CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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IN THIS ISSUE

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Scientists, others hold out hope that Obama will fix the "broken pipeline"

New administration needs to raise NIH funding

America's scientific and research future has looked grim because of under-funding for the past five years, but it could turn around again under President Barack Obama's new administration.

At least that's the hope shared by research experts, including several of the authors of a report about America's "broken pipeline" in research.

Scientists have been giving testimony before Congress for more than a year about how flat-funding of the National Institutes of Health (NIH) has led to a crisis in the research community. At a March 11, 2008, meeting of the U.S. Senate Committee on Health, Education, Labor and Pensions, the nation's top research institutions released a report, titled, "A Broken Pipeline? Flat Funding of the NIH Puts a Generation of Science at Risk."

The flat funding follows on the heels of NIH's budget doubling between 1998 and 2003. This earlier financial increase had led to many biomedical improvements and new therapies, resulting in a host of medications being studied now in clinical trials, according to Senate testimony at the March meeting. **(See chart on funding facts of NIH, p. 16.)**

Since 2003, the funding has been eroded, and the opposite impact is being felt, researchers say.

"What distinguishes the current climate at NIH relative to other periods of tight spending historically is the length of time this has been going on," says **Larry S. Schlesinger**, MD, a professor of medicine and director of the Ohio State University (OSU) Center for Microbial Interface Biology in Columbus.

"This spending trend has had more impact over a longer period of time, and we're seeing more consequences as a result," Schlesinger says. "Young, outstanding scientists have now been in the business of trying to get a first grant for a protracted period, and this is clearly influencing their productivity and, most importantly, their confidence in going forward in their careers."

Research institutions have employed a variety of strategies to keep young researchers on track, but they're fighting an uphill battle,

Schlesinger says. **(See story on research morale, p. 17.)**

The big chill

The NIH spending crunch has had a chilling effect on bringing new physicians and scientists into the field of basic research, and it likely will have a long-term impact on clinical trial research, as well, Schlesinger and others say.

"In the current situation we're losing not only young investigators, but also established investigators," says **William Lawson**, MD, an assistant professor in the division of allergy, pulmonary, and critical care medicine at Vanderbilt University in Nashville, TN.

Lawson is a junior faculty member who received NIH funding through a mentor grant program, which is a grant that helps young investigators get started.

While he has made his start, Lawson says he's concerned about how many very talented young investigators are leaving the research field out of frustration over how long it is taking to receive NIH grants.

"Young investigators are getting out of research completely or are going into private practice or are pursuing industry-sponsored jobs where they are not necessarily doing investigational or discovery research," Lawson explains.

"The world's experts may weather the storm and survive the process, but it's the people who are trying to break through right now who are at real risk of being lost in the shuffle," Lawson says. "So 20 years from now when my group should be the world's experts, we may be looking at a much smaller group of people."

Potential young scientists are seeing their colleagues struggle to obtain NIH grant funding, and so many are saying "no" to research and going with the offers they receive in clinical work instead, notes **Pampee Young**, MD, PhD, an assistant professor in the department of pathology and medicine at Vanderbilt University.

Young also has received a grant from the NIH, but she says that time is running out for many of her colleagues.

When young researchers are hired as an assistant professor, they're given three years to establish a research program, and they're expected to bring in a lot of extramural funding in that three-year period, Young explains.

Young researchers will apply for NIH grants, but their applications are not as competitive as those submitted by senior researchers because they haven't had time to develop their research program, she adds.

"So these often do not get funded," Young says. "The funding rate at any one cycle is around 10%, so 90% of us won't get funded."

They resubmit a grant proposal after spending months working on it, and then again wait for an

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answer from the NIH, she says.

"You become increasingly anxious because your clock is running out," Young says.

"Many of my colleagues have passed this three-year window, and they're getting gift funds from the university," Young adds. "But they're given the message that they have a very short time to turn this situation around, or else they're out of a job."

The lost generation?

This is why NIH's flat funding has had such a devastating effect on a generation of young researchers and why its long-term impact will negatively affect clinical trial research, as well, the experts note.

"Basic science provides the pipeline for clinical science," Young says. "If you leave off basic discoveries, then clinical discoveries are based on trial and error, and clinical science won't be built on a true understanding."

