CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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IN THIS ISSUE

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Special Report: Rare disease network drives trial innovations

[Editor's note: This issue of Clinical Trials Administrator *features the first part of a special report about how, according to the clinical trials industry, the Rare Diseases Clinical Research Network, sponsored by the National Institutes of Health (NIH), has resulted in enhancing new practices in clinical trial research, including collaborations among investigators and patient advocacy groups, mentoring new investigators and sites, and developing a national data center. Look for more stories about the network in the May 2007 issue.]*

NIH grant creates opportunities and supports new trial practices

Investigators say program was crucial to research

The clinical trials industry has reaped a variety of benefits from the federally-funded Rare Diseases Clinical Research Network (RDCRN), including the creation of dynamic partnerships between investigators and patients/advocates, according to **Charles Strange**, MD, a professor of pulmonary and critical care medicine at the Medical University of South Carolina in Charleston. "The network has been a very positive experience."

Research resulting from the consortium of rare disease investigators will contribute to general medical practice as well, experts say.

The National Institutes of Health (NIH) gave $71 million in funding over a five-year period to a central data and technology coordinating center and 10 research consortia to investigate rare diseases. Among the consortia are vasculitis, neurologic channelopathies, lung disease, thrombotic disease, genetic diseases of mucociliary clearance, bone marrow failure disease, urea cycle disorders, and Angelman, Rett, & Prader-Willi syndrome.

"One thing that has happened at NIH historically is rare diseases sometimes are not funded at the same level as more common diseases," Strange says. "But what comes out of rare disease research is you learn many basic mechanisms by which more common diseases can be manipulated."

For example, Strange's work is with the lung disease consortium, which is studying lymphangioleiomyomatosis, pulmonary alveolar proteinosis,

familial pulmonary fibrosis, and Alpha-1 Antitrypsin Deficiency, a hereditary condition that can result in serious lung disease.

"If you can understand the pathway genesis of Alpha-1, it can be expanded to more common diseases, such as emphysema and chronic obstructive pulmonary disease (COPD)," Strange says. "It will likely have the same public health impact as studying more common diseases."

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Editorial Questions

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Call **Leslie Hamlin** at (404) 262-5416.

Many of the researchers who have been awarded grants through the RDCRN have had a longstanding interest in the disorders they're studying, says **Steve Skinner**, MD, a senior clinical geneticist and associate director of the Greenwood Genetic Center in Greenwood, SC. Skinner also is the director of clinical services and studies Rett syndrome and Angelman's syndrome.

"The concept behind the network is that these are rare diseases that any one investigator or institution won't have a large volume of patients to enroll in a study," Skinner says. "So the network allows them to pull together and collaborate to have the largest number of patients."

Collaboration in the network also improves cooperation and sharing of ideas, Skinner adds.

"In the two studies I'm involved in, you get a chance to meet face-to-face and have frequent telephone conversations with other investigators," Skinner says. "It opens doors for sharing resources and sharing laboratory techniques and capabilities, and that makes it easier and natural to share things across institutional boundaries."

For some of the rare diseases, the network and NIH funding was the only way the research would take place.

"We could not have done this project without the RDCRN network — it's been critical," says **Richard J. Barohn**, MD, chair and professor of the department of neurology at the University of Kansas Medical Center in Kansas City, KS.

Barohn is conducting research within the neurologic channelopathies consortium, specifically studying Andersen-Tawil Syndrome (ATS) and nondystrophic myotonias (NDM).

"These are a rare group of genetic disorders, usually with autosomal dominance, and they pass from one generation to another," Barohn explains.

Patients' symptoms of NDM include muscle cramps, stiffness, and an inability to relax when the muscles contract, he says.

"A lot of people have cramps, but we don't all have sodium chloride genetic defects," he says.

Patients who are suspected of having melatonin disorders, a sodium channel defect, or a chloride channel defect are the ones who are included in the longitudinal pheno/genotype study, Barohn says.

"We're trying to analyze these patients, obtain a detailed family history, and perform detailed and rigorous series of neurophysiological tests at each of the sites," he says.

"We're trying to understand what is going on

in the muscles of these patients, and we're looking at the various muscle pathology, based on stimulating muscles with electric shocks and collecting that data," Barohn explains. "Based on what we find, the tests will tell us the story about these patients."

