studies we'll work out a streamline reporting process that makes it easier on sites and is less effort for them to report information," King says. "Maybe we'll report less information or the same information, but not so quickly."

This is because some studies have very sick populations with patients who are expected to die before the study ends.

"We had one study where we expected 60% of the patients to die from cardiogenic shock," King recalls. "So we used a streamlined approach so if the patient had arrhythmia, the site would log those on a case report form and send them within a scheduled time, such as 30 days."

If the site was asked to send out a separate form each time there was an incident of arrhythmia, then there might have been 10 SAEs reported for each patient, King adds.

"We have smart ways to collect information so we have all that we need for a study and we're not making it overbearing for the site," King says.

4. Educate investigators and staff about drug safety issues.

"In addition to processing events as they come in, we go to investigator meetings when a new study starts and we present the safety section of the protocol," King says. "All site investigators and coordinators are in attendance."

The drug safety group also trains clinical research associates and trial teams so they will know what type of events to look for and so they can help the coordinators, she adds.

"Usually the sponsors ask for us to make the presentation, but if the sponsor doesn't ask for us, then we ask the project leader to do the presentation," King says. "We go through the safety processes." ■

Q&A: Sponsor's perspective on site selection and patient recruitment

Precision recruitment modeling is current trend

[Editor's note: Joshua Schultz, vice president of worldwide patient recruitment, clinical research services of PAREXEL International of Boston, MA, answers questions from Clinical Trials Administrator *about how biopharmaceutical companies are responding to current pressures regarding patient recruitment and selecting the best clinical trial sites for studies. PAREXEL is a global biopharmaceutical services organization.]*

CTA: *The biopharmaceutical industry is increasingly challenged to meet patient recruitment goals. Given your experience in this area, would you please describe what data-driven patient recruitment means and how your company employs it?*

Schultz: Data-driven patient recruitment isn't new as a concept. In fact, investigators and sponsors have always used data to recruit patients and develop their estimates of likely recruitment speed. However, as the challenge of patient recruitment has continued to grow, the ability to refine these estimates through the use of

modeling tools, investigator-specific performance data, and site-level patient data has become increasingly important.

The use of sophisticated recruitment modeling tools is replacing the reliance upon straight-line estimates of recruitment that have been traditionally used. Previous estimates that neglected to include key factors such as seasonal variations, variable site activation periods by country or type of site, and site fatigue were often off by 25% or more.

Combining more precise modeling, enabled by widely available technologies, with improved recruitment rate estimates allows for further improvements. PAREXEL relies upon a dedicated feasibility and evaluation group to survey investigators and compare this information to previous studies run by PAREXEL as well as published literature. This approach provides additional data to make more effective decisions regarding the number of sites, the length of the trial, and necessary recruitment support.

Site-level data, used properly, can be a critical component of successful recruitment. Sites with searchable patient databases can be much more effective at identifying and contacting potentially relevant patients for trials, while also being more accurate in their predication of the number of patients they are likely to enroll.

CTA: *How might sponsor companies and sites best use technology to better model recruitment during the planning stage?*

Schultz: The ability to more accurately model patient recruitment is substantially enabled by technology, either through relatively simple calculation tools (e.g., Excel) or custom developed computer systems. Regardless of the technology platform that is chosen, common issues must be addressed to model recruitment from a sponsor's perspective, including:

- number of sites;
- start-up timelines by country;
- start-up timelines within a country for 20%, 40%, 60%, 80%, and 100% of sites;
- first month of enrollment at each site that is unlikely to be a full 30 days;
- gap between site initiation and patient enrollment; and
- miscellaneous factors such as site fatigue, seasonal issues, direct-to-patient outreach campaigns, and database "boosts."

From a site's perspective, accurate modeling is predicated upon having good data on the prospective patients—names, visit schedules, potential interest in the study, and other sources of patients such as referrals or patient outreach. While some of these factors, such as the likelihood of subjects consenting, are more art than science, many of them can be more accurately predicted through database searches and site staff analysis.