The funding problems might be resolved under the Obama administration and a presumably more sympathetic congress. But experts are concerned about the timing of any requests for extra funding given the bad economy, banking and automotive company bailouts, and Obama's stated priority of focusing on investing in renewable energy.

"If you look at what Obama said, he wants to double NIH funding," Young says. "But nobody said where the money was going to come from, and the worry is there are so many pressing needs simultaneously that I don't know where we're going to be in the hierarchy of needs."

Young attended the Senate committee meeting, which was chaired by Sen. Edward Kennedy, and she believes the committee was very supportive.

"I think most people will understand that the kind of health care we get in our country, the kind of innovation we get in terms of health care progress are amazing, and we all benefit from that," Young says. "It's expensive, but it's just a matter of where our priorities are."

The new presidential administration and Congress should come up with a plan that will allow the NIH to grow in a reasonable fashion that mirrors the health care requirements of our population, Lawson suggests.

"So as this new administration looks at this they should keep in mind that we need a long-term strategy for the NIH and not a quick-fix strategy," Lawson says. "Research discoveries take time, and it takes time to develop a researcher and research career."

While Lawson and other researchers say they hope to see a change in NIH funding soon, they acknowledge the challenges in today's economic environment: "The new administration is inheriting a lot of things that require funding right now, and I hope NIH is kept on that list," Lawson says.

A matter of perspective

One argument in favor of increased NIH funding even during a difficult budget year is that NIH's budget for extramural research is quite small when put in perspective, Lawson notes.

"It costs less than $30 billion per year and comes out to $100 per person per year," Lawson says. "If health care costs several thousand per person per year, then there's a little gap there and it makes me think we need to emphasize research to develop improvements in health care."

If researchers are to make any progress in improving NIH funding, then it will happen only because they've made the case for why basic science is essential to America's biomedical agenda. **(See story on the case for encouraging breakthrough research, below.)**

"It starts with the leadership recognizing the importance of the biomedical agenda for America," Schlesinger says. "We're in a competitive world from the biomedical research perspective, and with new research consortia springing up all over the world, there are many opportunities for trainees and scientists to join them."

The United States has enjoyed a great tradition of biomedical research that is the envy of scientists around the world, he adds.

"So it's important that our leadership recognizes that biomedical research fuels future discoveries that help improve the human condition, and that's the mission of the NIH," Schlesinger says. "We need to retain our best and brightest and allow for academic institutions to have the resources they need to continue funding outstanding and dynamic academic programs." ■

Research grants can lead to incredible discoveries

Limiting their reach is counterproductive

Biomedical researchers, whether MDs or PhDs, share a love of the excitement of discovery,

and they work the long hours at limiting wages out of dedication toward finding something in their research that will help medical patients, a research expert says.

"When I was in residency, I thought I'd be a clinician, but in my fellowship I got hooked on research," says **William Lawson**, MD, an assistant professor at Vanderbilt University in Nashville, TN.

"I chose this area of study because of my frustration in taking care of patients with lung-scarring disease of idiopathic pulmonary fibrosis," Lawson says.

"There are no treatments that are effective in reversing the disease process, so the frustrations I had as a clinician drove me to select this area of research," Lawson says. "I hope that something I do in the lab will help me discover a cure or treatment for these patients, and this is what drives a lot of physicians and PhDs."

Another area where more research funding is needed is in finding antibiotics that work against drug-resistant organisms, Lawson says.

"If you look at one of the big concerns out there right now then it's how we're encountering more and more antibiotic-resistant organisms," he says. "So we're in dire need of breakthrough discoveries of antibiotics, and those are not coming."

It would dramatically change the face of medicine if someone made such a discovery, Lawson adds.

Unfortunately, the National Institutes of Health (NIH) has been under-funded since 2003, and tighter NIH grant funding has created an environment in which scientists are less willing to take chances on breakthrough research and are opting for safer and more predictable grant proposals, Lawson says.

"So we're not having people going out there searching for the novel aspect of something that could totally light up a new avenue that has never been thought of before," he says.

"We should as a research enterprise be funding breakthrough research so we can have the next big surprise," Lawson adds. "It's important to be feasible with things and fund projects that are the next step because they'll get us there, but sometimes it's the big breakthroughs that get us there faster."