The research has been enhanced through the network and collaboration with peers.

"You learn a lot by talking with other investigators in completely different fields," Barohn says. "We go to meetings with all of the investigators, and it's interesting to see what other groups are doing with their rare disease — we sort of feed off of each other."

For these reasons and for the many other benefits that have come out of the RDCRN, investigators who received the first round of grants say they hope NIH will renew the grant when it comes up next year.

"We feel that in Rett syndrome we've been very productive and competitive and should be refunded," says **Alan K. Percy**, MD, professor in pediatrics, neurology, neurobiology, and genetics, and associate director of the Civitan International Research Center at the University of Alabama at Birmingham. Percy, who also is the medical director of the Sparks Clinics in Birmingham, studies Rett syndrome, and in 1983 was one of the first physicians in the United States to recognize Rett syndrome. **(See story about how network and NIH funded grants have benefited study of Rett syndrome, p. 41.)**

Rett syndrome researchers would like to collect at least 10 years of data in the natural history study, and patients weren't enrolled until about a year ago, Percy says.

"We were among the first to enroll patients, and we are far and away ahead in terms of overall numbers, but we would say it's critical that we continue this study for at least another nine years," Percy adds.

"The impression we've gotten is that NIH is committed to continuing this project," Skinner says. "I would imagine they would look at the different activities that have happened so far and make sure the money has been well-spent, maybe shifting and changing some sites."

The funding for rare disease research has long been needed, says **Thomas P. Loughran, Jr**, MD, director of Penn State Cancer Institute, and professor of medicine at the Penn State College of Medicine in Hershey, PA.

Loughran is involved with the bone marrow failure disease consortium and has phase 1 and 2 clinical trials underway.

"I've been contacting the Office of Rare Diseases on and off throughout my career to see if there were any funding opportunities," Loughran says.

While the first couple years of the five-year grants were spent building the ground work for the network, everyone has been pleased with the progress made, Loughran notes.

"Any time there's an actual funding source, it helps quite a bit with resources being kind of constrained these days," Loughran says.

The RDCRN grant has helped investigators do a better job starting clinical trials and building databases and registries, Loughran says.

"For LGL leukemia, I had already established a registry for that disease and rolled it into a bigger program," Loughran explains. "We were working in the lab before this grant was started, and we developed new drugs that might kill LGL cells in the lab, so that work preceded the founding of the funding stream."

Once the network was established and funding was made available, researchers could move more easily to clinical trials.

"The advantage of the consortium, from an accrual point of view, is that these diseases are rare, and so it's helpful to have a network that could guarantee certain numbers of these patients in the study," Loughran says.

Another advantage of the network is access to the data coordinating center, which is located in Tampa, FL, at Moffitt Cancer Center, Percy says.

"We collect massive amounts of data that would not be possible for us to manage with the limited resources we have," Percy says. "We can dump all the data into this data management system, and they're responsible for maintaining it."

Each site is responsible for its own data quality and analysis, but they have the advantage of using technology developed at the data coordinating center, he adds.

Sites also participate in meetings with other investigators and research staff in their particular consortia.

"The network has created a small community of like-minded individuals, and we've been very fortunate to have very good colleagues across the country and the world to expand our appreciation of this rare disorder," Percy says.

The RDCRN steering committee's representatives from each disease in the consortium meet twice a year and have conference calls on a more frequent basis, Percy says.

"This allows us to get some perspective against a broad group of disorders," he says. "And the data managers and clinic managers also have formed their own group." ■

Efficiencies resulting from rare disease network

Patients 'phone in' answers to questions

Researchers studying rare diseases have disadvantages in obtaining data that some have learned how to turn into assets.

For example, patients with rare diseases are difficult to study geographically because the numbers needed for a study's enrollment are too challenging for any one site to accrue, even in large cities.

So when several sites are working together to accrue a desired number of patients, there needs to be ways to bridge the geographical challenges.

Clinical trial sites involved in the National Institutes of Health's Rare Diseases Clinical Research Network (RDCRN) have found and developed innovative ways of meeting this challenge.

For example, the neurologic channelopathies consortium has been using a novel way to collect data on patients' symptoms.

"We're doing it over time, using an interactive voice response (IVR) call-in system," says **Richard J. Barohn**, MD, chair and professor of the department of neurology at the University of Kansas Medical Center in Kansas City, KS.

