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ADMINISTRATOR
An essential resource for managers of clinical trials

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IN THIS ISSUE

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Special Report: Opportunities in EHRs

New technology results in more interest in patient-reported outcomes

Technology also can improve adherence

[Editor's note: This is the second part in a series about the opportunities, challenges, and benefits of electronic health records (EHRs) and technology used by and for research projects. In this issue we have stories about using electronic patient reported outcomes and the proven benefits of IT and EHRs.]

Patient-reported outcomes have well-known challenges that clinical trial investigators have long sought to overcome. Now it appears that electronic patient-reported outcomes (ePROs) are able to enhance data integrity in the process.

Paper-based patient reported outcomes invariably lead to patients forgetting to complete the forms or finishing them retrospectively or even prospectively.

So there is a growing movement to use ePROs to improve data and efficiency.

Also, results from clinical studies using this technology indicate an improvement in patient adherence.

"The industry is using electronic technology to make research more efficient and less costly," says **Keith W. Wenzel**, senior product director of ePRO for Perceptive Informatics based in Boston, MA.

An estimated 25% to 30% of all clinical trials use patient-reported outcomes, and approximately 1,500 to 2,000 studies have used ePRO, Wenzel says.

"The adoption rates for ePRO technology are still below 50% market saturation, but it's a growth area for the industry," he adds. "We're in the early stages of sponsors looking to implement ePRO solutions and understanding the full advantages these systems can bring to increasing the efficiency and productivity of clinical trials."

Electronic technology also is growing in popularity for use in improving trial participant adherence, experts note.

"The World Health Organization (WHO) estimates medical adher-

ence at 50%," says **Joseph C. Kvedar**, MD, director of the Center for Connected Health at Partners Healthcare System Inc. in Boston, MA. Kvedar also is an associate professor of dermatology at Harvard Medical School in Boston.

There is a big gap between what clinicians and investigators tell patients to do and what they actually do, he says.

"One thing about the medical profession is that for about 2,000 years we thought if we instructed you as a patient to do something our job was done," Kvedar says. "You'd go off and do it because we as 'knowledge-workers' were kind enough to give you the knowledge to make you compliant."

Reality check

In reality, people are fallible, and until fairly recently that has not been adequately addressed by clinicians and researchers. **(See story about study using technology to improve adherence, p. 51.)**

There is growing recognition on the part of the research industry and regulatory agencies that technology might assist with research participant adherence and patient-reported outcomes.

"I think what is relevant here is that in February, 2006, the FDA [Food and Drug Administration] issued draft guidance on patient-reported outcomes," Wenzel says.

The FDA's guidance acknowledges that interactive voice response systems (IVRS) and other forms of electronic data collection can be used to ensure that patients make entries according to the study design and not just before clinic visits, he says.

The FDA's counterpart in Europe, the European Medicines Agency (EMEA), had addressed patient-reported, health-related quality of life a year earlier, he adds.

"Two of the major regulatory bodies in the world reinforced the importance of patient-reported data in clinical research," Wenzel says. "With ePRO, there is a level of data integrity that is not available in paper."

For instance, electronic reports can be documented at the precise time they are administered. So if a patient forgets to report his or her activity on Tuesday and puts in the information on Wednesday, the electronic report would note the Wednesday date.

Also, ePROs can be linked to electronic reminder tools that will prompt patients to make their reports at a particular time.

For clinical trials this level of data integrity is important.

"It's a critical element of what data are collected in clinical drug trials, which include EKGs, lab data, physician data and patient-reported data," Wenzel says.

"This is not limited to simple diary data," Wenzel says.

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Sponsors are using ePRO in trials in a multitude of ways, he adds.

For instance, ePRO is being used to determine study eligibility.

"For instance, in an insomnia study, participants have to average less than six hours of sleep on five of seven nights, or in a depression study participants may have to have a certain level of depression," he explains. "These types of eligibility data can be collected electronically at the beginning of a trial."

When the insomnia trial begins, for instance, and data need to be captured each morning and evening, ePRO can assist in the form of an interactive voice response where the study participant calls into an automated line and answers questions at the specified times, he adds.

"In the morning, the participant would call in to report how many hours he slept, when he awoke, and what the quality of sleep was," Wenzel says. "In the evening, he would report on daily function, for example."

