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IN THIS ISSUE

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Unethical Guatemalan study may undermine recruitment, trust

'For people who are skeptical, this [could] turn them further away'

Research sites that work with minority, international, or vulnerable populations should be particularly sensitive to continuing fall-out from recent revelations of strikingly unethical behavior by U.S. researchers in Guatemala in the 1940s.

The research world was rattled in October by the announcement that the U.S. Public Health System sponsored a study, from 1946 to 1948, where investigators purposely infected Guatemalans with sexually-transmitted diseases (STDs) and hid the research's true knowledge from them.

This latest chapter in the world's dark history of unethical research projects raises issues that are relevant in today's globalized clinical trial world, experts say.

"When I first heard the news of the Guatemalan study I felt that I wished I had been more surprised," says **James Lavery**, MSc, PhD, research scientist at St. Michael's Hospital in Toronto, Canada.

"Surely we've made progress over all these years, but have we really come to a clear understanding of what it means to be respectful of the communities we do research on?" Lavery says. "I'm not convinced that we have."

For instance, when western researchers conduct trials that involve the collection and use of human tissue in a developing part of the world, they often make decisions about how this will be done based on input from the local community's authorities and ministries of health, rather than talking to people in the community, he explains. *(See related story p. 135.)*

"The communities try to be polite and are good hosts, but they don't voice their concerns enough," Lavery says. "And when the trial is over, what is left is a residual distrust in a community; people are unhappy and believe the researchers' actions were disrespectful."

Global researchers likely will encounter some skepticism or questions about the Guatemalan study as they pursue trials in resource-poor areas. But the key will be to educate the public about the protections put into place.

The IRB system was established in 1974 by Congress with the National Research Act, and federal human subjects research regulations followed

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in the early 1980s, says **Robert J. Levine**, MD, professor of medicine and a lecturer in pharmacology at the Yale University School of Medicine in New Haven, CT. Levine also is a senior fellow in bioethics at the Yale Interdisciplinary Center for Bioethics, which he co-founded.

Both safeguards have been enormously successful in preventing research abuses as grievous as what occurred in the 1960s and earlier, Levine says.

"Since that time, all of our major news stories about unethical incidents in research have been about studies from the distant past," he adds.

"The Advisory Commission on Atomic Radiation Experiments reviewed the whole field and found nothing that looked bad that occurred after 1974, which was the year Congress established the IRB system," he explains.

Tuskegee parallels

The Guatemalan study has several parallels to the 40-year Tuskegee syphilis study, including the fact that the two studies shared at least one investigator, John Charles Cutler, MD, who was a central figure in both. Cutler died in 2003.

In the Tuskegee research, African American men were not told what the study was for or that they had been diagnosed with syphilis. When the study began in 1932, there were no accepted treatments of the disease. But the research continued well past 1947 when clinicians were using antibiotics to cure syphilis. The Tuskegee researchers did not offer any treatment to the men enrolled in the study, even as late as 1972 when national media reports caused public outcry and forced federal officials to close the study.

In the Guatemalan study, prisoners, soldiers, people with mental illness, and other marginalized members of the community were unknowingly infected with syphilis and other STDs for the purpose of studying whether antibiotics could prevent infection. The study never answered the question and might have remained buried and hidden from public view if it had not been for the work of Wellesley College historian Susan Reverby who discovered the archives and brought them to public attention. Top officials with President Barack Obama's administration quickly denounced the research and apologized to the Guatemalan people.

One of the ironies of the recent disclosure is that for decades there has been distrust among some members of the African American community toward researchers, particularly in light of the Tuskegee experiment. And one of the undercurrents of that distrust has been the circulation of rumors that U.S. Public Health officials intentionally infected the Tuskegee men with syphilis, says **Alex Capron**, a professor at the University of Southern California in Los Angeles, CA. Capron

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

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EDITORIAL QUESTIONS

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

also is a professor of law and medicine at the Keck School of Medicine, and he's the Scott H. Bice Chair in Healthcare Law, Policy and Ethics and co-director of the Pacific Center for Health Policy and Ethics.