Barohn is the principal investigator of the nondystrophic myotonias (NDM) group.

"Patients who enter into the study are instructed on how to call in on the IVR system every week for several months," Barohn says. "There's a telephone prompt device, and they're asked on a scale of zero to nine how much weakness they had this week."

Other questions include how much stiffness, pain, and fatigue they've experienced, he adds.

"That's never been done before in this series of disorders," Barohn says. "We show that with the IVR responses, the patient calls each week are very consistent."

Barohn and co-investigators will present information about this at the American Academy of Neurology meeting, held April 28 to May 5, 2007, in Boston.

The group will demonstrate how useful the phone data is, he adds.

"It sounds low-tech, but despite the fancy neurologic stuff we do, this method appears to be the most reliable way of following patients' symptoms over time," Barohn notes.

Another goal of the neurologic channelopathies group is to develop therapeutic trials in hopes of developing new therapies for muscle pain and stiffness, Barohn says.

"And we're working on those now," he says. "We've submitted to the FDA to study a drug that may reduce muscle stiffness and pain."

The IVR method of collecting data will continue to be used throughout the three-year trial, assuming funding comes through, Barohn says.

"We'd have two years of background IVR data before we go into actual treatment," Barohn explains. "In the treatment trial, we'll use new IVR data from patients put on the drug or a placebo, and every week they will call in for four weeks, and then they'll be flipped, and those on the active drug will go on the placebo."

This way, researchers hope to learn whether the drug works.

The RDCRN funding paid for the groundwork research that was necessary before investigators could reach the point of designing a therapeutic trial, Barohn notes.

"We're hoping RDCRN gets refunded, and our site is refunded," he says. "It's conceivable that if there is another round of funding to our site, we might be able to do the trial without additional funds — but you can never bank on it, so we're actively pursuing grant funding from additional sources."

The bone marrow failure disease consortium's clinical research also has advanced as a result of the network.

Investigators have conducted clinical trials involving a potential treatment for large granular lymphocyte (LGL) leukemia, which is a very rare form of leukemia, says **Thomas P. Loughran, Jr**, MD, director of Penn State Cancer Institute, and professor of medicine at the Penn State College of Medicine in Hershey, PA.

"We've identified a certain biological molecular pathway that the study drug Zarnestra turns off," Loughran explains. "In the lab, all LGL cells are readily killed by medicine."

The network enabled investigators to more quickly enroll patients in the first phase of the study, which tested seven patients with the rare disease to see what the toxicity and side effects

were in using the study drug, he says.

"Soon after the protocol was activated, for example, we had four patients at the Moffitt Cancer Center in Tampa, FL, and we had three from here go on the protocol right away," Loughran says. "So we enrolled our first seven patients very quickly for a rare disease."

Zarnestra, the drug's trade name, showed some definite biological activity in terms of killing the LGL cells in patients, Loughran says.

"The bone marrows improved, but there wasn't a definite response in terms of improving the actual blood counts," he adds. "So we're trying to figure out whether we go to a second phase of it which calls for increasing the dose of medicine or whether we change it and continue with the current dose." ■

Research, treatment benefit from NIH grant and network

Rett syndrome research offers good example

Many patients and families coping with a rare disease are offered some hope in the long term because of the research generated in the Rare Diseases Clinical Research Network (RDCRN), which was launched in 2002 by the National Institutes of Health (NIH) and $71 million in funding awards.

One rare disease called Rett syndrome is believed to affect between 5,000 and 20,000 girls in the United States. The NIH-funded research that is underway holds hope for both greater understanding of the disease process and potential treatments down the road.

Investigators studying the disease describe its impact on patients and how their research might improve the lives of patients and families:

• **Characterizing Rett syndrome:** Rett syndrome is a neurodevelopment disorder that predominantly affects females, says **Steve Skinner**, MD, a senior clinical geneticist and associate director of the Greenwood Genetic Center in Greenwood, SC. Skinner also is the director of clinical services, and studies Rett syndrome and Angelman's syndrome.

"Basically, these girls are normal at birth and have a period of normal development for the first six to 18 months of life, and then they start to have regression and lose skills they did have," he explains. "Then there's a period of stabilization, and most of these girls have no or very little verbal communication or speech."