Opportunities after trials

When trials end, there are more opportunities to use ePRO.

"At the end of trials, regulatory authorities are always interested in safety data and want to know about the discontinuation of side effects," he says.

Investigators can use ePRO to answer various types of study follow-up questions, he adds.

While there are clinician-administered tools that can be used in measuring a person's mental state with regard to depression, for instance, the FDA has stated in draft guidance that it's concerned about the impact of clinician interpretation of recorded data. "So having patient-reported outcomes has the advantage of having no bias introduced by a third-party," he adds. "The patient answers questions about his/her mood and eating habits via telephone or hand-held electronic device, and so there is no bias introduced from a clinician in interpreting these data."

Also, certain data are only available from the patient, and these might include the level of pain, insomnia, post-traumatic stress disorder symptoms, and social anxiety disorder, Wenzel says.

Another advantage to ePRO is that it provides easy opportunities for routine reporting, he notes.

"For instance, sites monitor patients who are not being compliant, and overall patient compliance at one location can be compared with compliance at other sites, he explains.

The data collected can be used in metrics reporting to determine which sites were high performing, for example. In addition, just the act of compelling study participants to report their data might have a therapeutic effect, Wenzel says.

When research participants visit the study site for check-ups there is the potential for a nurse or study coordinator to note the patient's condition aloud, and this could impact the research physician's ratings, he explains.

"The computer is totally objective and won't make any interpretations," Wenzel adds. "What the patient says is recorded."

While one could argue that the act of calling in the information could have a therapeutic effect, this would also be true for writing down the information on paper, he notes. "The fact is ePRO is based on a patient's self-assessment, and no questions or comments by another human will positively or negatively affect the patient," he says.

Perhaps one of the benefits that will have a big impact on how quickly ePRO is adopted in the clinical trial industry is its potential for cost savings.

For instance, in Phase IV trials where there potentially are 10,000-plus subjects, clinical trial sponsors are challenged to collect data with integrity and cost-effectiveness, Wenzel says.

"So ePRO can be used to collect eligibility data through an automated screener for a particular disorder," he explains. "Then ePRO can be used to collect data every week."

This leveraging of technology to keep costs down in late-phase trials makes sense and probably would lead to better than average compliance, he adds.

"Many Phase II or Phase III trials have been reported to have 90% compliance with ePRO," Wenzel says. ■

Information tech: Benefits and drawbacks for hospitals

Study shows hospitals want better IT

Health care technology researchers, who have taken a long and comprehensive look at the pros and cons of information technology (IT) use in health care systems, have found that health IT adoption has progressed considerably over the past decade.[1]

"As IT started being adopted, more and more hospitals became interested in the business case associated with adopting technology," says **Nir Menachemi**, PhD, MPH, an associate professor in the department of health care organization and policy at the University of Alabama at Birmingham School of Public Health in Birmingham, AL.

"These systems are very expensive to adopt and implement, so being able to know you'll get some kind of benefit that you can quantify from their adoption is very important for decision makers at hospitals," Menachemi says.

"Lots of studies that have linked IT to benefits of any kind — whether they're financial or clinical or operational benefits — have all come from studies that looked at single institutions," he notes. "The studies looked at before and after implementation to see what kind of advantages there are."

The studies were conducted at large academic medical centers where researchers had a lot of grant money or the institutions had the in-house expertise for developing IT, Menachemi says.

"They produced some very good and strong evidence that IT does improve whatever it was they studied in a given study," he says. "They produce pretty good, causal evidence between the development of IT and whatever benefit they studied."

Menachemi and co-investigators wanted to carry this research another step to see what the IT capabilities were of general hospitals and finally of specialized hospitals.

"With that information we were able to see across lots of hospitals to see whether those with more IT capabilities performed better," he explains.

In a study of IT applications used in Florida hospitals, Menachemi and co-investigators found that clinical IT adoption was related to more patient safety outcome measures. Moreover, hospitals with the most sophisticated and mature IT infrastructures performed the best on a large number of patient safety indicators.[2]

Children are not little adults

Children's hospitals are unique settings, Menachemi notes.

"We began to collect the IT data so we could quantify IT capability across a large number of children's hospitals," he says. "This was the first study to describe who among children's hospitals was doing what in terms of information technology."