"And now we know that Dr. Cutler was intentionally infecting people in Guatemala," Capron says. "So the main effect of the Guatemalan study might be that we see a conflation of those two things in people's minds."

The revelation might revive the Tuskegee rumors and increase concern among potential research subjects, he adds.

"The fact that as soon as this was discovered and revealed it was denounced by the president and Secretary of Health and Human Services and the Secretary of State with official apologies being made will differentiate it from the Tuskegee situation which took a long time before the government actually apologized to the victims," Capron says. "Those actions make it less of a festering situation."

American subjects infected

Observers looking at Guatemalan study revelation have speculated that researchers went outside the United States to avoid scrutiny of their research practices. But the cold truth is that U.S. investigators had been injecting American subjects with diseases for years, Levine says.

"Researchers induced malaria by injecting malaria parasites into our prisoners," he says. "There was great justification for this during World War II when our enemies took over places where natural anti-malarial agents were grown and we had to develop synthetic anti-malarials."

The researchers chose Guatemala more for the country's lax attitude toward letting sex workers visit prisoners, an environmental condition they thought would make it easier to study STD transmission, he adds.

The United States research community's history of using human subjects in these ways is a source of shame, but it wasn't limited to international studies, he says.

"The current stories of what happened in Guatemala don't have historical perspective," Levine adds.

So the key way to handle any anticipated fallout from the news is to educate communities – both domestic and international – about how federal regulations and local IRBs have been very effective in preventing these types of research abuses for 30-plus years.

Still, it's possible that American Hispanics will find news about the Guatemalan experiment relevant toward their attitudes about health care and research.

"I don't know if this will have an impact on current patient willingness to be a research participant," says Scott J. Lipkin, DPM, CIP, an associate vice president of research for LeHigh Valley Health Network in Allentown, PA.

"Perhaps for people who are skeptical, this will turn them further away from research," Lipkin adds. "But most people are intelligent enough to understand that this happened a long time ago, and there have been a lot of changes since it happened." ■

Earning respect, trust in international settings

PIs must put more time in to building trust

No one can predict yet whether or not the growing infamy of the Guatemalan syphilis study results in enrollment problems for researchers engaged in international research. It certainly will not help. Regardless, at least one expert believes that even with the protections and regulations put in place in the 21st century, international trial investigators need to do more to earn the trust of the communities they study.

"What I'm trying to understand is what makes community engagement effective at an operational level and what should we be doing at an ethical level," says **James Lavery**, MSc, PhD, research scientist at St. Michael's Hospital in Toronto, Canada.

"Fundamentally, this is the whole notion of humanizing trials," Lavery says.

If researchers walk into a Guatemalan village with the mindset that this person is a mother and daughter then it would be hard to treat her as the subjects were treated in the Guatemalan syphilis study of the mid-1940s, he adds.

In those trials, vulnerable populations in Guatemala were intentionally infected with sexually-transmitted diseases (STDs) without their knowledge or consent.

"It must be inevitable when these stories come to light that there is a deep suspicion that the peo-

ple doing research do not care enough about the well-being of the people they're engaging," Lavery says.

Investigators and the research ethics community need to move beyond the rhetoric of conducting informed consent in language and literacy-appropriate ways and instead try to meet study subjects on their own terms, learning what it is to them to be respected by researchers, Lavery suggests.

"Maybe this means going more slowly forward with the research project or giving [subjects] opportunities to have meaningful input or even to change what we do," he adds.

Lavery and co-investigators have developed a framework for community engagement in global research that lists 12 points to consider for effective community engagement. These include ensuring the research project's goals are made clear to the community and understanding the community's attitudes and perceptions of the proposed research project.1

"What I'm trying to accomplish with this work is to bring it up to the surface and bring it into the open so investigators are not caught napping," Lavery says.

Lavery lists these potential issues in engaging communities in global research:

• How do you represent the community?

"I've seen many different mechanisms for how communities are represented, and there are a lot of difficult problems there," Lavery says. "Conceptually, how do you represent a community?"

It might be that three people out of a population of 35,000 are chosen to speak on behalf of the entire community. Typically they'll be part of a community advisory board.