CTA: *In your experience, do sponsor companies and sites typically spend enough time in the planning stage of patient recruitment, and how can they improve this process? For instance, you've discussed creating more accurate feasibility estimates, and how might they do so?*

Schultz: While sites and sponsors routinely engage in feasibility activities, given the enormous impact an accurate feasibility process can have on major budgeting and operational decisions, it is PAREXEL's belief that the industry would be well-served by spending more time on robust feasibility activities.

Feasibility should be driven by previous recruitment results from similar trials, modified by input from internal and external experts to address trial-specific issues. In addition, internal and external experts can identify other important factors such as standard of care by country, patient concerns, or site staff issues. Literature reviews can also provide insight into how others have solved similar problems and what has been achievable in comparable situations.

Through the combination of these elements, a reasonably tight range of most likely enrollment rates can be developed. This information should be compared to results of a blinded survey of potential investigators in each relevant country regarding likely enrollment rates, Institutional Review Board (IRB)/Ethics Committee (EC) issues, and other factors that may influence the conduct of the trial. This process plays a critical role in refining the analysis (described above) and identifying potential high enrollers.

This entire process should be coordinated by a central group separate from the trial team, allowing for process efficiency and objectivity, which are critical to accurate planning.

CTA: *Does PAREXEL identify the high-quality and high-performing sites based on data, and what do you do with this information? Also, why don't more biopharmaceutical companies follow suit?*

Schultz: To improve patient recruitment performance, the industry must rethink its use of investigator databases, which typically contain

little more than contact information, previous trial participation, and areas of therapeutic specialty. Choosing the right sites is particularly critical given PAREXEL analyses showing 80% of patients typically come from the top 20%-30% of investigators across a range of therapeutic areas and countries.

By using a more data-driven approach to choosing investigators that includes previous enrollment performance (relative to peers), external data, and key metrics, it is possible to more accurately identify "high potential" investigators that are much more likely to be top sites that will drive recruitment for the study.

The industry has not managed this issue as aggressively as required for two main reasons. The first reason is that there is an ongoing misperception that the patient volume coming from most investigators is roughly equal; rather, the vast majority of patients comes from a small minority of investigators on any given trial. The second reason is that the industry has experienced difficulty in collecting and processing all of the relevant data from disparate systems. Fixing this issue often requires dedicated resources to implement and integrate systems for more efficient data management.

CTA: *How can sponsor companies apply contingency-based escalation principles to manage recruitment during a study?*

Schultz: PAREXEL has implemented a process of Predictive Management that focuses on using improved data assets (such as those described above) to plan for Last Patient In (LPI) and staging the appropriate tactics to manage this milestone despite changes in the environment. Predictive Management builds upon many of the traditional tools used to determine recruitment timelines, such as self-reported data from physicians and estimates from previous trials, and augments them with ongoing analysis of recruitment data gathered from systems such as Interactive Voice Response Systems.

For this contingency planning to be maximally effective, it is critical to develop early warning analytics and "triggers." These analyses should be driven not only by recruitment results, but also by variances to planned study start-up timelines, screening/enrollment rates, and average speed for sites to begin enrolling their first patients. These factors can provide early evidence of delays long before they are typically spotted using only recruitment results.

The recruitment plan should incorporate both the current situation as well as multiple levels of contingency activities based upon the potential need. Resources required, lead times, and expected impact should be part of this plan to allow for thoughtful and timely implementation of contingency activities. Developing these types of explicit escalation plans allows for thoughtful preparation to begin, such as getting patient outreach materials approved as part of the initial IRB/EC submission, which allows for substantial time and cost savings if enrollment results lag.

CTA: *What is your advice to clinical trial sites that hope to survive in the increasingly competitive, global research world?*

Schultz: With the right data and tools, patient recruitment can be more accurately predicted, monitored, and managed, while avoiding expensive and risky trial delays.

Clinical trial sites will need to partner with contract service providers and study sponsors to take a more strategic approach to patient recruitment execution, which can reduce costs and bring new products to market faster—improvements that are invaluable in today's highly competitive and increasingly global biopharmaceutical marketplace. ■

One-stop shop web site provides CR sites with tools, templates

Content offers raw materials

Clinical research sites in the process of revising tools or forms might find a new web site, funded by the National Institutes of Health (NIH) a useful place to begin the process.