Investigators looked at what the barriers were and the future IT adoption intentions in the specialized children hospital setting, he adds.

"We're laying the foundation for a series of articles looking at outcomes in this children hospital setting," Menachemi says. "We're looking at whatever systems the hospitals have, and we're not focused on a specific vendor."

The type of studies the investigators have been doing complement the single institution studies. But while single institution studies can link causality to information technology, Menachemi's research cannot.

"The big disadvantage of our study design is we cannot detect causality, but we do have [general information benefits] that causal studies do not have," Menachemi says.

"The single institution studies track outcomes before and after random assignment to the system, and those methodologies are designed for causal relationships," he explains. "The results have not been universally positive."

Some studies have identified unexpected bad outcomes associated with IT adoption, Menachemi notes.

"Some studies even show that error rates can go up, and there's a loss of productivity in the short run," he says. "So the literature isn't unanimously positive, although there is overwhelming evidence that IT plays an informed role in improving outcomes."

In a survey of 109 children's hospitals the most common clinical IT applications used by the hospitals were clinical scheduling, used by 86%; transcription, used by 85%; pharmacy information system, used by about 82%, and laboratory information system, used by about 81%.[1]

In many ways information technology would be ideally suited to the pediatric hospital setting because it makes it easier to provide clinicians with point-of-care information that is directed toward the right patient at the right time and place, Menachemi says.

"It's information that otherwise would be inefficient to bring at that moment in time to the person," he explains. "So the child's health environment benefits from this."

For example, children's weight and health are fragile in health care settings, and so it's very helpful to have information that can help clinicians decide on the precise prescription dosage based on a particular child's age and weight and condition.

Unfortunately, IT vendors have not yet lived up to the promise of their product, Menachemi says.

"One of the findings of our study was the biggest barrier to IT success was dissatisfaction with the products vendors have," he says. "They were unable to deliver based on the expectations of people in children's hospitals."

As a result, vendors now are trying to develop systems that will include child-friendly functionality.

Menachemi's research has also found that the biggest obstacles to IT success involve the health care institution's culture and the people factor.

Short staffed

Nearly 30% of respondents in the survey of children's hospitals said that lack of staffing resources was a major barrier to use of IT, and more than half of respondents said it was a minor barrier.

"Roughly 80% of the challenge isn't technological in nature, but sociological in nature," Menachemi says. "There are workflow redesigns that need to be carefully thought through and planned out."

Doctors and nurses have their daily routines, and they develop skills based on their experience and how they see things over time, he explains.

"As soon as you automate any part of the workflow information, you suddenly change the way they do their jobs, and with change comes some pushback -- particularly if the change isn't viewed as beneficial to the end user."

Not everyone will buy into the benefits of IT, at least not until the older group of health care professionals retire and make room for younger providers who have grown up with computers and technology, Menachemi says.

But studies are showing that IT is a positive factor in many different measures of performance, including quality of care, operational efficiencies, and financial performance, he says.

"One issue that keeps coming up when I interact with hospital executives is they want me to show them the evidence so they can show their board of directors and receive an allocation of funds to invest in IT," Menachemi says. "They think it can work, but they want evidence, and these types of studies are the evidence."

Reference

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Text-messaging reminders spur treatment adherence

New technology creates opportunities

Clinical trial treatment adherence is an ongoing issue for investigators, just as treatment adherence problems plague the clinical world.

Investigators have studied novel ways to improve adherence, and many of these have involved using new technologies.

One investigator has found that reminding patients to adhere to treatment through text messaging worked very well.

"The lack of adherence has multiple different factors, and we're not suggesting that reminding people is the only way to solve that problem," says **Joseph C. Kvedar**, MD, director of the Center for Connected Health at Partners Healthcare System Inc. in Boston, MA. Kvedar also is an associate professor of dermatology at Harvard Medical School in Boston.

"But we were intrigued by the idea of something as simple to implement as text messaging," Kvedar adds.

Researchers have experimented with other technological adherence prompts, including using emails and instant messaging features, but these require patients to be tuned in and receptive to receiving the message.

"Whereas, with a mobile phone, a text message is hard to ignore," Kvedar says. "You have it, it beeps, and you process the information right then and there — so it's a unique way to give someone a reminder."