"But what does that mean?" Lavery says. "It's easy for investigators, but most people in the community do not know the board exists."

One key is to spend time in the community before the research project begins and get to know people who could be impacted by the study, he suggests.

Another strategy is to purposely look for dissenting opinions and include these people in the community advisory board.[1]

"One thing we believe in that investigators virtually never do is actively seek different views rather than seek people who will agree with everything you do," Lavery says. "There's a moral obligation to seek out people who may not agree with your practices in the overall trial."

Give these people an opportunity to express their views even if it will take time and make investigators uncomfortable, he adds.

"We think that's a requirement of respect and being a good host," he says. "Try to listen and understand people who may oppose the research."

If this strategy were applied at various time points in human subjects research history, then it's easy to imagine that the Guatemalan and Tuskegee study abuses would never have occurred.

"Imagine if you had to as an investigator talk to people in Guatemala and ask them if they thought it was a good practice to infect people without their knowledge?" he says.

• What do members of the community feel about trial procedures?

It's better to find out how the community might react to controversial or slightly risky procedures before the trial begins. Although this might take time and result in complaints by researchers, it's preferable to the worst-case scenario of the community expressing its views after the study is underway.

"People stop complaining when trials shut down because communities say, 'We've had enough,'" Lavery says.

This has happened in international HIV research where well-developed activism has had an impact on clinical trials, he notes.

"You have hundreds of millions of dollars in these trials, and if they fail or if you have to go to new sites and start over, it can take years," Lavery says. "There are hardship costs on the side of investigators and funders, but the communities have some power, and we want to avoid those kinds of problems."

For example, if a study requires blood draws and exporting blood samples to another country, then investigators should do extensive ground work to find out how this will be perceived by a community's populous.

"What might happen is the community says, 'I'm not sure we're happy with your exporting our blood samples to another country,'" Lavery says.

Investigators should think about what it means to be a good guest in these communities and demonstrate why these blood samples are important.

"It's fundamentally about respect," Lavery says. "How confident are we that we have really learned how to be respectful of the communities we're engaging?"

International researchers do a good job overall, but there are ethical gaps that need to be resolved,

and this is what Lavery and other researchers are trying to address with the global health research framework project.

The project, funded by the Bill and Melinda Gates Foundation, looks at what makes community engagement effective.

"We have done nine case studies in seven countries where we look at in-depth details to reveal insights into what kinds of practices contribute to effectiveness," Lavery says. "We focus on what people do, the operational level, and what are the practices and mechanisms and what is gained on the ethical side by each of these practices with a strong emphasis on community."

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COMPLIANCE CORNER

Producing best-practices in research compliance

A well-run program can alleviate PI burden

Academic researchers spend a large chunk of their time on paperwork. Regulatory and institutional burdens could seem overwhelming. However, a well-run compliance program could alleviate some their load and documentation responsibilities.

"A survey of researchers done a couple of years ago indicated the faculty are spending 42% of their research time on administrative duties rather than doing research, and these findings made a lot of people sit up and pay attention," says **David L. Wynes**, PhD, vice president for research at Emory University in Atlanta, GA.

"I'm always aware of the burden on researchers," he notes. "We can't cut corners, but that doesn't mean we can't do efficiencies and reduce the burden so researchers can spend more time doing research and less doing paperwork."

Wynes oversees a large research program with 175 employees. It encompasses these areas: an IRB office, research compliance office, conflicts of interest program, technology transfer program, environmental health and safety program, sponsored programs office, and animal care and use committee.

Despite its size and the potential for bureaucratic encumbrances, the research program has a strong and effective compliance program. The key is its cohesive and empathic framework. Wynes describes these elements of compliance program best practices:

• **Establish practices for how various research offices interact:** "First and foremost you must recognize that none of these units operate in a vacuum," Wynes says. "You have to figure out how that office is going to interact with all the other offices, including some external constituencies."

Think of the research organization as a network that operates under a common framework that includes compliance standards. Ask these questions when creating the framework:

— What are the compliance goals you are trying to achieve in the office?

— What are the ethical goals, apart from research regulations?

— Which ethical and safety goals match the various compliance requirements and regulations?