Also, research discoveries take time and they require a long-term investment in researchers' careers, Lawson says.

"NIH does a tremendous job, but what has happened is that NIH has been handcuffed by decreased amounts of funding," he adds.

If the NIH funding trend isn't reversed, then the research pipeline will no longer flow with projects.

"We go from the bench to the bedside, and it's important to keep this pathway completely open," Lawson adds. "It's not uni-directional."

While most people assume that scientific discoveries are made at the bench and lead to bigger studies and eventually to clinical research, the process can work in the reverse direction, as well, he notes.

"Sometimes we see things at the clinical side that we take back to the bench to learn more about and then take back to the patient," Lawson says. "It's important to keep these lines completely open and flowing." ■

Dire documentation: NIH funding facts

Only 20% of grants ultimately funded

The U.S. Senate committee on Health, Education, Labor and Pensions held a hearing on March 11, 2008, that discussed how consecutive years of flat funding of the National Institutes of Health (NIH) have put a generation of science at risk.

According to testimony by **Drew Gilpin Faust**, Harvard University president, here are some of the ways the flat funding has damaged America's scientific environment:

- First-time recipients of NIH's premier research grant are older now than they were two decades ago. In 1990, the average age was 39 years old; now it's 43 years old.
- The success rate for one of these premier research grants is only 12% today upon a first submission; in 1999, the success rate was 29%.
- Even top scientists may have to submit a grant applications three times over a two-year period before they receiving grant funding that is substantially less than it was five years ago.
- When grants are rejected, research institutions downsize their labs, lay-off post-doctoral fellows, and the morale suffers, resulting in scientists shying away from the big research questions.
- In all, only 20% of grants will ultimately be funded.
- First-time investigators received 29% of premier NIH grants in 1990; today they receive 25% of those grants.

Research morale low among young researchers

Ripple effect continues through career track

Young, bright science and medical students who once knew that their purpose in life was to try to make the world a better place through study and investigation now question whether they should be following the research career track at all.

So academic research institutions are struggling with improving morale in a demoralizing era.

"Questions regarding the viability of careers in medical science are being raised more frequently," says **Larry S. Schlesinger**, MD, a professor of medicine and director of the Ohio State University (OSU) Center for Microbial Interface Biology in Columbus, OH. Schlesinger also is the director of the medical scientist program and of the division of infectious diseases.

"In the scientific community, we are communicating more about the importance of maintaining a positive attitude for the people we supervise so that we can at least sustain academic programs with the best morale as possible," Schlesinger says.

The current morale problem is related to flat funding at the National Institutes of Health (NIH) and increasing competition for fewer grants.

Plus scientific research is becoming more expensive with regard to maintaining buildings, performing cutting-edge platform technologies, and making discoveries, Schlesinger says.

"So it's getting more expensive to execute at a time when funding is tighter, and that puts more stress on the situation," he adds.

"We always talk about how a competitive scientific environment is good because it serves to weed out those who are less committed and allow those who have the most promising futures to rise to the top," Schlesinger says.

"But with persistent flat funding even our brightest young superstars are having trouble," he adds. "And this climate of flat funding has ripple effects that will continue for the next five to 10 years, and that's worrisome."

One of the effects is that some of the best and brightest are not entering biomedical research, Schlesinger says.

"Some of our brightest young students are not even going into research, and if you don't attract the best and brightest then you're already influencing the quality of your discipline, and that's frustrating to see," he explains.

"The second most severe effect is that some of our brightest graduate students now are opting for jobs rather than post-doctoral fellowships," he says. "They see that as a way to accelerate a movement toward stability in their job instead of having continued training where there's an uncertain future."

The problem is that many of these younger PhD and MD scientists have not yet discovered what they want to do with their career and when they opt-out of post-doctoral training, then they're closing some doors permanently, Schlesinger says.

"The post-doc gives scientists additional training and momentum in the form of more papers and grants makes a scientist viable for a faculty position at an academic institution," Schlesinger says. "So additional post-doctorate training is critical."

Then there's the problem of morale among those who do stay on the tenure track.

"There's really a morale and confidence issue," Schlesinger says. "The tenure track is a defined period of time, and one of the standard bars to pass is the acquisition of significant extramural funding."

