CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

July 2010: Vol. 8, No. 7
Pages 73-84

IN THIS ISSUE

Financial Disclosure:
Editor Melinda Young, Executive Editor Coles McKagen, Managing Editor Gary Evans, and Nurse Planner Elizabeth Hill, DNSc, report no consultant, stockholder, speaker's bureaus, research or other financial relationships with companies having ties to this field of study. Physician Reviewer Raymond Plodkowski, MD, has a research affiliation with Orexigen Therapeutics, Abbott Pharmaceuticals, Lilly Pharmaceuticals and GlaxoSmithKline Pharmaceuticals. He is on the speakers bureau of Lilly, GlaxoSmithKline and Novartis.

Research sites face unprecedented challenges in data security

"When people steal your private information it looks bad — it makes people nervous."

Clinical trial sites trying to ensure data security face the rapidly changing threat of increasingly small and mobile technologies capable of breaching privacy and confidentiality, experts say.

Data security and privacy issues that were top priorities 10 years ago are eclipsed by new challenges today, says **Elizabeth Buchanan**, PhD, director of center for information policy research at the school of information studies, University of Wisconsin in Milwaukee, WI.

For example, social websites and the transformation of formerly private websites to public sites have created numerous data privacy issues for investigators who conduct research online, Buchanan says. *(See related story, p. 75)*

Accidental security breeches can and do happen to anyone, even those renowned for secrecy and vigilance like Apple — which learned recently that one of its i-Phone prototypes was lost in a bar and ended up sold to gizmodo.com for $5,000. Lost cell phones and laptops are very common and could easily happen to any clinical trial site, says **Jeffrey A. Cooper**, MD, MMM, director of Huron Consulting Group of Washington, DC.

"We tend to think we can put our cell phones somewhere safe or lock our laptop in the trunk of the car and they won't be stolen," Cooper says. "But the fact is that in this day and age and with the sensitivity of information that's on a laptop, you can't just assume that."

For example, CREDANT Technologies of Addison, TX, reports that more than 30,000 mobile phones and thousands of laptops, iPods, and memory sticks are left behind in New York taxicabs every six months to a year, Cooper says.

"You should assume that these devices will get lost or be stolen, and you should have something in place so your subjects will not suffer the consequences of that," he says.

There also have been some notorious cases in which researcher's laptops were stolen for the hardware, not for the data.

"The problem is when people steal your private information it looks

AHC Media LLC

bad, and it makes people nervous," Cooper says.

Cooper and Buchanan offer these ideas of high-tech security issues and how to deal with them:

Disappearing mobile devices: Clinical trial sites should assume that an investigator or coordinator or someone else involved with research will lose a mobile device with research data at some point in time.

"The general vulnerability is the same, but now it's applied to smaller things that get lost more quickly," Cooper says. "People need to no longer consider the loss of a mobile device or even the loss of a computer as being an unanticipated event."

There are a number of ways CT sites can improve mobile device security.

"The number one thing an investigator can do is encrypt his mobile devices," he adds. "That's certainly possible to do, and it's relatively inexpensive, and it provides a very large amount of protection."

Another simple action to take is to use password protection on mobile devices whenever it's possible, he says.

If research staff is using USB memory sticks or flash drives to transport CT data from one computer to another, then they should secure these with encryption software.

"I use TruCrypt, which if you type it into the Internet, you'll find a website where it can be downloaded for free," Cooper says. "It's industrial strength, and you can completely encrypt the USB drive so it will save the data securely."

The only way to read the encrypted memory stick would be to run it through TruCrypt, using the password the user created.

"When you type in the password it appears to be a non-encrypted device on your laptop, so you copy it, take it off," Cooper says. "It's not difficult to use, and it's pretty straightforward."

Handling IP addresses: Information studies, research in computer science and engineering, and epidemiology are among the areas that use transaction log analysis. Buchanan notes.

"This is where you look at IP addresses to see where people are coming from, what kinds of access points there are and so forth," she explains. "It's a means of looking at patterns in usage."

In the European Union, the governments consider IP addresses to be a form of identifiable information. The United States does not treat IP addresses this way, she adds.

"Late last year, the EU said the IP address is personally identifiable, and, as such, it should be considered open for ethics board review," Buchanan says. "As researchers now do transborder research using the methodology of transaction logs, they might be faced with two different realities."