— How will you meet the goals the laws were designed to accomplish?

The common framework has to make operational, as well as ethical sense, Wynes notes.

"It's easy to sit down and write a process for absolute compliance, but then you have to look at it and say, 'Will this really work?'" he explains. "Many times the answer is 'No.'"

For example, sequential committee reviews does not work operationally, Wynes says.

When a research site starts a new clinical trial the proposal needs to be reviewed and approved by the IRB, the research billing office, and other entities, including sponsored program negotiations, he explains.

"The easy way to do this would be to have one office review it at a time and then hand it off to the next office," he explains. "But by the time you finish that process, the trial will be closed to enrollment before having a single subject."

So what is the easy way does not work operationally.

Instead, the research organization needs to find a way to have concurrent reviews while keeping communication channels open between the different groups.

"We're constantly fighting a misperception

investigators sometimes have that they have to do things in a sequential order when they can go on in a parallel process," Wynes says.

"We had to develop parallel processes and ensure there was cross-communication at the right points between the offices," Wynes says.

• **Improve communication within and outside of the organization:** An efficient way to do this is to use an information technologies (IT) solution.

Research sites can have automatic notifications built-in to their systems.

"For example, a person might answer certain questions in an IRB application, and their answers will send a notification to the research billing office, saying there are clinical trial charges and bills for these procedures," Wynes says. "Then someone in the research billing office will see the email and ask if the office had received an application from the person and, if not, they can contact the person."

Another strategy is to keep research units physically near one another within a large organization.

At Emory, the various groups, including the IRB office, are located in the same building, Wynes says.

"They see each other at lunch in the cafeteria," he says. "The IRB office is down the hall from the billing group and one floor away from the contracting group."

Since employees working in one unit are neighbors with those working in another unit, they begin to get to know each other.

"They're not just people on the other end of the phone," Wynes adds. "You can't dodge them. You have to confront them face-to-face."

The research office can facilitate keeping the line of communication open by holding regular meetings and bringing different parties together to speak openly and frequently.

"We do staff recognition gatherings where everyone gets together and has lunch, and we identify new employees and people who've been here five years, 10 years, etc.," Wynes says. "I encourage people to find someone they don't know and talk with them, finding out what they do and how it might relate to what they do."

• **Obtain feedback from stakeholders:** Emory has a survey questionnaire about customer service. The customers are faculty members and research coordinators. The various research units are encouraged to include a link to the survey in the emails they send to researchers, Wynes says.

"So we have feedback on individuals and whether they were customer friendly and helpful," he says.

It's particularly important to learn how the research community perceives the IRB office and the quality assurance (QA) people who work with investigators on research compliance, he notes.

The QA staff obtains indirect feedback about their performance when they work with investigators and review protocols and compliance issues. For instance, if there are patterns of problems among researchers, then that's a sign that the education process needs to be improved, Wynes says.

"If we find lots of people not doing things the right way, then I presume we're not educating them correctly," he adds.

• **Encourage research staff to document immediately:** It's easy for busy research officials to let their documentation slip. The problem is that it's more difficult to recall details that might go into a documentation note once some time has passed, Wynes explains.

"If you don't keep on top of the paperwork that needs to be done and attempt to construct it a month later, then you will have problems and miss things," he says. "In some of our monitoring visits we've identified that as something we need to work on."

This is a point that should be continually reinforced until it becomes a habit. People have to be habituated to a new process, he notes.

"In part we use technology to help people along so information is captured automatically," he says. "You remind people of these expectations through workshops and monitoring visits, and you remind the entire team so it becomes a team issue."

So maybe at weekly research meetings, a principal investigator will say, "Let me see the records" or "Is everything here that needs to be here?" This builds group awareness, he adds.

After time, immediate documentation becomes a habit like brushing teeth.

But initially there needs to be pressure of some kind to get people to recognize why this is important.

• **Use information technologies solutions whenever feasible:** "We have a great IT solution with our conflicts of interest (COI) program that we've developed over the last two years," Wynes says.

When researchers enter the Emory system, they list any outside consulting activities they do. Then they answer questions about their research projects. The IT system asks them if the projects are tied to any of the consulting work.