Boys born with the syndrome typically have a more severe form of it and do not survive into the second year of life, says **Alan K. Percy**, MD, professor in pediatrics, neurology, neurobiology, and genetics, and associate director of the Civitan International Research Center at the University of Alabama at Birmingham. In 1983, Percy was one of the first physicians in the United States to recognize Rett syndrome.

People with Rett syndrome communicate through eye gazing, and they have significant motor and balance problems. One characteristic of the syndrome is stereotypic hand mannerisms in which the girls engage in repetitive activities such as ringing, clapping, posturing, Skinner says.

"They have a fairly normal lifespan, but frequently have feeding and growth issues," he says. "Many are small in stature, with small heads, small hands and feet."

From age four to eight years, the girls will become more attentive and interactive and may be able to use special communication techniques, such as using computer switches to indicate choices, Percy says.

• **How it can be treated currently:** There is no treatment for those afflicted, but recent research in the United Kingdom has shown that, in mice, it is possible to correct the genetic defect, even late in the disease process, causing a reversal of genetic problems, Skinner says.

"That gives hope to families," he says. "Previously with neurological disorders we felt you had to intervene and treat early before you lost development during the critical periods of development."

• **Research to achieve better understanding of disease:** The Rett syndrome group has enrolled 500 patients at three institutions, and the goal is to enroll 1,000 patients in a natural history study, Skinner says.

"To do that, we've teamed up with the Universal Rett Syndrome Association," he adds.

Since Rett syndrome has not been long recognized, its long-term course and predicted survival have yet to be studied, and that's what the natural history study will accomplish, Percy says.

"We're in the process right now of wrapping up data entry for survival studies so we can give information to families of what they can expect in terms of longevity," Percy explains. "That has

major implications for long-term therapeutic interventions."

For instance, if Rett syndrome is a short-term disorder, then public schools might not be interested in assisting families with educating these patients. But if it's a long-term disorder, then the schools might provide long-term interventions, Percy explains.

• **Other goals of research into Rett syndrome:** Research focusing on common mutations in the disease might help explain the relationships between specific individuals and their severity of illness, Percy says.

"We have some idea of which mutation provides more mild involvement and which produces more severe involvement, and this information will guide clinicians in treatment," he says.

Some of the growth data collected in the research will lead to the development of growth charts, Percy says.

"The model we're using could be adapted to develop similar growth curves for other disorders, such as for Down's syndrome, for example," Percy says. "It does help to know where a child with a given disorder fits in with the general disorder in the population."

Also, girls with Rett syndrome have a higher rate of fracture, and their bones are very thin, Percy notes.

"One investigator is actively pursuing this and is finding that treatment giving more calcium by mouth could be generalized to other disorders," Percy says.

For example, many girls with Rett syndrome have surgery for scoliosis, so this research could provide some outcomes for a range of disorders, he adds.

"And then because some of the work emerging out of the laboratory with animal models suggests that certain behaviors associated with Rett syndrome could be treated with existing medications, these girls are very anxious and fearful, and we're looking at the possibility of treating them with anti-anxiety medications to see if these improve their behavior and their ability to interact with other individuals," Percy says.

• **A quality of life measurement as substudy:** "A quality-of-life measurement for Rett syndrome families hasn't been done on any large level in the United States, but we're assessing and measuring the quality of life of caregivers and caregivers' perceptions of quality of life for their daughter," says **Jane Lane**, RN, BSN, a research nurse manager at Civitan International Research Center. Lane works with Percy in the study of Rett syndrome.

"There are no measurements or tools specific for Rett syndrome, so we piloted a general childhood health questionnaire about diseases for children and applied these to our group of girls and women," Lane says.

"We think that will have interesting data," Lane notes. "We've spearheaded that substudy, also."

Since there had been no previous measurement of life quality for Rett syndrome, investigators worried that girls with the disease would bottom out on some of the questions, Lane says.

But the pilot study showed that the questionnaire could be used and answers would vary enough to be informative, she adds. ■

Compliance Corner

More efficient systems improve site compliance

Make sure change of scope is understood

Research sites need to document their contract negotiating positions in policies and then give staff the authority to act on their own within those guidelines, states **Kris Rhodes**, MS, CRA, director of grants administration for Wake Forest University Health Sciences of Winston-Salem, NC.