First, they might never have to go to their U.S.-based IRB when doing a transaction log, but if

Clinical Trials Administrator (ISSN# 1544-8460) is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Clinical Trials Administrator, P.O. Box 740059, Atlanta, GA 30374.

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 18 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 15 Contact Hours.

This activity is intended for research nurses and physicians. It is in effect for 36 months from publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

SUBSCRIBER INFORMATION

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcmedia.com). Hours of operation: 8:30 a.m. -6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.

Subscription rates: U.S.A., one year (12 issues), $299. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Back issues, when available, are $50 each. (GST registration number R128870672.)

Editor: Melinda Young.
Executive Editor: Coles McKagen,
(404) 262-5420 (colesmckagen@ahcmedia.com).
Managing Editor: Gary Evans, (706) 310-1727
(gary.evans@ahcmedia.com).
Production Editor: Ami Sutaria..

AHC Media LLC

EDITORIAL QUESTIONS

Questions or comments?
Call Gary Evans at
(706) 310-1727.

some subjects are based in the European Union or Canada, there's a very different reality, she says.

"This is something that's starting to bubble up because the Internet is global," Buchanan says. "It's great, but it's also confusing because there are different regulations and different approaches to understanding the Internet."

Backing up data: CT sites need to regularly back up data or risk data not being available when needed.

They can do this by investing in external hard drives that easily connect to laptops and desktop computers, or they can have tape back-ups, Cooper says.

"There are two issues in backing up data, and the first is considering the loss of data," Cooper explains. "The second is about business continuity."

Research site managers and investigators should consider both of those issues when determining how much they are willing to invest in data back-up.

"Usually the back-up is a cost in terms of time and money, so you have to balance that cost versus how much you're willing to live without the data for some period of time," he says. "Consider how much you're willing to lose in data."

If an investigator believes that losing a week's worth of data would be undesirable, but not a disaster, then the goal should be to back up data once a week, he suggests.

"If you want to back up data daily, then do it daily," he adds.

To some people it might be worth the additional effort to back up data each time they make a change, but for most the trade-off would be at a longer interval for backing up data.

To maintain business continuity, a site might invest in out-of-region data back up.

For instance, some CR sites in New Orleans, LA, lost their research data when Hurricane Katrina struck, followed by flooding. Sites that used data back up at off-site locations where the hurricane was not an issue, were able to retrieve most data fairly quickly.

Many hospitals use off-site data back up, and companies like SunGard in Wayne, PA, specialize in this field, Cooper notes.

"They house computers for major companies and have computer software pre-set," he adds. "So if your computer system blew up, they could flip a switch, and you're connected to back-up hardware."

This type of solution is very expensive, so research sites have to weigh the potential benefits with the cost by asking themselves these questions:

- What are the potential disasters in our area?
- What is the cost of mitigating them?
- What are we willing to live with?

There are other options, as well. For instance, a clinical trial site could buy its own computer to use as a back up in a remote location.

Cooper once used this back-up method, spending money on the initial computer equipment and then paying a monthly fee to access the remote computer for backing up data. For even more money, sites could use a rent-a-server for $300 to $400 a month, he adds.

"You could do periodic tape back-ups and store them offsite," Cooper says. "Another thing you could do is store things on a cloud server that has less security to it, but you'd have to make sure the back-ups are encrypted."

Protecting passwords: Another risk to CR sites is the potential of a lost password.

"If you lose your password, you're in trouble," Cooper says.

"There are programs that will simply encrypt your hard drive, so that anything you put on there is encrypted," Cooper says. "The only thing you have to be careful of is if you have a strong password and lose it."

It's like having your valuables in Fort Knox and losing the key, he adds.

"When people die at a site, problems can happen," Cooper says. "I periodically give all my passwords to my wife to keep somewhere safe."

For research sites, the password back-up might be in a safety deposit box or safe or locked drawer.

"If there's a laptop on a desk, and a password is in a locked drawer, then I'll assume that password goes with that laptop," Cooper says. "If the password is located somewhere else in the building then it's safer." ■

Who moved my computer? Online research challenges

Technology changes ethical considerations

There are invariably new and unexpected problems when research involves the Internet. And

just when investigators and IRBs find a way to resolve some of these issues, new ones appear as the technology rapidly evolves.

From obtaining informed consent to ensuring data privacy, there are problematic concerns when the Internet is the research vehicle.