Then when investigators submit a new grant application, the system brings up their consulting activities, showing them the list they have created and asks if the grant would relate to any of these, he explains.

"We'd have close communication both verbally and through IT between the office of sponsored programs and the IRB office to make certain no one falls between the cracks," he says. "The system is tied into the school's annual reporting requirements of outside activities."

The system does require their personal knowledge of conflicts: "I need the investigator to say, 'Yes, one drug made in this study is made by this company and I'm on the scientific advisory board,'" Wynes explains.

"We provide investigators with integrated information and they don't have to give a lot of thought to it," he adds. "Anytime they enter a new consulting activity, the program gives them the list."

The conflict of interest affiliations are current and can be changed whenever an investigator begins a new consulting activity or study. The IT program also prompts them to update their list each year, as well.

"We have a very comprehensive process for identifying any kind of financial activity related to research and needs," he says. ■

Discerning between disease, drug reactions

Novel method used with cancer population

One of the chief problems with adverse event reports is these often cast a net so wide that many disease symptoms are swept up with the reports. This particularly is an issue with oncology clinical trials. Investigators have developed a strategy that should make it clearer which symptoms are related to the medication and which are related to the disease.

"I've been interested in adverse drug events, injuries related to the medical use of drugs," says **Steven M. Belknap**, MD, a research assistant professor at Northwestern University Feinberg School of Medicine in Chicago, IL.

"I was interested in cancer because it's often difficult to distinguish the toxicities of a cancer drug from the effects of the cancer itself and from comorbid conditions," he adds. "So we looked at the quality of the data reported in clinical trials and found it striking that the data quality is quite poor."

There was no good evidence that the adverse events were caused by the drug.

"It was difficult to distinguish the adverse events from all the other things going on with the patient," he says.

Belknap previously has looked at adverse event reports and was struck by how inaccurate these can be.

For instance, he came across a case where a patient had allegedly died from a reaction to an antibiotic. But when he looked through the record he found that the antibiotic had been ordered, but it was never given to the patient.

"In another case, the adverse event occurred before the first dose of the drug was given," Belknap says. "There are many problems like that."

These findings convinced him and other investigators that there might be a more accurate method of evaluating causality in adverse events in a clinical setting.

"We did that and had an amazing result," he says. "The drugs we thought were the main problems were not the main problems."

Once investigators found the root cause of the problems they assisted the hospital in reducing adverse events, he adds.

In the cancer research, investigators developed structured, symptom-specific case report forms that improved ADE reporting.[1]

They found that of 115 serious adverse drug events reported to the IRB the overall completeness of adverse event descriptions was 2.4 times greater for the structured case report forms versus the corresponding forms from IRB reports.[1]

The key to separating cancer disease symptoms from cancer drug side effects is to know the expected adverse events for any particular drug. Start with the medication label, Belknap advises.

"Cancer chemotherapy drugs are toxic and can be beneficial," he explains. "Applying this approach to cancer, we thought we'd look at how people were distinguishing cancer drug policy from other things happening to patients."

Investigators found that the ADE reporting lacked key elements needed to make causality, including the reporting done for clinical trials.

Questions guide process

A validated causality assessment tool, such as the Naranjo instrument, which was used in the ADE study, could have helped with this process. For instance, researchers could ask these simple questions:

- Are there previous conclusive reports of this reaction?

• Did the occurrence of adverse events occur after the drug was administered?

"We were interested in looking at how cancer drugs were reported, and the simplest thing was to look at cancer drugs and clinical trials done at 49 National Cancer Institute-designated centers," Belknap says.

When researchers examined the adverse event reports that were submitted to the IRB, they found that the forms and instruments used to collect the AE data did not explicitly ask for information that would be useful to describe adverse events, he says.

"We had a panel of experts convene, and they came up with a set of 34 items of criteria that we consider essential for describing an adverse event," he explains. "The median number of items present on the forms at the centers was four and the most was 11, so very few of the items that were necessary were being requested."

To capture the important information, all 34 items were needed and a form would be the best way to do so, he adds.