Kvedar and co-investigators studied the use of text-messaging reminders in a study involving having patients apply sunscreen.

"Some research suggests that adherence with topical regimens is poorer than adherence with taking tablets," Kvedar says. "So we chose sunscreen because we could tie it to a very important public health need: the prevention of skin cancer."

Text variety a 'hook'

The six-week, randomized study had a control arm that received no reminders, and an intervention arm in which participants received mobile phone text messages with a weather report and a reminder to use their sunscreen, he explains.

"Those text messages varied," he adds. "We called that a hook."

The idea is that if someone is sent the same five-word message each day, then it would be easy to ignore. So investigators varied the message, including slang and catchy expressions in hopes of enticing participants to check the message each day.

Both the control and intervention groups used sunscreen containers that had a cap device that would record each time the cap was removed, presumably for the purpose of putting on sunscreen, Kvedar says.

"It wasn't a perfect measure," he notes. "If someone wanted to game the system they could just take the cap off and do nothing."

But the study's results showed a big difference between the two groups.

"Adherence in the control group was pretty abysmal," Kvedar says. "Adherence in the control group started off at about 60%, and then it plummeted quickly in the first couple of weeks until it fell to 20%."

The precipitous drop appeared to mirror a real life clinical adherence experience.

"These people were motivated enough to volunteer for the study and be part of the program, and they're paid to be part of the program," Kvedar says. "They receive a gift certificate at the beginning and at the end of the study, and they knew we were measuring their adherence since the cap device is obviously on the sunscreen tube."

On the other hand, the group receiving text message reminders also started at about 60% adherent, but remained constant at that rate throughout the six-week period, Kvedar adds.

"It was a statistically significant difference at week three, and it remained statistically significant," he says. "It was a striking story."

The preliminary evidence suggests the technological tool used to motivate participants improved adherence, Kvedar says.

"For some individuals, a daily reminder with some kind of cute language around it is a motivator," he adds.

Later, investigators attempted the use of technology to motivate participants and improve adherence with an exercise intervention, and this study demonstrated similar success, Kvedar notes.

"Our second scenario was measuring activity in people with a smart pedometer that sends a wireless message to one's computer," he explains. "You walk around with this device on."

The motivator in the not-yet-published study was an elaborate set-up that used a virtual computer avatar coach. Once or twice a week, participants would have a coaching session with the avatar coach, he adds.

"The same phenomenon was noted," Kvedar says. "Our control group rather quickly faded in terms of adherence to the activity goal, and the avatar group was stable throughout the program in terms of activity goal."

These study findings suggest that if investigators have a tool to measure something relative to the condition they are researching, then maybe 10% to 15% of the population will change behavior according to the findings, he says.

"Another 30% to 40% will respond to the same intervention if you have a coaching component," Kvedar adds.

Gold standard: DOT

The gold standard for maintaining treatment adherence is directly-observed therapy (DOT), Kvedar notes.

But the technological tools are good examples of reminder systems that are easy to implement, easy to scale, cheap, and which have impressive results, he adds.

Similar adherence aids include the class of products that send out a signal when patients open their pill bottles.

"When you either take the cover off the pill bottle or when you ingest the pill, that signal can be captured and used to create a report for the patient, family members, or doctor," Kvedar explains. "The idea is that if I ask you the patient to take a pill twice a day, and if there's someone you are accountable to through your social network, health plan, or doctor, then that will improve your compliance."

This method uses technology to assist with creating social network or peer pressure for better adherence.

"We have clinical trials going on now to test

two products like that," Kvedar says.

"The other thing we're seeing is that products that will remind you by beeping or sending you some kind of message to take your medication are helpful," he says.

There even is new technology that will help patients make certain they're taking the correct medication.

"If someone is on a complex regimen of seven or more tablets per day, there's a high incidence of not getting this right," Kvedar explains. "So scanning technology shows that you've taken the right pill by comparing your pill to a database."

Some of these new technologies might enable investigators to design trials in which participants can be monitored without as many study visits, he suggests.

"You could recruit people from a wider geography and not have people come in for check-ins," Kvedar says. ■

CR education: From AEs to recruitment

Everything taught over five half-days

A research university has found that a five-session program provides the right mix of clinical research introduction and education.