"There are different ways of thinking about the issues from different disciplinary models," says **Elizabeth Buchanan**, PhD, director of center for information policy research at the school of information studies, University of Wisconsin in Milwaukee, WI.

Buchanan offers this view into some new and complex problems that might occur in conducting Internet research:

• **Data ownership:** When researchers conduct studies online, using observational or survey data posted on a particular website, a question can be raised about who owns that information.

For example, a researcher who intends to study social or political interactions on Facebook might find that the Facebook company owns any data collected, and there is the possibility that anything the researcher has posted or collected could exist indefinitely.

"We need to make sure researchers understand that if you get consent to study people on Facebook, the boundaries are much different," Buchanan says. "What are you really allowed access to?"

When researchers step into an Internet world where boundaries are very fluid and unclear, there are multiple questions about parameters, she adds.

"When you have access to a person's Facebook data, you have to be clear about what you're studying, quoting, and how you represent the data," Buchanan says. "That's one of the challenges with online research in general."

• **Identifying subjects:** Researchers should be sensitive to the possibility of inadvertently identifying subjects of online research. This can happen more easily than they might imagine.

For instance, suppose a researcher quotes a few, seemingly unidentifiable lines in a subject's Facebook page. Someone else might be able to trace these lines back to the correct person, thereby identifying him or her. It might be possible to put exact quotes in an Internet search engine and come up with the correct person.

"There's a good chance a person can be found out," Buchanan says.

Here's another example of what can happen: "A few years back, Google bought all of these previously private news groups and medical support groups," Buchanan says. "These used to be private and not searchable, and you had to register to enter them."

But this all changed with the buy-out.

One researcher working these groups discovered just how public the private information had become when she did a Google search and one of her own private research questions popped up in the search results, Buchanan adds.

"She had posted this question in a news group that she thought was private," she explains. "So with technology we have to make these judgment calls, and when someone says, 'I'm going to look at a private news group,' they can't tell participants that the information will remain private because they don't know who will buy it and have access to it."

The track-back ability is a real possibility, Buchanan says.

"There are some real and serious moral questions that researchers and IRBs need to ask themselves when they engage in different types of research," she adds.

• **Think about privacy on a continuum:** Researchers need to think of online data as being along a continuum from the extreme of very private and sensitive data including medical information that no one wants available in any public forum to the other extreme of data that is not damaging even if it is released and identified, Buchanan says.

For instance, a post to a recipe group likely would cause no harm.

"I encourage researchers and IRBs to think about the type of data and this continuum of what's private, sensitive, and not sensitive," she says. "There's a lot of room for compromise, but you have to make sure the risks don't outweigh the benefits of research."

Also, investigators need to consider the unanticipated and uncontrollable repercussions of their Internet research.

"When we're dealing with third-party websites, which we frequently are doing now, we can't control for these variables," Buchanan says. "Facebook changes its privacy policy about every week now, and we can't control for that, so we're encouraging a guarded, flexibility with Internet research." ■

CR site process optimizes workflow, reduces delays

Simplify timelines, follow best practices

If your research site has not tackled the issue of optimizing its workflow and reducing the number of study delays, then now is the time to do so.

This is a process that can be done with incremental improvements and trial and error, says **James L. Mulshine**, MD, a professor in internal medicine and an associate provost for research at Rush University Medical Center in Chicago, IL. Mulshine was a moderator for a forum on translational research and reducing regulatory burdens at the Research Community Forum 2010, sponsored by the Office for Human Research Protection (OHRP), and held May 21, 2010.

Clinical research (CR) sites can improve their overall trial process by simplifying timelines and following best practices, he says.

When the goal is to move novel clinical practice to the research arena and then back to standard clinical practice, a more efficient research enterprise is crucial.

"What we're trying to do is broaden the discussion so there's an understanding that at academic medical centers there is a core mission to improve health outcomes related to health care delivery," Mulshine says. "And discovery is fundamental to what many people expect from an academic medical center."

To improve a CR site's workflow, one strategy is to use electronic tools to help expedite the process and improve documentation.

Rush University Medical Center uses a web-based software tool that supports IRB processes, grants, related administrative processes, and contracts work, Mulshine says.

"Four years ago we did due diligence, looking at these types of tools and anticipating the development of a web-based process," he says. "We looked at all of the functions we were committed to putting on the web, and we identified all processes."