"The next step is to take the 34 items and set up tools that would extract all those and get better methods for doing it," Belknap says.

"We did not publish an instrument that has been tested," Belknap says. "Our next step would be to take our results and the criteria we used to judge these forms and then create an instrument."

One reason for the inaccurate data regarding adverse events is that researchers will make it a priority to protect subjects by withdrawing them from trials after they've had an AE, but they pay less attention to documenting the AE, he notes.

"The patients often are managed correctly," he says. "But there's not as much attention paid to making sure we learn from these AEs."

This is unfortunate because with better AE information, investigators and sponsors could learn better strategies for protecting patients during treatment with toxic cancer medications, Belknap says.

"But the first thing to do is get high quality data to obtain these insights," he adds. "If you don't get the data then you won't have information that can be turned into practical information that people can use."

Another strategy that will elicit better quality data on AEs would be to have two experts review each adverse event and agree on its cause.

"I did another study that looked at all the patients who came into an emergency room at an academic medical center, and we described adverse events and got a very good agreement when we had two experts review each record," Belknap says. "We implemented a system for inpatients in the hospital, doing much the same thing, and this approach has general applicability and not just for cancer drugs."

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Using wireless bio monitoring in studies

Tool proves popular in obesity research

Investigators at the University of Southern California in Los Angeles, CA, have found an electronic solution to the problem of collecting accurate data about subjects' daily activities.

They developed the wireless network sensor solution to use in research involving preventing and treating obesity among minority youth. But it has a variety of potential applications, including being used in research involving rehabilitation patients or disabled people.

"It's a set of wireless network sensors that kids can wear," says **Donna Spruijt-Metz,** MFA, PhD, an associate professor in the department of preventive medicine at the Keck School of Medicine of USC.

The electronic device holds a great deal of potential for research, as well as clinical use. It has the potential of gathering greater amounts of information and more accurate data than self-report diaries and other types of automated devices. It also can be used as part of the intervention.

For instance, it can be programmed to provide automated alerts to subjects. These are in the form of text messages.

The youth wore an unobtrusive set of Bluetooth-enabled wireless sensors and carried a mobile phone. The sensors can detect motion and transmit their data to the mobile phone, which is GPS enabled.

Study subjects wear the bio monitoring device throughout their typical daily activities, and the

device sends immediate electronic feedback to researchers about how much and where subjects are moving around. This would make it possible to provide immediate interventions based on what is going on with the subject at any particular moment.

For instance, the device's data sent to a lab researcher who is monitoring it might indicate that the subject is walking by a fast food restaurant. The researcher could text the youth a message about how the restaurant's choices are unhealthy and counterproductive to the goal of losing weight.

In another example, the device could indicate that the youth has moved to a home near a park where he or she might benefit from a regular walking routine.

"Eventually, we'll be able to know where they are, and we'll monitor them on a website," Spruijt-Metz says. "We'll see that someone was sedentary for two straight hours, and we can call the person and tell him or her to get up and move around."

While researchers already can use small motion loggers that will store data about subjects' activities, these are less useful than a real-time wireless device, she notes.

"The small motion logger will store data, and when I come back to my lab I can download the data," she says. "But I might find that the person returns the motion logger and has not worn it."

Kids liked to wear it

Research subjects can turn off the wireless device too, but the 12 youths introduced to the technology in a recent pilot study liked it so much that they wore them frequently.

"The kids were responsive in an exciting way," Spruijt-Metz says. "We used the devices in a dry run to see if they would wear them and if we could deal with the monitors over a long distance and to see if the youths would change the batteries on time and receive the text messages all right."

Investigators found that everything worked very well, she adds.

They also obtained information about the subjects' lifestyles that has resulted in their changing the intervention goal.

"The youth were incredibly sedentary," she notes. "We were going to intervene by encouraging physical activity, but we changed our mind after seeing them sit around."

Now the intervention goal will be to have the youth engage in less sedentary behavior rather than pushing them to actively exercise, she adds.

Researchers also found that the youth were very engaged with using the electronic devices. They'd actively communicate with research staff throughout the day.

"One person said, 'I really like the texting back and forth,'" Spruijt-Metz says. "They'd text us nine times a day — it was like they had a doctor in their pocket."