"It was called the study coordinator course, but we wanted to make it clear that we wanted junior investigators and others to attend," says **Susan Sonne**, PharmD, BCPP, an associate professor of psychiatry and pharmacy at the Medical University of South Carolina (MUSC) in Charleston, SC. Sonne also is the chair of the MUSC IRB 2 and co-director with Tom Heusey of the Clinical and Translational Research Center (CTRC).

Called the core clinical research training (CCRT) program, the course is available to study coordinators, research nurses, regulatory specialists, principal investigators, and others interested in learning more about the clinical research process.

"In our last class we had 40 people registered for the course," Sonne says.

Even some experienced researchers, who serve as investigator mentors, have attended the class, partly so they will see what their trainees will learn, she adds.

While everyone involved in research at MUSC has to take a basic CITI training course, the CCRT is voluntary, and participants who complete it and pass the 50-question exam at the end receive a completion certificate, Sonne explains.

An IRB might require an investigator to take the CCRT as part of a remediation effort when there have been compliance findings during an in-house audit, but these are very rare, she adds.

"We've had the program for over three years and have trained more than 300 people," Sonne says.

The program — which is held 8:30 a.m. to 12:30 p.m. on five days over two weeks – is designed as follows:

• Day 1 — Good Clinical Practice (GCP): Sonne spends this whole first session reviewing human subjects research history, regulations, good clinical practice, and some of the major research ethical lapses that occurred 50 to 60 years ago.

"Part of this discussion is to give research staff a better understanding of why we have the rules," Sonne says. "In the past they focused on the research question and didn't pay attention to ethical considerations."

Sonne provides attendees with a few ethical scenarios and asks them what they might do in these situations.

And she emphasizes that she and others at the IRB are available to answer questions whenever an investigator or research assistant has an issue to discuss.

• Day 2 — IRB submission and standard operation procedures (SOPs): "One thing we like to do is an IRB application walk-through," Sonne says. "We have an experienced regulatory specialist who is used to accessing the IRB Web site, and this person has a computer out to show people how we do the initial application."

On the second day, the class also focuses on SOPs, what they are, how they might be helpful, and how to write them, Sonne says.

Operational SOPs might include the following:

- How do we recruit participants?
- What are we going to do in the trial?
- How do we set up a petty cash account?
- Where is the money kept?
- Who is responsible for petty cash?

"We go through some sample SOPs and discuss things like what if you change the rule during the course of the study," Sonne says.

Another module on the second day involves

investigational drugs. "We talk about regulations around drug accountability and give some tips, telling them about our investigational drug services at MUSC," Sonne explains.

This module also covers what the Food and Drug Administration (FDA) requires for investigational new drug (IND) applications.

"We discuss packing slips and how you actually organize study medications, depending on how it comes to you," Sonne says.

A final module, led by the MUSC compliance officer, goes over self-audits and discusses preparing for audits and using a GCP checklist.

The checklist includes the types of standards that most auditors would look for, including these:

- Is the informed consent there?
- Does the site have training logs?
- Do they have an original copy of the informed consent?

• Day 4 — Informed consent, HIPAA & adverse events (AEs): "We talk about the informed consent process and HIPAA as they relate to research," Sonne says. "Our IRB does HIPAA authorization, and we talk about what they need to know."

Sonne tells attendees about basic informed consent rules and best practices, including describing how to provide the initial informed consent to a potential study participant.

"You give them a copy of the informed consent document to read and put them in a quiet room where you'll leave them alone," Sonne says. "Then you check on them and when they're finished reading you ask them if they had a chance to read the document."

Sonne suggests researchers ask potential study participants what their general understanding is of what the document says.

"This way you'll know the level of detail you need to talk about for the rest of the informed consent process," Sonne says. "Make sure people understand that informed consent is something that occurs at every single visit, and it's a continuous process."

On the fourth day, Sonne also talks more specifically about the IRB and different levels of review, including exempt, expedited, and full board reviews.

"We talk about what the requirements are and how you decide where the application fits within those review types," Sonne says.

A regulatory specialist will discuss how to manage regulatory binders.

"We talk about how to organize all that stuff and what you need to keep and what you don't need to keep," Sonne explains. "And if you have obsolete stuff, then you shouldn't throw it away because you can have a binder for the obsolete items."

Also, the binders should include all sponsor correspondence.

Another module involves adverse event reporting.