The eroding NIH funding is impacting young scientists' movement toward tenure, he adds.

Ninety percent of a scientist's time is spent in systems development, which is working to improve assays to get a repeatable result, Schlesinger explains.

"Then 10% of the time is spent in the crank-out phase where your assays are working and you're getting a lot of data," he says.

"The execution of science is very labor intensive and often fraught with failure to begin with, so when the prospect of getting funding is very low, then one begins to question whether it is worth the effort," Schlesinger says.

This is making it increasingly difficult for research institutions to retain academic researchers, and it might lead to career disappointment among the people who pass on such a career, he notes.

"Say you've decided to go into industry at age 28, then it'd be a shame if five years later that individual is frustrated at a job in industry," Schlesinger says. "Then it'd be very hard to get

back into academics."

While increased NIH funding is crucial, there are some things academic research institutions can do to improve the situation, as well.

"First, we as scientists need to continue to look for ways to work together efficiently and effectively," Schlesinger says. "Intramural programs should be working hard on that concept."

Also, researchers should economize and share equipment, supplies, and other resources to be more effective and efficient, he adds.

"And I think we need to create the most positive environment that impacts our trainees and elevates the esprit de corps to enable our trainees to see the future," Schlesinger says. ■

Sift through ethical issues of subject recruitment

Expert offers advice

Clinical research sites and principal investigators should not wait for an IRB to weigh the ethical considerations of their subject recruitment practices. Everyone involved in human subjects research needs to consider whether a particular practice is appropriate or not, an expert suggests.

"I think what's most challenging is finding potential subjects who are willing to participate in a study and who also know what they're getting into," says **Lindsay McNair**, MD, MPH, senior medical director of clinical research at Vertex Pharmaceuticals Inc. in Cambridge, MA. McNair spoke about enhancing subject recruitment at the recent PRIM&R "Advancing Ethical Research Conference," held Nov. 17-19, 2008, in Orlando, FL.

"We need to make sure subjects are appropriately informed and understand that this is research," McNair says.

McNair has worked in all facets of research, including working as an investigator at an academic research institution, serving on the IRB at the Boston University Medical Center in Boston, MA, and working in the pharmaceutical industry for 10 years.

What she's learned is that CR volunteers have various levels of understanding depending on the particular disease being studied and other features.

"With some diseases, people are extremely well informed about their illness, and in some case they're not so well informed," McNair says.

"From the site's perspective, especially when there are new drugs in development, it's a hard thing for a research team to separate [doctors] wanting to get access to potential new therapies for their patients from the issue of conducting research and not knowing which new therapies will become available," McNair says.

Another problem for sites is the result of optimism about new studies.

"Often when a study starts out no one thinks they're going to have difficulties recruiting subjects until study recruitment is slowing down and measures are put into place to find more subjects," McNair says.

This means that sites need to vigilant in updating their recruitment activities in correspondence with the IRB, or else they risk falling out of compliance.

"IRBs don't always know that additional measures are added," McNair notes.

"So the question is how IRBs can make sure they know what's going on to recruit subjects and how sponsors can be educated about what IRBs find appropriate and inappropriate," she adds.

McNair offers these examples of inappropriate recruitment practices:

• Finder's fees: "Offering a financial amount for referral to a study and offering financial or tangible rewards to study teams that recruit more subjects or recruit above a certain number of subjects are what most sponsors realize are inappropriate," McNair says. "These create a conflict of interest for the study team, although not everyone thinks about it this way."

For instance, a sponsor might think that it would be a good incentive to offer sending a study coordinator to a research conference/meeting if the coordinator's study recruits 10 more patients, she suggests.

"To them that sounds like an appropriate incentive, but the IRB might consider that a conflict of interest," McNair says. "So it's not that the sponsor doesn't care about what's ethical, but it doesn't occur to them to think about it in that way."

• Sliding-up scale of payments per subjects: It's also inappropriate to pay sites according to the number of subjects enrolled in the trial, if that amount escalates after a certain level, McNair says.

"Say you offered $2000 for the first 10 subjects and $4000 for each subject above that -- that

would clearly be inappropriate," McNair says.