"Ensure you have clear internal documentation on what you preferred position is and what secondary and tertiary positions are and clearly state what the deal breakers are," advises Rhodes. Rhodes was scheduled to speak about the legal fundamentals of sponsored research at the Society of Research Administrators (SRA), North Carolina Chapter, conference held March 5-7, 2007, in Cary, NC.

"Make sure your staff is aware and trained on those positions," Rhodes adds. "When employees move beyond those guidelines, that's when they need to seek input from management."

Sponsored research units should stay in close coordination with the legal department, Rhodes says.

"Legal can be an asset and can push sponsors on intractable issues," Rhodes says.

"For example, if they feel very strong about indemnification language in relation to a particular study, or if the funds are flowing from one organization to the other, I think legal can help push the need to get all the parties together," she explains. "For most of the work I've done, I haven't had to have a lot of legal input, but occasionally it helps."

Rhodes also offers these tips:

• Understand different challenges of individual studies.

"If it's a phase 1 or phase 2 study, the intellectual property is different than if it's a phase 3 study," Rhodes says.

Also, the challenges with billing to Medicare versus the research sponsor are critical to many institutions, she says.

"Unfortunately, it's somewhat subjective still," Rhodes says. "Is it medically necessary? Is it part of the study? It's the billing issues that place institutions at significant risk when those costs are billed to Medicare."

• Improve staff training.

Institutions should provide good training to study coordinators as a best practice in compliance, Rhodes says.

"We spend a lot of time focusing on compliance at study start-up, but the real challenge for compliance is balancing it with study administration and all of the other obligations study coordinators have," she adds.

"Organizations that have good study coordinator training are going to be in the best position for compliance," Rhodes says.

• Use best available billing system.

"I also think organizations that have solid systems in place that can help with billing decisions are going to be in a better place than those that have weaker systems," Rhodes says.

"Unfortunately, I haven't seen much in the way of commercially available billing systems that take a lot of subjectiveness out of the decision-making process," she adds. "It's something we need, but I haven't seen a really solid system that helps with this."

While there are systems that help to ensure clinical trial billing is taken care of and that costs are allocated to the correct study, most of these systems are focused on billing, she notes.

So it's up to research sites to make certain the budget is well-developed and that staff understand how to distribute budgets appropriately, Rhodes says.

At Wake Forest University, there is a study Excel spreadsheet for budgets that outlines items, she notes.

"But the challenge still remains," Rhodes says. "Would this be provided under standard of care or would it benefit the study? What if it falls under standard of care but still benefits the study and should be a study cost?"

• Rely on systems to run reports.

"I'm a big systems person," Rhodes says. "I like to rely on systems to run reports, do tests, and check proposal commitments against actual contributions."

It's wise to enter as much data into the system from the front end as possible, Rhodes says.

"There is some risk to this strategy," she notes. "The more data you maintain, and if you are maintaining and not checking it, your risk is heightened."

• Check effort reporting.

"In terms of grant administration, we focus on effort deviation," Rhodes says. "We also have to work with our progress report certification, and we're submitting progress reports to the National Institutes of Health (NIH)."

For example, these questions must be answered:

- Has there been a change in effort for key personnel?
- Has the site extended funds as originally projected or is there a carryover greater than 25%?
- Is the site reporting on key personnel for the past reporting period?
- Does the reporting match what was said in the prior reporting period?
- Are there any deviations to address?

• Look for changes in scope.

Sites receiving grants should link grant proposals to the protocol, looking at end points, variation in charges, and changes in scope, Rhodes says. **(See NIH guidance on change of scope, p. 44.)**

All sponsors want the opportunity to approve any change in scope prior to it being implemented, Rhodes notes.

Changes in scope can be sticky issues.

For example, if a site would like to use a significant new piece of equipment that was not in the original projection, then these questions should be answered and documented:

NIH offers this guidance about change in scope

Here's what feds say

The National Institutes of Health (NIH) offers this information about change in scope, via the NIH Grants Policy Statement:

Change in Scope. In general, the principal investigator may make changes in the methodology, approach, and other aspects of the project objectives. However, the grantee must obtain prior approval from the NIH awarding office for a change in the direction, type of research or training, or other areas that constitute a significant change from the aims, objectives, or purposes of the approved project (hereafter "change in scope"). The grantee must make the initial determination of the significance of a change and should consult with the GMO as necessary. Actions likely to be considered a change in scope and, therefore, requiring NIH awarding office prior approval include, but are not limited to, the following:

• Change in the specific aims approved at the time of the award.