"You could spend a whole day on this, but we have 1.5 hours of it," Sonne says.

This module, led by the director of the university's new research help desk, covers what is reportable as serious adverse events at MUSC.

"We offer different scenarios, showing what study participants say at the study visit and ask what the AEs are," Sonne says.

The fourth day's instruction then moves to recruitment and retention issues.

It focuses on how to determine what your target audience is and the characteristics of a good recruiter.

"A good recruiter is someone who is personable, who likes talking to people, and who has a little salesmanship or cheerleading ability," Sonne says.

"Someone who is drab and doesn't like to talk to people won't be able to recruit," she adds. "We need someone perky and energetic."

Some trial sites try to rely on provider referrals to enroll their studies, but experience at MUSC has shown that this doesn't work, Sonne notes.

Their colleague doctors have other priorities and typically don't remember to send patients over to a researcher's office, she adds.

"You need face-to-face interaction with potential participants," Sonne says. "The best thing is to have direct patient access to people who are potential study participants."

One way to do this is to set up a booth in a clinic lobby. Or trial sites could advertise to potential study participants.

"We talk about what kind of ads might work best," Sonne says. "Sometimes it's radio or television, or it could be the newspaper where you put in an ad."

Investigators and research staff also could take advantage of unique marketing opportunities, such as running ads on the weather station during hurricane season when everyone tunes in, she adds.

"We also talk about how you need to pay

attention and track that method, and if it doesn't work, you should try something else," Sonne says. "And we talk about how all recruitment methods need to be IRB approved."

The ads need to be approved, and if the study includes having trial staff call potential participants, then the verbal script needs to be approved by the IRB, she adds.

The last part of day four focuses on research misconduct, a module that's taught by staff in the research integrity office.

This module focuses on defining, identifying, and reacting to research misconduct, Sonne says.

"The instructor might give the class a vignette and ask them what they think of this," she adds.

In one example, basic scientists might ask their laboratory staff for blood samples to use in their research, Sonne says.

"What are the issues there? Is it okay to ask your staff for the blood samples, or if it's not, why not?" she says.

"We also need folks to know that if they feel uncomfortable with something going on in the study they're obligated to report it and can report it anonymously, and there's a hotline for doing so," Sonne adds.

• Day 5 — Exam and budgets: Most of the last day is spent on the two-hour exam, Sonne says.

"We also talk about the research support desk, called the Success Center," Sonne says. "The Success Center's staff will come in so everyone can meet them, and they explain what they do and how they can help research staff."

Also, a representative from the Association for Research Professionals in the Low Country comes in to talk about the association and benefits of joining it.

"And depending on our class audience, we might offer a little section on budgets," Sonne says. "We tell them how there are regulations for how to spend research dollars and how it's better to ask permission than forgiveness."

The exam period includes a 15-20 minute review. The exam itself is designed to cover practical information, as well as to assess whether attendees understand the big picture in human subjects research, she says.

"It's a 50-question, true and false or multiple choice test," Sonne says. "It's a minimum competency exam, and a score of 75% is passing."

["Regulatory Documentation" chart inserted in this issue. Source: Vanderbilt University, Nashville, TN.] ■

Compliance Corner

QI monitoring forms, tools put compliance checking at fingertips

Check boxes, bullet points make it clear, concise

A good compliance program can be built around monitoring tools. At least that's what has worked well for one research institution.

"We started our compliance plan with our monitoring tools," says **Julie Ozier,** MHL, CIP, an associate director of the IRB at Vanderbilt University in Nashville, TN.

"It's really evolved over the past six years," Ozier says. "The forms and tools we used were interview-based where we'd go to a research site and with an interview gather data, check forms, look at the program, check source documents and regulatory documents, and put together a report."

Over time the tools have evolved into streamlined forms with "yes" and "no" check-boxes, making it visually easy to comprehend, she adds. **(See sample regulatory documentation tool inserted in this issue.)**

"It's much easier now to give feedback to an investigator, saying, 'Yes, this is present,' or 'Yes this is correct or not,'" she says. "At the end we do an exit interview with our preliminary findings and then come back and compile them all and give them a report."

Also, the monitoring tools are fluid and Web-based with the ability to adapt based on a principal investigator's (PI's) answers

"That seems to work better when we give PIs feedback, rather than giving them narratives and lumping findings together," Ozier says.