This is a recruitment practice that is clearly appropriate to use:

• Referrals without incentives: Study listings on standardized Web sites like clinicaltrials.gov are clearly appropriate, so long as they have IRB-approved wording. These types of recruitment practices do not have incentives tied to them, McNair says.

There are some ethical issues to consider with these types of recruitment postings, however, she notes.

Although clinicaltrials.gov is great for information about protocols, there are potential problems with how people might use it, McNair says.

"When you post inclusion/exclusion criteria, could a subject come to your site and lie about their history because they know the inclusion/exclusion criteria?" McNair says. "They might say, 'No, I never had an alcohol problem or seizure disorder,' because they saw that they would be excluded from the study if they have it."

Or potential subjects who screen fail at one site might go to another site listed on the Web site and not tell them how they had failed the other site's screening, she adds.

These are the kind of issues that IRBs and researchers should think about, McNair says.

For instance, they could abbreviate their study listings to not provide explicit inclusion/exclusion details, she adds.

"They could include enough information so that subjects will know if the study fits them but not enough information that they could fudge any part of their medical history," McNair explains.

And then there are sponsor recruitment methods that fall in a gray area:

• Charting recruitment progress: "Some sponsors put out newsletters with charts of who has enrolled the most patients and who has enrolled the fewest," McNair says. "Is that appropriate? Or does it create competition between sites, potentially creating a conflict of interest?"

For example, if the study coordinators all know each other, then creating a chart that lists top enrollers would create a competition and give public recognition to some sites, McNair explains.

Some people might say that this would be enough of an incentive for some study coordinators to create a conflict of interest in their motivations for enrolling subjects, she adds.

"Others might say the more people they enroll, the more recognition they should receive," McNair says. ■

One from the many: Honing multicenter clinical trials

IRB, post-grant work done

At least one research institution has found that a departmental research infrastructure is needed to make clinical trial (CT) research more efficient and feasible when multicenter CTs are involved.

The obstetrics and gynecology research network (OGRN) has a multicenter clinical trial group that includes seven different clinical trial networks that are funded by National Institutes of Health (NIH) grants and contracts.

"Most of them are being conducted at anywhere between five and 12 different hospitals that cross four health-care systems," says **Michael W. Varner**, MD, a professor of obstetrics and gynecology and vice-chair for research at the University of Utah School of Medicine in Salt Lake City, UT.

The OGRN is a consortium of more than 40 research personnel who administer obstetric and gynecologic clinical trial networks, including NIH-funded clinical trials in hospitals and more than 100 offices of women's health providers in northern Utah. It began 13 years ago with a staff of three, Varner says.

Running clinical trials related to obstetrics has some unique challenges, Varner notes.

"NIH has figured out that in order to have enough cases of any significant outcome and reasonable length of time, then they need to do multicenter clinical trials," Varner explains.

"There's also the fact that there is more and more required oversight compliance with various federal regulations," Varner says.

Having one office handle IRB work, subcontracting, time and effort reporting, and research activities has created a more efficient and effective process, he says.

The networks primarily receive funding by capitation: they receive a small base amount and then piece work pay reimbursement for each task, including screening, recruitment, enrolling subjects, and study completion, he says.

Tracking time and effort is complicated.

"The reality is that you have individuals working on multiple projects so there never is any down time," Varner explains.

This is what is hurting CR sites financially

because they have employees who are on a fixed salary, but the sites lack the ability to accurately track time and effort and move effort per individual employee from one protocol to the next, he says.

The OGRN subcontracts with sites and receives for its work a portion of the NIH funding, Varner says.

"We're at least breaking even, although it varies from year to year," Varner says. "The only reason that we are breaking even is because we have a cadre of experienced research personnel that can shift from one project to the next as we need them to."

The OGRN focuses more on post-grant administration than on writing grants, but there soon may be more emphasis on the latter, he notes.

"The reality is that administering grants is complicated and an expensive business that has to be done in order to be in compliance, and you have to have good people to do it," Varner says. "And they have to be compensated appropriately, which takes money."

The OGRN has two fulltime financial employees and two fulltime research administration employees, plus one person handling the IRB and compliance issues.

"We're looking to add a grant specialist," Varner says. "We sent in eight NIH grants last October, and we've been writing grants on the side, so we need to add somebody whose job is to identify funding sources and help us put together competitive grants."