Called CTNBestPractices, the web site was created three years ago at the Duke Clinical Research Institute (DCRI) in Durham, NC. A study coordinator advisory committee, consisting of 10 coordinators representing nine research sites, met twice a month to identify content for the web site, says **Buddy West**, webmaster of CTNBestPractices and a clinical research communications specialist at DCRI.

The committee designed the page and content and provided their own tools, which were

revised to be more general, he says.

"The study coordinator advisory committee tries to get together twice a month to review the content we have posted and look at new content and improve it, edit it, and discuss it," West says.

Initially the web site was launched in March, 2005, at a meeting of the American College of Cardiology (ACC), West says.

"We presented it at an investigator meeting of ACC, and they used an audience response system to get immediate feedback during the meeting," he explains. "With the feedback, we overhauled the web site dramatically."

The web site now features a variety of assistance for clinical research professionals and sites.

"We wanted to provide a lot of tools for people new to research," West says. "It's difficult for them to find out more about clinical research and processes, and this provides that background."

If web site hits are any indication, the project has been a success: It had nearly 12,000 hits in September 2007, and the average daily count has increased to more than 400, West says.

"It's increasing dramatically," he says.

All but 20% of the site can be accessed without registration and a password, West notes.

"That's part of the web site's success," he says.

Frequent updates and additions

Another reason for the web site's popularity might be its dynamic nature. The web site is continually being updated and added to.

For instance, there will be three new modules added to the essential regulatory documents web page in early 2008. These include a module on device studies, a module about federally funded studies, and a module about Canadian regulations, West says.

"Our newest edition to the web site involves central regulatory documents," West says. "It talks about sponsors' responsibilities and investigator responsibilities."

As new programs and modules are added to the web site, they make use of improvements in design and technology.

For example, the latest modules permit a participant to click on a link to the precise page he or she desires, rather than forcing them to scroll through the program, one page at a time, West explains.

Unfortunately, there aren't enough resources to revamp the existing modules and provide the same luxuries, he says.

"We have to cut our costs, so while it'd be wonderful to go in there and put in that new format, it would take more money and time," West says. "We'd rather put more money on expanding the web site."

The education and training section includes some modules and some links, such as:

- Building a successful research site;
- Clinical research introduction;
- Clinical research writing;
- Essential regulatory documents;
- Evidence-based medicine;
- Human research subject protection; and
- Therapeutic area training.

"The second biggest area we've worked on, and I've focused on this area, is the clinical site resources, where we provide templates and tools that coordinators need every day," West says.

"Most of the templates came from the committee members' sites," West adds. "We first took out any site-identifying information and made them generic, and then we focused on the content itself."

The web site's clinical site resources include:

- Adverse event/serious adverse event sample forms **(see AE/SAE chart, p. 141)**;
- BMI table and calculator;
- Budget tools;
- IRB facts and functions;
- Master subject log;
- Materials readability;
- Pre-study activities checklist; and
- Suggested site standard operating procedures.

A library link contains this information:

- Acronyms, abbreviations, initials;
- Clinical study terms;
- Links;
- Presentations;
- Publications/articles; and
- Site personnel profile library.

There's a best practices forum where coordinators and investigators can share information and best practices, West says.

The best practices forum includes these links:

- Add/edit your profile;
- Share our site with others;
- Share your best practices;
- Provide your feedback;
- Meet our principal investigator; and
- What is CTN Best Practices?

The web site also provides links to various other resource web sites and research institutions.

Under a hot topics link, there are topics addressed at investigator meetings.

Some of the site's most popular features were a complete surprise.

"When we first posted temperature conversion charts, which I assumed every site could get their hands on quickly, we had 400 to 500 downloads on it in the first month," West says. "That was a surprise, but when I tell study coordinators this, they have nodded their heads knowingly."

Exploring alternate funding

The web site's popularity will ensure that it has a future even when the NIH money runs out next fall, West says.

"We will be an operation under this name and contract through Sept. 30, 2008," West says. "I always get the question of whether the web site will end, but there's no way the web site will end."

DCRI will explore different options in funding and continuing the web site, he adds.

"My personal favorite option is if several academic research organizations (ARO) would band together and support it financially," West says. "Representatives from each ARO could have a study coordinator on an advisory committee that continues to broaden content and improve content."