• Substitution of one animal model for another.

• Any change from the approved use of animals or human subjects.

• Shift of the research emphasis from one disease area to another.

• A clinical hold by the FDA under a study involving an IND or an IDE.

• Application of a new technology (e.g., changing assays from those approved to a different type of assay).

• Transfer of the performance of substantive programmatic work to a third party through a consortium agreement, by contract, or by any other means. If the third party is a foreign component, this type of action always requires NIH prior approval.

• Change in key personnel. (see "Change in Status, Including Absence of Principal Investigator and Other Key Personnel" for requirements for NIH approval of alternate arrangements for or replacement of key personnel).

• Significant rebudgeting, whether or not the particular expenditure(s) require prior approval. Significant rebudgeting occurs when expenditures in a single direct cost budget category, deviate (increase or decrease) from the categorical commitment level established for the budget period by more than 25% of the total costs awarded. For example, if the award budget for total costs is $200,000, any rebudgeting that would result in an increase or decrease of more than $50,000 in a budget category is considered "significant rebudgeting." The base used for determining significant rebudgeting excludes the effects of prior-year carryover balances but includes competing and non-competing supplements.

• Incurrence of research patient care costs, if costs in that category were not previously approved by NIH, or if a grantee desires to rebudget additional funds beyond those approved into or rebudget funds out of the research patient care category.

• Purchase of a unit of equipment exceeding $25,000. ■

[For more information about the NIH guidance, visit the Web site at the Office of Extramural Research web site at http://grants2.nih.gov/grants/OER.htm.]

- How will equipment acquisition not adversely impact data continuity?

- How will equipment not result in a change in the original scope of work or specific aims?

- How, based on the original scope of work, is the equipment necessary and reasonable for continuing the project?

"If the new equipment is a replacement piece, I assume it's not a change in technique, but it can impact continuity," Rhodes says.

If the equipment is a completely new technology that wasn't anticipated, but now is necessary, then Rhodes will ask even more questions, including this one: "Is this moving us outside what we originally proposed to capture and report on, and if it is, is that a change in scope?"

Other changes in scope may include rebudgets for subcontractors and investigator departures and additions.

"If we have an investigator who is moving to another institution, we have to get prior approval for that investigator's absence," Rhodes says. "We have to carry out the same work, but if we find someone who can take our data to another step, then that can be a change in scope."

Sometimes the best action is to change a study, and it's necessary to receive approval for the change from the program officer, she notes.

"Getting approval for a change in a study is

directly related to an individual's relationship with the program officer," Rhodes says. "It's important to have a good working relationship."

The request is best handled by first calling the program officer and then following it up by having the program officer review the request prior to official submission to ensure clarity and consistency of the written request with the program officer's expectations based on the informal phone conversation, Rhodes says.

"There needs to be a one-on-one discussion, and it doesn't need to be in person," Rhodes says. "But the phone conversation does need to discuss how the study is changing, what direction the investigator would like to take, and whether this is appropriate."

If the conversation doesn't take place and the support is not there for the change at the program level, then the investigator is going to receive a response asking for more details, and this back-and-forth can go on several times, Rhodes explains.

"If the questions and answers are taken care of before the first official piece of documentation goes to the sponsor, then you're in a much better position of getting it approved," Rhodes says. "And the sponsor has some paper trail that it's a reasonable request." ■

Sponsors, others trying new trial methodology

This could soon be a trend

Clinical trial sites may soon see more studies with adaptive designs, reflecting the industry's movement toward a more efficient clinical trial process and a growing trend of treatments targeted to specific groups and populations.

While there are a variety of ways clinical trial methodology can be made more flexible and adaptive, one definition is as follows: "Basically, what it means is you have upfront defined criteria of how you monitor the trial, and based on emerging data from the trial, you modify it to the duration of the trial, size of trial and, possibly, to the importance of end points," says **P. K. Tandon**, PhD, a senior vice president of BioMedical Operations for Genzyme Corporation in Cambridge, MA.