Enrolling for the studies poses its own challenges, but having the consortium helps create some efficiency, says **Tonya K. Edvalson**, BS, CIP, research compliance manager of obstetrics and gynecology at the University of Utah School of Medicine. **(See story about enrollment strategies, right.)**

"Most of our hospitals don't have a dedicated clinic for obstetrics, so we rely a lot on community-based recruitment," Edvalson says.

"Our research personnel are going out to private practice facilities and enrolling from that patient base," she adds. "And we have a good relationship with clinicians in the community who allow us to recruit their patients."

The system is mostly electronic, but it's difficult to train research staff on all of its applications, Edvalson notes.

"Theoretically, they should be able to log in and pull up the information," she explains. "But it's complicated teaching them how to use it, so finding a better way to relay that information is one of my bigger challenges."

Edvalson sends emails to site research nurses and expects them to disseminate the information to their staffs.

"We have a nurse at each of five hospitals who is in charge of operations for that hospital and associated clinics," Varner says. "Some of our hospitals and some of our IRBs are not converted to the electronic world yet, and they're doing every application on paper." ■

Research network relies on shoe-leather recruiting

Being there is half the job

When clinical research sites need to recruit pregnant women, it can be a time-consuming and challenging task.

However, the Obstetrics and Gynecology Research Network (OGRN) of the University of Utah School of Medicine in Salt Lake City, UT, has found that the old-fashioned method of hitting the pavement and meeting repeatedly with referral sources works best.

"We go out in the community and establish relationships with physicians to show them what we can offer their patients if they were to enroll in our studies," says **Tonya K. Edvalson**, BS, CIP, research compliance manager of obstetrics and gynecology at the University of Utah School of Medicine.

Research nurses or assistants will visit a clinic and spend a day there, working with the clinic's staff to let them know which studies are enrolling and who might be a candidate for the study, says **Michael W. Varner**, MD, a professor of obstetrics and gynecology and vice-chair for research at the University of Utah School of Medicine in Salt Lake City, UT.

These visits need to accomplish two important goals: one, they inform the clinic staff and obtain some buy-in to finding potential subjects, and, two, they do not interfere with the clinic's workflow.

"The key is you can't slow down the clinic staff," Varner says.

"We let them know that their role is important," Edvalson says. "It takes a lot of work, space, and time to go out to the clinics, and we keep reinforcing and reminding our employees that they

cannot impact the workflow of the clinics."

It's also important that the recruitment person who visits a clinic is the same person each time, to build continuity and to reduce confusion, she notes.

"We want this to be the same person as much as possible for all the studies," Edvalson says. "We don't want to have one nurse from each study showing up."

By developing a long-term relationship with the clinic staff, the research nurse sometimes is offered a small corner of the office or a cubicle where she can speak with patients about the study, Edvalson explains.

"The clinic staff might say, 'This person has five minutes before Dr. Smith is coming in, do you want to talk with her?'" she adds.

In addition, the recruitment nurse leaves fliers in the offices for patients to review.

"The fliers are generic and talk about our studies in a snapshot way," Edvalson says. "We've gotten a lot of response from those."

The recruitment process is time-consuming and labor intensive, but it's also effective.

For instance, for one study, there might be one in 50% women who would meet the enrollment criteria, Varner says.

"So we'll screen 100-plus pregnant women a week between the different clinics," he says.

One point that helps with the referral sources' buy-in is that collaborating on a National Institutes of Health-funded research study is a prestigious enterprise, Varner notes.

Also, there's an educational incentive.

"One thing we've done is put on a continuing medical education program at no charge for the people who allow us into their offices and give us access to their patients," Varner says. "We bring food and do this as a token of appreciation for their allowing us to access their patients." ■

Software Solutions

Electronic system shows potential for CR site

CR field integrates with eIRB

Washington University School of Medicine (WUSM) in St. Louis, MO, is in pursuit of an efficient, integrated, and comprehensive electronic communication and information system for every step of the research process.

The institution is very close to a goal which could become a model for clinical research (CR) sites seeking an electronic solution to improve the CR process.

"We're still in the development process of a clinical studies management system (CSMS) that was started in February, 2007," says **Sara Kukuljan**, BS, RN, CCRC, director, Center for Applied Research Sciences at WUSM.