One of the goals is to provide one-stop shopping on the web site, West says. "We would like

Adverse Events and Serious Adverse Events

Expedited Reporting of Serious and Unexpected Adverse Events (AEs)
For questions regarding Serious Adverse Events (SAEs), contact:

_____
_____
_____

Definitions of different types of adverse events

An AE is any untoward medical occurrence in a clinical investigation (patient-administered) of a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, finding, symptom, syndrome, or disease* temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Laboratory abnormalities and changes in vital signs, 12-lead ECG, and telemetry are considered AEs only if they result in withdrawal from the study, necessitate therapeutic intervention, and/or the investigator considers them to be AEs.

* This definition will also include intercurrent diseases and accidents observed during the treatment and post-treatment periods.

SAEs include any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;[A]
- requires hospitalization or prolongation of existing hospitalization;[B]
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect; or
- is another medically important condition.[C]

A. The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
B. Hospitalization for convenience does not constitute an SAE.
C. Medically important conditions that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or a home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Source: The entire, four-page AE/SAE template can be found as an open source tool at: www.CTNBestPractices.org.

everything you need for research to be in one location," he adds.

For instance, the upper right hand corner of the site's home page has a link where CR sites can submit profiles and find information about available studies.

"They have a list of clinical trials currently enrolling sites," West says. "And there's a link where they can indicate their interest in those trials."

Right now that service is limited to DCRI studies, but it has already proven useful, West notes.

"We've recruited some good sites that otherwise might not be a part of our trials," he says. "It's a pilot project until Sept. 30, and we've had about 120 people enroll in the program since we unveiled it around April 1, 2007."

This service could be expanded, and the web site also could serve as a repository for repetitive CR information, such as an investigator's curriculum vitae (CV) and other site biographical information, he says.

If this occurs, then investigators and CT administrators won't have to fax over every CV and other general information each time they are negotiating a new study contract.

These possibilities and others would make the web site a time-saving tool for CR sites.

"I hope the web site will be the place every clinical site would go to for anything involving their research efforts," West says. "So they wouldn't have to hunt around." ■

CR changes result in more trial site work and challenges

Electronic data entry is time-consuming

Clinical trial sites and CT coordinators increasingly feel pressure to fit more work into an already long day.

"I feel sorry for monitors because they've gotten so pressed for time," says **Jane K. Downs**, RN, CCRC, research director of Raleigh Neurology Associates of Raleigh, NC.

"The CRO wants them to come out and see as many sites as they can," Downs says. "Monitors are crunched for time because everyone wants them to go faster."

This means the monitor typically has very little time to answer questions or return phone calls, and this leaves coordinators with some confusion. **(See story in the January issue of *CTA* about improving relationships with monitors.)**

Delegating or gatekeeping?

While the monitor used to be the site's point person for everything, now the CROs are using other staff for handling investigator and coordinator questions and reviewing the site's regulatory documents, Downs notes.

"You now have your site's regulatory document person deal with their regulatory document person," she adds. "And for some companies, there's an in-house monitor who deals with different issues."

So CT coordinators might have to report a problem to several people, or they might have difficulty finding the one person who is supposed to handle a particular issue, Downs says.

"For small sites that have just one coordinator, there might be three or four people you deal with," Downs says.

"Every company has a different way of doing it," she says. "One pharmaceutical company just instituted a policy where you don't call the monitor him or herself."

Instead, CT coordinators are expected to call a different, in-house person who takes care of all the issues that arise and then gives the information to the monitor only when the in-house person believes it's absolutely necessary, Downs adds.

Raleigh Neurology Associates has eight full-time coordinators, including Downs, plus a full-time regulatory/documentation employee and a full-time data entry person. The latter two jobs have become essential because of the workload that CROs have shifted to CT sites when they use an electronic data capturing (EDC) system, Downs says.

"So many studies are going to EDC, and pharmaceutical companies are hesitant to pay for that data entry person," Downs says. "They used to have data entry at their office, but they say it's faster and more economical for them to put it in our house."

But the workload can be crushing for a CT site.