The brief messages often were of the nature of saying, "Hi — I'm awake," or "I took it off because I'm going to play soccer," she explains.

"They keep us posted during the day," she adds. "These are kids with parents holding many jobs, and they like the attention."

Key questions

The trial run gathered information on the bio monitoring device's strengths and limitations, answering these kinds of questions:

— How well is the device working?

— What can and cannot be automated?

— How much work is it to monitor the subjects daily?

— What is possible with the device?

— To what extent does the intervention need to be personalized so that the messages that each subject receives relates particularly to that person's circumstances and activities ?

Investigators had plans to start the first intervention in November 2010. The first intervention will be a simple application of the device, using general text messages, such as telling subjects at 3 p.m. that it's time to exercise.

In future trials, researchers could personalize the device to give an intervention that is event-based, such as telling a subject who has been sedentary for hours to do something different, she says.

"If I know that every time you come home from school you pass a McDonald's and buy french fries, then I can text a message that says 'Don't do it,'" she adds.

These events are time-based and fit in with some researchers' goals of finding random moments for collecting data about subjects, she says.

The device has caught the attention of rehabilitation clinicians, who would like to apply it to physical therapy and other rehab activities. So it likely will be applicable to more than the obesity

and youth research, she says.

"We started development of the device out of my complete frustration with current technologies," she says. "Every kid has a mobile phone, so we started amassing a backlog of off-the-shelf monitors that are Bluetooth-enabled," she explains. "At the same time we were developing these patterns of recognition algorithms."

Then researchers recruited youths and their parents to participate in a trial that was designed to see how youths would use the devices. These subjects also performed various activities and exercises while wearing the devices so investigators could gather data on the monitors and use these to develop algorithms that would recognize patterns of behavior, Spruijt-Metz says.

"Then we did some qualitative work with kids to talk with them about wearing monitors and to find out what their parents thought about it," she adds. "Their parents also wanted to wear KNOWME, and that was interesting." ■

Not-for-cause audits can keep program on track

Discover trends early to fix system problems

Quality assessments can be a good strategy for finding compliance problems that otherwise would fly under the radar. These not-for-cause audits require some staffing resources, but if handled efficiently they uncover problematic trends and bad habits before an issue becomes serious.

For instance, a quality assessment found a student researcher who was running a small study's funding through a personal bank account. The student was unaware of the correct budgeting procedures, says **Susan Rose**, PhD, executive director of the office for protection of research subjects at the University of Southern California in Los Angeles, CA.

"This researcher was keeping careful records, but it's not okay to run a study like that," Rose says.

The assessment's findings gave the research office an opportunity to educate this budding researcher, as well as to improve communication and education for all new researchers about how to handle grant and other sponsor funds.

The research office now has changed its application form to ask if a researcher has funding, and if the answer is "no," then the form asks if there is funding that is pending. The communication needed to be made clearer because inexperienced investigators often would say they didn't have funding because the money was not yet in their hands, Rose adds.

Now the office has a clearer picture of who is doing funded research, and a "yes" answer can trigger additional communication and information about how to handle budgets and sponsor or grant money.

In another example, a quality assessment found that student investigators were using the wrong informed consent forms. They were supposed to use the form that had been corrected, approved, and stamped, and they were not using that one.

"The second time we saw the wrong informed consent form we knew we had a problem," Rose says. "That immediately identified a pattern."

They discovered that students were using the wrong forms because they couldn't find the correct ones when navigating the online system. So the research office fixed the online system and continues to refine its navigation and communication features.

"Now we have a direct link in the electronic approval letter, and it's much easier to find," Rose adds. "We made sure the source of approved documents is labeled and much more visible."

The quality assessments often result in some findings — large or small — that require a fix and process change.

For instance, the research office staff discovered that investigators misunderstood an application question pertaining to whether they had initiated a drug or device trial, Rose recalls.

"We had dozens of folks saying, 'Yes,' even to applications for studies funded by the National Institutes of Health (NIH)," she explains. "So we changed the language in the application so they now understand that even though they have the study, they're not the sponsor if they receive grant funding."