The goal was to create simplified workflows that would help in the implementation of the electronic tool, he adds.

The research site used the electronic tool to move its processes from paper-based to web-based.

"We went through every process having to do with IRB submission, grant submission, and research contracting to try to figure out the most efficient way to do all of these things," Mulshine says.

"There were many moving parts, and I can't say we're perfect, but we did greatly simplify an enormous amount of our activities," he adds. "And we implemented those simplified workflow processes using these software tools."

The result is the site now has a web-based environment that incorporates all activities from managing protocol submission, required ongoing reporting, and grant submission to the National Institutes of Health (NIH) or the U.S. Department of Defense.

"We've been developing the system for four years, and we're maybe at 75%," Mulshine says. "We keep building."

The benefits of moving to an electronic system include the following:

- "We provide portable computers to staff, and they can do the work electronically," Mulshine says. "Minutes can be distributed much more rapidly, and all dates of document submission, approval, what's received, what's submitted, and all notable points are now captured and can be scrutinized by anybody across the institution who is involved in that process."
- The timeline for completing the protocol submission, review, and approval process has improved. Previously, paper documents would move physically from one desk to another and then sit in piles, sometimes getting lost, Mulshine notes.

"No one knew where they were," he adds. "The electronic system eliminated all of that ambiguity."

- The environmental system saves paper, time, and money by eliminating the process of making 20 copies of a protocol or protocol changes.

"All of that unproductive labor over the process of a year went away," Mulshine says.

- When Rush applied to NIH for the fast-track grants available through $10 billion in national stimulus package funding for research, there were tight deadlines creating bottlenecks, Mulshine notes.

"There were problems with volume relative to NIH to receive all these things," he says. "By having the electronic system, we had a direct point-to-point transit system to NIH that voided a certain

In switch to electronic technology, learn QI from CR coordinators

Those in the trenches often know best

One of the lessons Rush University Medical Center in Chicago, IL, learned as the research site spent more than four years transitioning to an electronic process was that sometimes coordinators really do know best.

"It's interesting, because the observations study coordinators had were about how we could implement the electronic process in a much more thoughtful way for our users," says **James L. Mulshine**, MD, a professor in internal medicine and an associate provost for research at Rush University Medical Center in Chicago, IL.

"Investigators look at data from the regulatory perspective, but coordinators have a complementary, but different perspective on the nuts and bolts of what's going on," Mulshine says.

Both perspectives need to be taken into account as a research site transitions to electronic documentation and activities.

"Coordinators are grounded in knowing how documents traverse the review process," Mulshine notes. "Coordinators are very attentive to the fact that they have to know every second where that protocol is in the process."

Investigators see the process from the macro level and leave the day-to-day transit issues to coordinators and the IRB.

The important thing for research sites is that they can count on coordinators to assist with checks and balances during the pre-initiation of research process. Coordinators will attend to data capture and capability issues, tracking a protocol's review process with the IRB, as well as with scientific and other boards.

Also, coordinators will stay on top of budget approvals and other issues. So if they discover the new electronic process is flawed or bogged down in some area, they'll let an institution know that some adjustment should be done to the new technology. ■

amount of traffic jam and allowed us to be very efficient, ensuring our grants were submitted in a timely fashion."

So Rush didn't get caught in the application gridlock and did very well in terms of awards, he adds.

"We won grants on faculty development, grant supplements to existing projects, instrumentation grants, grants to do very focused things to enhance goals, and a whole array of things enabled by the stimulus funding," Mulshine says.

The electronic infrastructure allowed the institution to handle the grant process very efficiently with minimal stress on faculty, he adds.

As research sites increasingly move to electronic processes, they should make certain investigators, coordinators, and other research staff are fully invested in the change.

"At the time we started doing this, the product had been used in 14 to 15 institutions, and we took advantage of the best practices from that previous experience," Mulshine says. "We took the best version and sat down with coordinators, investigators, and administrators to talk about how to accommodate the generic version to meet the needs of investigators at Rush."

It was important to engage research staff in helping to define processes and adjusting these to meet the specific needs of the facility, he adds. *(See story on coordinator's comments, lessons learned, above.)*

For six to 10 months, the new process was handled as a voluntary compliance change. Once it was fine-tuned and made more efficient, the staff who had been early adopters of the technology helped spread enthusiasm and interest in the technological change.