"We initially pursued this for billing compliance needs," Kukuljan says. "We are co-developing with Johns Hopkins University, who had started this project two years earlier with mdlogix."

The project which is being developed with Medical Decision Logic Inc. is still under development, and pilot groups have recently been selected, she adds.

"This system will integrate with other systems at the university, including the eIRB and the financial system, the hospital, and physicians," Kukuljan says. "The system will be used for clinical studies, and it will help the investigator manage the study from the start to the finish."

Included in the system are modules involving subject recruitment with a database of research volunteers; a subject and protocol registry that has study demographics; subject screening and informed consent information; protocol schema and patient calendar, which has a detailed protocol schedule of events and research volunteers' scheduling calendar, and case report forms, including electronic forms that can be integrated with clinical result systems.

Here are some examples of how the system will be integrated with various CR functions:

• Financial module: When investigators and the CR site are trying to decide the feasibility of a protocol, the financial module will make this an easier process.

"The principal investigator (PI) can build out the protocol's schedule of events, and the system automatically will build out the budget," Kukuljan explains.

"We've loaded the system with chargemasters and research pricing and all procedures, including over 14,000 CPT codes," she adds. "So PIs don't have to call individual departments for pricing."

The system has forced everyone involved in research to agree on prices and it puts all of the

financial figures in one place, she says.

Once the financial module provides a PI with pricing information for a particular protocol, the PI can decide whether the protocol will be financially feasible, Kukuljan says.

If the answer is "yes," then it's time to move to the next step in the process.

• eIRB: PIs will be able to submit IRB applications electronically, and, eventually, the CSMS and eIRB systems will be linked, Kukuljan says.

When investigators move between the CSMS and eIRB systems, they will have to populate the data fields only once because the other system will pull up the information as it's needed, she explains.

"We've recently joined forces to get the CSMS and eIRB projects moving forward because we'll have such close interactions within the two systems," Kukuljan says. "They're working parallel with each other."

• Electronic applications for all review bodies: The eIRB is a Smartform, which is a term coined by Click Commerce to describe their application that can consolidate several different forms into one form with several sections and "branch submitters" to the applicable sections.

Washington University in St. Louis (WUSTL) developed a "hide/show" feature that shows applicable questions within a Smartform section, based on previously answered questions, says **Diane Clemens**, DC, CIP, an eIRB education specialist at WUSTL.

"Combined, these two technologies can significantly reduce the length of an IRB application," Clemens notes.

"There are trigger questions for all 34 ancillary bodies at the university," Clemens says. "If investigators indicate they'll do research in a neonatal intensive care unit, then that will trigger an application to be sent to the NICU review body."

This way, PIs can complete one eIRB application and all of their review applications will be automatically generated and routed to the appropriate boards, she adds.

Investigators, IRB members, and others in research acknowledge that the new electronic systems will be a great benefit to the research process and will save PIs and IRBs time, Kukuljan and Clemens say.

"PIs are thrilled with the concept of it, but like many of us, they don't like change," Clemens notes.

As the system's construction continues and a roll-out is planned for later this year, the CR institution is developing a communication and training plan, Kukuljan says.

"There will be different phases of training," Kukuljan says. "This type of system will impact everyone's workflow, so we'll have to go to each department and discuss this with them."

The training will be based on these discussions and each department's particular workflow, she adds.

"It probably will be a year-long process, and we'll also have a continual type of training process," Kukuljan says. ■

Protecting suicidal teens in research a daunting task

Participants bring special risks, but research is vital

Research with adolescents who are at risk for suicide can create daunting ethical and practical challenges for investigators. But a researcher who has been working with suicidal teenagers for 20 years says it's possible to craft protocols that protect them as much as possible while still providing valuable data. And she notes that the need for such research is vital: Suicide is the third most prevalent cause of death among youths ages 13-19.[1]

Cheryl King, PhD, ABPP, chief psychologist in the Department of Psychiatry at the University of Michigan in Ann Arbor, says dealings with her IRB over the years have been relatively untroubled.

The key, she says, is communication between the IRB and investigator, especially when a protocol involves unusual issues or particularly vulnerable subjects. In fact, she recommends that the investigator be present at the IRB meeting to answer questions and explain details in those instances.