Each year the research office summarizes the findings and changes and communicates these to the research community. The office also publicizes the results of its annual survey that is sent to every investigator who has an active project.

"We let researchers know what fixes have happened from their comments on the survey and on

the audits," Rose says.

The quality assessments are performed 10 times a year by a continuous quality improvement (CQI) team that consists of one person who works in the IRB office and one person who works in the office for the protection of research subjects. There are limited funds for the role, so staff resources are pulled from other work, and the CQI team takes time each month to do one review, she explains.

"We spent a whole year learning how to do them and interviewing every auditor on campus, including the finance people, compliance staff, and others," Rose says. "We had two students who interned with us, and they both were from other countries where they had done audits previously, and we learned from them while they received credit for it."

Selection criteria

The research office established an outline, checklist and matrix for conducting the audits. Since the staff time is limited, they decided to have selection criteria for quality assessments, rather than to make these random. The selection criteria is as follows:

- Schools and/or departments that submit high volumes of studies to the IRBs;
- Investigators who have a high volume of active protocols;
- Investigator-initiated protocols;
- Studies including vulnerable subjects;
- Studies conducted outside of the United States.

"We ask people for suggestions of studies," Rose says. "We have one phone call a month with the whole team, including IRB directors, chairs, and our office, and we ask folks if there's anyone we should take a closer look at."

When a study is selected for an assessment, the CQI team writes to the principal investigator and requests that documents are made available.

"The team reads everything they can ahead of time," Rose says. "I want them to focus on the style of the PI's study conduct."

The CQI team also reviews the informed consent forms and privacy/HIPAA documents.

The quality assessment activities, according to the research department's policies and procedures, include the following:

- Interviews with the PI/research team to assess their knowledge of the study procedures;
- Obtaining feedback from researchers on the IRB process;
- Inspection of subjects meeting inclusion criteria;
- Records inspection and storage facilities;
- Inspecting documents and coding mechanisms used to protect confidentiality;
- Review of adverse events and unanticipated problems documents;
- Inspection of PI and researcher curriculum vitaes (CVs) and education certificates (human subjects, HIPAA, as applicable);
- Inspection of payment logs.

"The CQI team spends two to three hours on the review," Rose says. Then they write a report, which Rose edits. It includes items that need to be corrected, and it's sent to the PI.

"We might say we will have to come back or that we're available for education sessions and could help them stay on track," Rose says.

Education includes a list service and news bulletins in which regulatory and policy changes are posted.

The department also has held large educational sessions that were so well attended that $2,000 was spent on pizza, which was the incentive for attending, she notes.

One change resulting from the quality assessments involved more formalized education for faculty mentors of students who are engaging in human subjects research.

The faculty members who were not doing research themselves had objected to having to attend the educational sessions, but the research office informed them that they'd have to learn more about human subjects research since they were mentoring students engaged in those types of studies, Rose says.

"We also made a booklet for faculty advisors," she adds. ■

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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.

CNE/CME QUESTIONS

21. What year was the IRB system established by the U.S. Congress?
A. 1968
B. 1974
C. 1979
D. 1986

22. When creating a best practice, common framework for compliance standards, which of the following is an important question to ask?
A. What are the compliance goals you are trying to achieve in the office?
B. What are the ethical goals, apart from research regulations?
C. Which ethical and safety goals match the various compliance requirements and regulations?
D. All of the above

23. Recent studies have shown that reports of adverse events in clinical trials sometimes list a drug as the cause when a close review of documentation would have ruled this out. What simple question should investigators ask to prevent this type of mistake?
A. Did the adverse event occur after the drug was administered?
B. Did the drug cause similar symptoms in other study subjects?
C. Was the patient on placebo?
D. None of the above

24. California researchers recently developed a technological solution that can obtain more accurate data and be used in interventions in studies involving obese youth. What type of solution is this?
A. A motion logger with downloadable data storage
B. Bluetooth-enabled wireless sensors with motion detection and GPS-enabled
C. Mini wireless texting equipment
D. None of the above

Answers: 21. B; 22. D; 23. A; 24. B

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2010 Index

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