"Good word of mouth helped us transition this uniformly throughout the campus, and the process went quite smoothly and rapidly," Mulshine says. ■

Negotiate better payment terms for your CT site

Six steps to better terms

Clinical trial payment agreements are improving for sites, but there are strategies that can make these even better, an expert says.

Over the past several decades, clinical trial sites have witnessed changes in how sponsors pay them

with the time spent waiting for a check almost quadrupling this past decade.

Two decades ago, sponsors typically paid clinical trial sites every 45 days with loose monthly payment terms, says **Terry Stubbs**, MA, CCRC, president and chief executive officer of ActivMed Practices & Research in Haverhill, MA.

Sponsors then switched to quarterly payments, which greatly lengthened the time between when the money was spent on a clinical trial to the sponsor sending the site a check.

"It went from being paid every 45 days to being paid in 120 to 165 days," Stubbs says. "Most people assume that you'd get paid every 90 days when its on a quarterly basis, but in reality it's from 120 to 165 days to receive payment, and this was the practice for a long time."

The good news is that within the past year, the pendulum has again swung. Payment times are shortening with many sponsors returning to monthly payment terms, she adds.

The reason for the change is obvious to those in the CT industry who have witnessed a rapid turnover of research sites.

Five years ago about half of CT sites went out of business, according to a survey by Ken Getz, because they couldn't stay afloat with terms that left them cash poor, Stubbs says.

"Now the industry is listening and hearing us and doing payments on a monthly basis, so we're paid from day 45 to day 60," she adds. "This is so much easier because we don't have to cover our staff salary for six months while waiting to get paid."

Sponsors also are more amenable to other changes in CT agreements, so now is the time to strike a good deal, Stubbs says.

"From 2003 to 2006, you saw all kinds of things in clinical trial agreements that would not be good for keeping your cash flow positive," Stubbs says. "Now the industry understands the pressures it created at sites."

It was harder to negotiate five years ago because so many physicians flooded the CR market, and many did not truly understand how difficult it would be to live within the budgets being offered by sponsors.

For example, an inexperienced physician researcher might accept a payment of $1,800 per patient for a hypertension trial that requires 13 visits, blood work, and EKGs, Stubbs says.

It'd be difficult to pay staff salaries and cover your malpractice insurance and other expenses with that budget, she says.

"If the same doctors were to look at an insurance reimbursement at that rate with all of those procedures, then they'd say they wouldn't contract with that insurer," she adds.

Now the market pressures have changed, and research sites have more power to negotiate better payment terms. Here are some of Stubbs' suggestions for getting better terms:

1. Analyze your site's expenses thoroughly.

Sites need to look at their normal expenses, monthly expenses, and their cash reserve to determine how long they can carry costs without compensation, Stubbs says.

If the site determines it cannot carry expenses longer than 60 days without compensation, then the site should negotiate a monthly payment term and make certain the sponsor doesn't stretch this out beyond 60 days.

"Once sponsors understand that it's not greediness, but the reality of trying to stay in business so a site can continue to do research trials, then that's where the sponsor's bending comes into practice," Stubbs says.

2. Negotiate with positive statements.

Pull information from industry trends and use these to help with your negotiation, Stubbs suggests.

"Discuss something you've seen or experienced in a positive way," she adds. "Negotiate with the positive, not the negative, and don't intimidate."

The more the site's negotiator explains the site's expenses and budget in a positive way, avoiding adversarial stances, the better the negotiations will go, Stubbs says.

3. Know the contract's fine print and details.

Here are some questions to identify in the proposed contract:

- How long it will be between payments?
- What's being paid in the payment?
- Should extra expenses for advertising or items like dry ice be added into the contract or invoiced and paid within 30 days?

Advertising reimbursement is a particularly sticky point because radio stations and newspapers will insist on being paid immediately, Stubbs says.

"It's important if you do advertising and ancillary services that you get paid on a 30-day basis and not have it put into the quarterly or monthly payments, she adds.

"This lesson came early in my career," Stubbs says. "I had two trials running, and I called the radio station to run another $4,000 in ads, but the radio station said I'd have to pay cash first before I could do the next round of advertising."

This payment could cause cash flow problems, particularly if sponsors are slow to reimburse for these expenses.