For a post-monitoring report, PIs are given a paper document, although the next step is to make these Web-based, as well, Ozier says.

"We do manual data entry into a database, and we give them paper," she says. "The review could be up to eight or nine different sheets of information, depending on what type of review has been done."

Most reviews are specific to one particular area, Ozier notes.

"For instance, we might say we'll look at the

consenting process," she explains. "And I'll pick some PIs and studies to do just that piece."

Monitors also will try to visit an informed consent process as it takes place, she adds.

"Most of the random compliance reviews we do are not of the entire program," Ozier says. "Although, certainly if the committee directed us to do an audit and look for specific problems, say an allegation or a finding, then we might do a more thorough review."

The compliance review reports also have evolved into a more readable format, Ozier notes.

"Before we might take a whole paragraph of text and tell them the findings in a paragraph format," she says. "Now we use bullet points and don't go through every detail, covering only the areas where there are concerns and saying that otherwise the program looks good."

The new format does include recommendations and suggestions for improvements, however, she adds.

The changes were made based on PI feedback, and they've resulted in PIs understanding more precisely what it is they need to do to improve their programs, Ozier says.

"There's been less back and forth between sites about what it is we wanted," she says. "We tell the PI: 'To correct this, you need to do this,' and then they implement the change, and that's it — so the process has been streamlined."

Previously, PIs would call for clarifications about findings, Ozier says. ■

Stick to the statistics on risk in informed consent documents

Researcher says numbers aren't subjective

IRB members, investigators, and others sometimes believe that potential trial participants will find hard data and numbers confusing when reading these as descriptions of risk in informed consent documents.

They think using numbers will scare away people, but this is a misguided notion, according to a biostatistician.

"I don't buy that argument because people use numbers all the time," says **Yen-Hong Kuo**, ScN, MS, a PhD-candidate and biostatistician at the Jersey Shore University Medical Center in Neptune, NJ.

"My opinion is you present both," Kuo says.

Investigators should put in the IC document both the statistics related to possible risks and descriptions or characterizations of that risk, he suggests.

"It's a very simple idea because there's nothing wrong with presenting both, especially since risk is a key component for them to make that decision," he says. "As long as it's your principle to be informative, then you can provide the best possible information for people to know."

This way, if a person reading the IC document doesn't like seeing numbers in it, they can read the explanation and make their decision based on that part, he adds.

"Or if they like the numbers, then they can see it right away instead of having to ask for more information," Kuo says.

For example, in a phase III study, the sponsor might have data showing that 10% of people receiving treatment experience hair loss, Kuo says.

The informed consent document could be worded to say that hair loss has been common in this study, and it is experienced by about 10% of people taking this drug, he adds.

IRBs might insist on characterizations of risk, such as describing a risk as rare, common, minor, moderate, or serious.

If investigators choose to classify the risk, that is their choice, but they should keep it simple and clear-cut and put the percentage next to the classification, as well, he says.

"Describe it in a way that people might read it, but put in the word and percentage side-by-side," he says. "A number is a number and does not change, and people know what percentage means."

Investigators also could translate percentages, saying perhaps that one person in 100 might experience a stroke, instead of just saying the risk of having a stroke is 1%, abut Kuo doesn't believe this is necessary.

People commonly read nutritional statistics now, and they're aware of the odds listed when they buy lottery tickets, Kuo says.

"So I feel strongly that we might overprotect our subjects," he says. "Percentages are a common way to communicate," he adds.

"The point I emphasize is the perception of the subject may be different from the perception of the researcher," Kuo says. "If you give a number that is a 1% risk and you call it a 'rare' risk, the

subject might feel like 1% is a high risk."

So if the investigator omitted the number and just used the term "rare," he or she might be giving the potential subject information that seems inaccurate to them, and so there is a discrepancy, he explains.

"But if you say the risk is a 1% risk, then it's clear information, and it's the same no matter how it's worded, and subjects can make their own decisions based on it," he adds.

The best way to handle descriptions of risk is to put in the percentages and then have the investigator spend time with potential participants, describing what the number represents, Kuo says.

"If subjects feel like they have no idea about what 1% means, then the investigator can provide that kind of help," Kuo says.