"I recommend a chance for that back-and-forth discussion," King says, noting it saves a lot of time that otherwise would be spent sending written notes back and forth.

One important point for IRBs, King says, is that they understand the teens being sought for these studies, and the inherent risks they bring with them. She says an IRB may look at a suicide intervention protocol as too risky when it's not the intervention that carries risks, but the subjects themselves.

"They're at risk because of their condition," she says. "We know that multiple suicide

attempters are at higher risk than others for suicide and if someone has made a suicide attempt, they're at higher risk than someone who has only thought about it."

King says researchers "An outcome study on what happens to those youth over the next five to 10 years is very relevant to understanding the cohort," she says. "IRB members should understand what we expect as outcomes and try to differentiate between what is anticipated or expected and what is unanticipated or unexpected."

King routinely in her field now list suicidality and potential suicide attempts as an anticipated outcome in informed consent documents, based on long-term outcome studies of teens at high risk. King routinely uses a data safety monitoring board, even though her minimal risk studies generally don't require them. "I think between the IRB and the data safety monitoring board, we have a collaborative effort going to be sure that we're balancing scientific rigor with protections for the subjects."

Meet the parents

A common issue in research with suicidal teenagers is the relationship between those teens and their parents or guardians, who must give consent. Everyone must understand and approve the youth's participation. Usually, King says, she approaches the parents first, and then meets with the teen either with his parents or separately, depending upon the circumstances. Disagreements over whether the teen should participate aren't common, but make up "a significant minority," she says.

"Emotionality is often high if a youth has just been psychiatrically hospitalized and they really don't want to be," she says. She says that while the parent has initial veto power, it should be clear to everyone involved that the youth has the final say. King says there may be unusual situations where it may be necessary to bypass parental consent — when the parents are suspected of abuse or when the child is homeless, for example. Those are the cases where she suggests an investigator should meet with an IRB in person. Other points for IRBs to keep in mind, include knowing the limits to confidentiality, she says.

Often, King says, her investigators must end up revealing something a teen has said, usually having to do with harm to the youth or someone else. She says it's essential that the limits of confidentiality be spelled out clearly in the informed consent.

"You don't want a big breach of trust," she says. "They need to know up front when they sign that if we have serious concerns about any safety issue, including self-harm, that we will let someone know who can take care of it."

Reference

1. King, CA, Kramer AC. Intervention research with youths at elevated risk for suicide: meeting the ethical and regulatory challenges of informed consent and assent. *Suicide Life Threat Behav.* 2008 Oct;38(5):486-97. ■

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

- ■ Avoid common CR mistakes
- ■ Use PDSA to improve site performance
- ■ Here are tools for managing specimen repositories
- ■ Learn how the consent conference model works
- ■ Improve communications with research families

CNE/CME*questions*

5. According to "The Broken Pipeline" report, flat-funding for the National Institutes of Health (NIH) has resulted in which of the following problems?
   A. First-time recipients of NIH's premier research grant had an average age in 1990 of 39; now the average age is 43 years
   B. The success rate for a premier research grant by NIH is only 12% today upon a first submission; in 1999, the success rate was 29%
   C. In all, only 20% of NIH grant applications will ultimately be funded
   D. All of the above

6. Which of the following was cited as an example of inappropriate subject recruitment practices:
   A. finder's fees
   B. referrals without incentives
   C. sliding-up scale of payments per subjects
   D. A and C

7. The Obstetrics and Gynecology Research Network (OGRN) of the University of Utah School of Medicine in Salt Lake City, UT, has found that which of the following recruitment methods works best?
   A. Having a research nurse visit clinics and wait there to discuss studies and possibly screen research subjects
   B. Advertising in local parenting publications
   C. Sending emails to local obstetricians discussing the available studies and inclusion/exclusion criteria
   D. All of the above

8. Which of the following modules is included in clinical studies management system (CSMS) being implemented by Washington University School of Medicine (WUSM) in St. Louis, MO?
   A. Research subject and protocol registry
   B. Subject screening and informed consent information
   C. Protocol schema and patient calendar
   D. All of the above

Answers: 5. D; 6. D; 7. A; 8. D.