4. Improve terms of hold back payments.

"Originally the hold-back payments came in during that time when there wasn't good business reality among sites, so sponsors or clinical research organizations would hold 20% of the entire budget until the end of the study," Stubbs explains. "That could mean by the end of the entire clinical trial when every site is finished or at the end of your site's recruitment period and all of your data are collected and answered."

This can have a big impact on a site's cash flow.

"If you are involved in a three-year trial and you have 30 patients in that trial, then whatever money is held until the end of the 3 to 3.5 years is a huge amount," she adds.

Sites should negotiate for more reasonable hold-back terms, such as a 10% hold back, Stubbs suggests.

"That's a little easier to deal with," she says. "They just want to make sure everyone cooperates and gets their data in, so 10% is returned when all data are in."

5. Ask for a regulatory fee.

The industry used to give sites a 10% start-up fee. But this posed problems since many sites receiving the fee never enrolled subjects, Stubbs says.

Now sponsors will pay regulatory fees, typically of $1,500 to $2,000 upfront, but they won't give these to sites at start-up unless they know the site has a positive track record in enrolling, she adds.

"If you've done well then you can get start-up money with the understanding that if you don't provide services you'll pay it back to the sponsor," she says.

This fee is for training staff, using electronic data capture, getting regulatory documents submitted to the IRB for approval, making amendments to informed consent forms, and covering other regulatory issues.

6. Look for other items to improve in negotiations.

If your site develops an enrollment plan that details what you're going to do with advertising, then you're more likely to get a better advertising budget from the sponsor, Stubbs says.

Sites also can negotiate more sensible payment terms by knowing what the cost of living is for their region of the country.

Sponsors and sites take into consideration that CR sites in Boston, MA, and California will have higher expenses than sites in Texas, for instance, Stubbs says.

"The sponsor will base this on the area and part of the country in which you're located and based on what the cost of living is in your area," she says. "If you are located in California, then you should ask for more money in the contract."

One way to do this is to determine your employees' monthly cost for working in research plus your monthly overhead costs, and show the sponsor that the proposed budget is considerably less than what the work will cost you, she adds.

While it's unlikely sites will win everything they want in budget negotiation, they should keep in mind that now is a good time to ask for better terms.

"I see a lot more positive energy from sponsors and CROs as far as working things out with sites," Stubbs says. ■

BEST PRACTICES

Timely tips on improving Good Clinical Practice

Staff training is crucial

From communication to documentation to staff training, clinical trial sites need to adhere to Good Clinical Practice (GCP) guidelines.

One key is to focus on federal regulations in obtaining informed consent, completing clinical research forms, and submitting protocols to the IRB, says **Gina Nesbit**, RN, CCRC, research manager at Northeast Georgia Heart Center in Gainesville, GA.

While principal investigators (PIs) are responsible for all practices at their clinical trial sites, there are multiple other research individuals involved, including sub-investigators, pharmacists, laboratory staff, and research coordinators, she notes.

So staff training is paramount.

"When we hire staff they get their training program here," Nesbit says. "We focus on FDA regulations, the informed consent process, IRBs, CRF completion, and all of the things required with the

conduction of clinical research and protocol deviations."

Principal investigators should emphasize communication between research staff and have regular meetings with coordinators to discuss enrollment, adverse events, MedWatch reports, safety reports, and participants' lab values, she adds.

"The PI should always be aware of what's going on," Nesbit says. "So we meet regularly with PIs and have a research committee that discusses what is going on with the trial."

Monitoring MedWatch reports, adverse events, and the trial's execution are all part of GCP. Nesbit offers these tips on improving GCP:

• **Keep patients informed:** "At our site we spend a great deal of time with patient education," Nesbit says.

As a cardiology practice, many of the site's trials deal with people who have had a heart attack.

"When someone has a heart attack, that's new to them, and they're overwhelmed with the process," Nesbit says. "So when we come in to discuss a clinical trial it's really overwhelming to them."

This means that the informed consent process must focus on what is going on with the patient's disease and treatment and helping them understand that process, she says.

"Once they understand the medical process, we say, 'Now let's talk about the study so you can compare what we do every day to what we propose in the study,'" Nesbit says.

"Informed consent is not something that occurs one time at the beginning of the trial, it's something that is ongoing throughout their participation," she adds. "So with follow-up visits, talking to patients, and throughout the patient's time, you're constantly reiterating study procedures, what the study is about."