For example, one CRO that uses a special Internet site requires all regulatory documents to be faxed with an individual fax sheet to the web site's main hub, Downs explains.

"So if you have 15 doctors, and they each have a 20-page curriculum vitae, then your regulatory documentation person is faxing information for

eight hours straight because each fax has to have its own barcode," Downs says.

While this system is faster for the CRO, it means more paperwork for the CT site.

One solution might be to have coordinators tote around laptop computers, but this is impractical from a patient care standpoint, Downs says.

"And we have to have source documents," she adds.

No two systems are alike

Another challenge is dealing with many different computer software systems.

Each CRO and/or sponsor has its own software system, and CT sites need to learn how to navigate each one as they input data.

Some of these systems are inflexible and force answers from questions that have no known answer.

For example, one software system requires CT coordinators or data entry workers to answer every question precisely.

If the acceptable response isn't recorded, the software system won't let the CT coordinator continue through the document, Downs says.

"So if we have an 85-year-old patient with Parkinson's disease, the computer wants to know the day the woman first was diagnosed with PD, and it won't take the answer 'unknown,'" Downs says. "You have to come up with some date, but how can you come up with a date?"

This type of software glitch is particularly frustrating when CT professionals need to take care of an emergency, such as a patient hospitalized because of a serious adverse event (SAE) that is associated with the study product, Downs adds.

"So we have to hospitalize a patient, but the computer won't move because I can't give it the exact date her Parkinson's disease started 20 years ago," she says.

And the solution varies widely according to which software is used. One type might permit dashes in place of months and days; another will put a default date, and the data entry worker will have to put a note in the program that says the date is a default date that is not accurate and does not match the source documents, Downs says.

The risk is that an inexperienced coordinator might put in any date to satisfy the computer's technical requirements, but risk posing problems if the site is audited by a regulatory agency, since the electronic data won't match the source document data.

This is the type of situation that must be avoided, and it means the CT site will have to expend more staff time and energy on coming up with a solution that will not result in audit findings, Downs says.

And these types of issues are why it helps if a site can have a dedicated data entry worker.

The data entry worker will need some training, but otherwise should learn the job through experience, Downs says.

"Until they get in there and learn to work with the [various electronic systems], they won't know the ins and outs," she says.

CE/CME Objectives / Instructions

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

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

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

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

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

COMING IN FUTURE MONTHS

- Prospective monitoring reaps benefits for CR center
- Study examines what influences study completion speed
- Biostatistics knowledge needed by potential researchers
- Learn about new rules for Medicare coverage of CTs

At times the CT site and data entry person will find themselves dealing with an untested computer software system, and their time and energy spent on helping to get out the glitches are not financially compensated.

"We've worked with one electronic system where it would take 30 minutes to finish a page of data," Downs recalls.

CE/CME *questions*

21. Pharmaceutical companies increasingly are using risk management action plans. What regulatory change has most influenced this change?
    A. The FDA requires that risk MAPs be conducted for all investigational new drugs.
    B. The European Union now requires every drug submitted for marketed authorization to have a risk management plan.
    C. Japan, Canada, and Australia now require risk management plans for all investigational drugs.
    D. All of the above

22. According to a biopharmaceutical expert, sophisticated recruitment modeling tools are replacing reliance upon straight-line estimates of recruitment that have been used traditionally. Which of the following is a factor the new tools calculate?
    A. Seasonal variations
    B. Variable site activation periods by county or type of site
    C. Site fatigue
    D. All of the above

23. Which of the following is *not* a result that might occur from a serious adverse event that had an untoward medical occurrence?
    A. Results in death
    B. Requires oral antibiotic treatment for bronchitis
    C. Requires hospitalization or prolongation of existing hospitalization
    D. Results in persistent or significant disability or incapacity

24. A new web site at www.CTNBestPractices.org includes open source content that any clinical research site might use, including which of the following?
    A. BMI table and calculator
    B. Budget tools
    C. IRB facts and functions
    D. All of the above

Answers: 21. (b); 22. (d); 23. (b); 24. (d)

The coordinator or data entry worker would click on the save link, but the system wouldn't complete the task for 20 minutes or so, she said.

Yet the site had no option but to transfer the information in this format. ■

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