"If we used some other words to translate every percentage you use in the informed consent, then you'll make the document much longer than planned," he explains. "The researcher should be responsible and explain to the subject what it means and answer any questions the person has."

When dealing with studies where there are no data and percentages related to risk, the informed consent document should say the risks are unknown, Kuo says.

"You could say, 'We're going to study what the risk will be, so we don't have data yet,'" he suggests. ■

Clinical Research News

European journal revises tumor size guidelines

The European Journal of Cancer has revised its 2000 guidelines used to measure tumor size, called the Response Evaluation Criteria in Solid Tumors (RECIST) in the journal's January, 2009, issue.[1]

RECIST is used by clinical trial investigators for phase II and phase III studies of new anticancer drugs. The guidelines assist investigators with measuring tumor shrinkage and time to the development of disease progression as trial endpoints.

The revised guidelines address some of the changing methodologies and treatments, simplifying and standardizing the assessment of tumor burden.

For example, one change calls for a reduction in the number of lesions to be assessed for response from 10 lesions to five. Also, the number of lesions per organ was reduced from five to two.[1]

In addition, the revised guidelines redefine disease progression to include both a 20% increase in the size of the lesion and a 5 mm absolute increase. This eliminates defining increases in very small tumors as disease progression when they might be within the range of measurement area.[1]

For more information about the revised RECIST guidelines, visit the journal's Web site at www.ejcancer.info.

CNE/CME Objectives / Instructions

The CNE/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

- ■ Study finds flaws with outsourcing CTs
- ■ Marketing tips for attracting African Americans to CTs
- ■ New university course prepares biomedical researchers
- ■ Learn more about a statistical concept to determine CT risk
- ■ Try these strategies in communicating risk in Phase I studies

CNE/CME*questions*

17. Electronic patient-reported outcomes (e-PRO) are being used more in clinical trials. Which of the following is not a stated benefit of using electronic rather than paper-based patient reporting systems?
    A. ePRO is more efficient and immediate
    B. ePRO can improve data integrity
    C. ePRO has higher subject acceptability
    D. ePRO can record the precise date and time the patient inputs information

18. In a survey of 109 children's hospitals, what was the most common clinical IT application used by the hospitals?
    A. Laboratory information system
    B. Pharmacy Information system
    C. Transcription
    D. Clinical scheduling

19. Which of the following might be included in a clinical trial course on writing operational standard operating procedures (SOPs)?
    A. How do we recruit participants?
    B. What are we going to do in the trial?
    C. How do we set up a petty cash account?
    D. All of the above

20. True or False: When presenting information about risks of adverse events in an informed consent document, it is better to leave out the percentages and numbers and instead try to characterize the risk with words.
    A. True
    B. False

Answers: 17. C; 18. D; 19. D; 20. B.

Reference

1. Vervweij J, Therasse P, Eisenhauer E. Cancer clinical trial outcomes: Any progress in tumor-size assessment? *Europ J Cancer*. 2009;45(2):225-227. ■

Tools for QA/QI

Regulatory Documentation

No Action Indicated Voluntary Action Indicated Directed Action Indicated

Is the most recent approved protocol on file? No Yes
Are there previous versions of the protocol? No Yes
If yes, are all previous versions on file? List below.
Is this an FDA regulated study? No Yes
Is there a signed 1572 on file? No Yes
Is there a signed 1571 on file (when PI is IND sponsor)? No Yes
Are there 1571s on file for the following:
Original No Yes
All amendments No Yes
Annual Reports No Yes
Is there a subject enrollment log? No Yes
If yes, is the enrollment log complete? No Yes
Is/will the site (be) monitored? No Yes
How often? _____
Is there a monitoring log? No Yes
If yes, is the log complete? No Yes
Is there a monitoring plan in the approved protocol? No Yes
If yes, has plan been followed? No Yes
Is there a DSMB for this study? No Yes
If yes, is a DSMB report or indication of DSMB review and/or recommendations on file? No Yes
Have all KSP completed human subjects training? No Yes
Is there an investigational drug or device? (Drug Device) No Yes
If yes, is product information on file? No Yes
Are lab tests required? No Yes
Is the lab internal or external/commercial? Int Ext
Are normal lab values on file? No Yes
Is lab certification on file? No Yes
Is the lab director's CV on file? No Yes