• **Communicate continually with IRB:** "We constantly communicate with the IRB with regard to adverse events, protocol deviations, MedWatch reports, and the continuing review process for the trial," Nesbit says.

When the trial has an adverse event, this is reported on a specific form and sent to the IRB. The MedWatch reports are compiled and sent to the IRB at the continuing review.

The site reports all AEs, even if they are unrelated to the product being studied, Nesbit says.

"We have a lot of cardiac trials, and if a patient is admitted to the hospital with a cold, then it's an adverse event because it's a hospitalization," she explains. "But it's not product-related."

Or if a patient is seen in the emergency room because he broke a toe, then that's reported, depending on how the protocol is designed, she adds.

• **Document everything:** "If it's not documented, it didn't happen," Nesbit says. "Documentation is extremely important with this patient population."

If a patient has an adverse event that requires sponsor action, then it's very important all documentation related to that AE is complete and accurate.

"If it's not complete then that makes the adjudication much more difficult for the sponsor, so every effort is made to make sure the documentation is complete," Nesbit says.

Look at the documentation as telling a story, she suggests.

"I once had a monitor tell me that when you are putting together your regulatory books and case report form binders about the patient you want to `tell a story,'" she says. "It has to have a flow to it, and so the way we've organized our regulatory binders, patient binders, and flow of communication is to make sure it's always telling a story."

• **Train staff and create checks and balances:** Everyone who works with the institution's IRB has to go through GCP training online, Nesbit says.

"Every year we review GCP within our own practice so everyone remains up-to-date, and it's always on the forefront of everyone's mind," she adds. "Also, at investigators' meetings, they reinforce GCP and remind them of those principles."

For clinical trials that have outside sponsors, the checks and balances primarily come from site monitors who regularly review data, comparing what's in the case report form to the patient's chart, Nesbit notes. ■

CASE STUDIES: ETHICAL ISSUES

When does clinical care trump trial protocol?

Good intentions can lead to bad results

Occasionally a physician investigator will be torn between the need to adhere to the clini-

cal trial protocol and the desire to help a patient/subject obtain a better medical outcome. The question is: Is it ever right to follow that desire and vary from the protocol?

The answer probably is never unless the principal investigator and/or the sponsor agree, a research ethics expert says.

"There are many times in trials where the clinician decides that something else needs to be done, and, in consultation with the sponsor or PI, they agree to remove the subject from the trial," says **Charles W. Lidz**, PhD, a research professor in the department of psychiatry at the University of Massachusetts Medical School in Worcester, MA.

The problem is when it is done covertly, Lidz says.

"This is an issue that people who are implementing clinical trials have, and we need to address it and not insist that it doesn't happen," he adds.

"I became interested in this issue when I was doing research on therapeutic misconception," Lidz says. "I kept running into clinicians who were saying to me, 'There's no therapeutic misconception because we always take the patient's point of view and meet the patient's needs."

Then clinician investigators gave Lidz a number of examples of how they'd override the protocol in the interest of the patient's medical care.

This is an alarming practice, he notes.

"If we violate the rules of the protocol in order to provide good clinical care for the subjects, then I believe that's a threat to the validity of the trial," Lidz says. "And how do you fix that?"

On the other hand, some clinical trials are designed so rigidly that it's difficult for physician researchers to manage the care properly, he notes.

"I've certainly talked to lots of people who tell me, 'In general of course, I always stick to the protocol,'" Lidz says. "But then they tell me about a specific case, and they didn't stick to the protocol that time because the patient needed such and such."

Lidz also has met clinical researchers who will not recruit people who meet the full study criteria if the subjects already are doing well on conventional treatment.

"That's fine, but the problem is we're no longer testing the intervention in everybody who meets the criteria," Lidz says. "We're testing it in people who have failed on conventional treatment, and that's a biased sample."

It would be fine if a protocol was designed to study only people who have failed on conventional treatment, but it's deceptive when investigators make that decision without the sponsor knowing.

"Often those decisions are not visible, and the people who write up the trial are not aware of the bias in the sample," Lidz says.

For example, suppose a sponsor is studying the efficacy of a new drug for treating diabetes. The study is supposed to enroll anyone with the disease. But instead of having a general diabetic population, physicians receive referrals and enroll only people who have glucose levels that are uncontrolled by current interventions, Lidz says.

When the diabetes treatment study's results are analyzed, the intervention group's results might look considerably better than the control group that is receiving conventional treatment since most of the people in the trial already had failed on the conventional treatment, he explains.

This means the study's results are a poor indication of how well the new drug does when compared with the conventional treatment. The only comparison was between the new drug and conventional treatment in people who already had poor results in conventional treatment, he adds.

"People implementing these trials typically are people who have a commitment to their patients, and we can't ignore that potential bias when we design clinical trials," Lidz says. "We need to appreciate that they may have a default way of doing things to match the patient's needs."

This type of bias can be managed through staff education about protocol adherence, increased vigilance over study documentation, and by considering the potential for bias in study design, he says.

"If we try to ignore the existence of these problems, then we just get into invalidating general data," Lidz says. "To me that's a big problem."

Another example of this type of problem involves an open trial in which a patient asked his physician to be put on the investigational medication because he had already failed on the control drug.

"The clinician told the patient, 'Look, if you don't get the experimental medication you can always drop out of the trial,'" Lidz recalls.

While one could understand a physician's desire to obtain the latest and possibly best treatment for his or her patients, the fact is these potential treatments need fair and honest clinical trials before they can be considered the best treatment, Lidz says.

"The key issue is that when one designs trials one has to think about how to design them in such a way that clinicians are most comfortable with

the trial," he says. "Also, one has to work at educating the people implementing them to make sure they understand that this trial is not for the purpose of making a sponsor or investigator feel good or to improve their resumes."

The purpose is to obtain the best answer to the study question, and there is no sense in going through the time-consuming and expensive clinical trial process if someone involved in the trial is going to mess up data, he adds.

"I'm all for patient advocacy, but we're putting time, money, energy, and to a certain extent a patient's risk to gathering these data, and if data are incorrect, then it's an awful waste," Lidz says. ■

CR NEWS

AHQR clarifies grant app rules under stimulus

The Agency for Healthcare Research and Quality (AHRQ) issued on May 26, 2010, a notice about its expectations with the completion of grants awarded from the funding provided by the American Reinvestment and Recovery Act (ARRA).

AHRQ issued the notice, as listed below, for these reasons:

1. To reaffirm to AHRQ grantees that the primary goals of all AHRQ Recovery Act awards are to create U.S. jobs and accelerate the pace of health services research;

2. To remind project directors/principal investigators (PD/PIs) and grantee institutions that AHRQ fully expects Recovery Act grantees to expend project funds in a timely and expeditious manner in accordance with the expected pace of research;

3. To remind grantees that all Recovery Act expenditures remain subject to terms and conditions on the Notice of Award, including the AHRQ-HHS Standard Terms and Conditions for ARRA Awards (see http://www.ahrq.gov/fund/arraterms.htm) and all referenced regulations and OMB Circulars;

4. To notify grantees that AHRQ Recovery Act grants will not be issued under Expanded Authorities; and

5. To notify grantees that AHRQ expects all grant activities to be completed consistent with the schedule of the approved project period.

AHRQ has received funds from ARRA to stimulate job creation and economic development activity related to health services research for the nation. ■

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

■ Experts offer advice on handling emergency research

■ Conflicts of interest policies are evolving at research sites

■ Know the difference between noncompliance and misconduct

■ Minority subject recruitment requires sensitivity to community issues

■ What's latest in reproducible research?

CNE/CME QUESTIONS

1. What's the simplest and best way to improve the security risk of having a researchers' mobile phone or laptop lost or stolen?
   A. Insure the device
   B. Encrypt the device
   C. Back up all data on a second hard drive
   D. Forbid researchers from carrying these off premises

2. Which of the following is a good reason for having an electronic submission process at research sites?
   A. The timeline for completing the protocol submission, review, and approval process will improve
   B. The environmental system saves paper, time, and money by eliminating the process of making 20 copies of a protocol or protocol changes
   C. Electronic grant submission can improve speed with landing contracts
   D. All of the above

3. When clinical trial sites are negotiating with sponsors over contracts, which of the following is a good question to ask during the process?
   A. How long will it be between payments?
   B. What is being paid in the payment?
   C. Should extra expenses for advertising or items like dry ice be added into the contract or invoiced and paid within 30 days?
   D. All of the above

4. True or False: Everyone who works with an institution's IRB should go through GCP training online.
   A. True
   B. False

Answers: 1. B; 2. D; 3. D; 4. A.