Tandon is scheduled to offer a half-day tutorial on the subject on June 16, 2007. His lecture, titled, "The Scientific and Economic Benefits of Flexible Adaptive Trial Methodology Designed to Achieve Early Registration and Robust Results: Raptiva and Fabrazyme as Case Studies," is part of the 43rd Annual Meeting of Drug Information Association (DIA), which will be held June 17-21, 2007, in Atlanta.

The way the adaptive methodology works could be of significant benefit in a phase II clinical trial, for example, Tandon says.

"In a phase II trial setting there are some diseases where you don't know what the primary end point should be," Tandon explains. "And when looking at the data it might say that 'This end point is not working, but this one is working.'"

Biologically this might make sense, and a researcher could use that new end point as some kind of inference-based decision, Tandon says.

"But your trial is basically important for learning how to interpret the data," he adds. "This could be used in designing future studies."

The same flexibility could be applied to finding the best dose during a phase II trial, Tandon says.

In the typical drug development scenario, investigators will complete the trial and have a negative outcome, which could result in the sponsor abandoning the intervention or starting over with something new, Tandon says.

"But the beauty of flexibility and adaptive design is there is still some hope for the product," he says. "We can use existing data to understand what is going on in some diseases."

One example can be found in biomarkers. "We may be looking at biomarkers where it turns out that a particular biomarker is not really doing what you hope for," Tandon says.

"Sometimes what happens is the patient population used for that phase II study is showing something different than what you expected," Tandon says.

Or maybe the sponsor underestimated or overestimated the efficacy of a particular drug, he notes.

Designing clinical trials with flexibility and adaptability built-in could help improve investigators' and sponsors' understanding of the drug and disease, especially in certain patient populations, Tandon says.

"At the same time you want to be very careful and acquire pretty sophisticated timing and methodology," he adds.

"In phase II settings, you can see how some patients of a decent number are really behaving

differently [with treatment], although the overall results are not that impressive," Tandon says. "But maybe this one patient population we can go after and start recruiting more patients in this particular subgroup."

Since mid-2005 when the Food and Drug Administration (FDA) approved the drug hydralazine/isosorbide dinitrate (BiDil), which treats heart failure, as the first drug ever approved for one specific ethnic group, the door was opened for targeted medicine and treatment.

Hydralazine/isosorbide dinitrate was approved by the FDA on June 23, 2005, for use in African Americans.

There were 2 clinical trials of hydralazine/isosorbide dinitrate among the general population, and these found no benefit from the drug, an FDA media release says.

The FDA-approved hydralazine/isosorbide dinitrate is based on results from the African-American Heart Failure Trial (A-HeFT), which involved 1050 self-identified black patients with severe heart failure who had already been treated with the best available therapy.

Black patients in the A-HeFT study had a 43% reduction in death and a 39% decrease in hospitalization for heart failure when compared with placebo, the FDA notice says.

Although targeted treatments are possible, they'll continue to be challenging to study because of the regulatory requirements, Tandon notes.

"One has to be careful in changing a trial that is ongoing because you need IRB approval; you have to change the case report forms," he says. "It's not easy — not a slam dunk."

It requires very careful planning in the same way as a football game strategy, Tandon says.

"You have a plan A, B, and C," he adds.

Nonetheless, adaptive methodology is catching on and could become a trend because of the financial pressures inherent in drug development, Tandon says.

"If you can make a decision faster, then it benefits the scientific community and companies," he says.

To do it right requires a strong investigative team, including statisticians who are very careful, Tandon says.

"The consequences are very severe because it could be that you killed a product that is very good, or it could be you say a product works well, but down the road you find that you had a false positive," Tandon explains. "You need to make sure you have the right methodology and that appropriate caution is taken into account." ■

Improve project management by following best practices

Key: smart budgeting that captures all

Clinical trial sites can develop solid relationships with sponsors and improve their accuracy with study budgets if they put in the up-front work and time, an expert says.

When a pharmaceutical company contacts you, it's important to obtain as much background about the study as possible and then do the research necessary to make certain you have the necessary patient population, says **Joanne M. Chilton**, BS, CCRP, clinical research associate with SUNY Upstate Medical University, bone marrow transplant program, in Syracuse, NY.

"If it's a study we're not going to accrue patients for, then we say, 'We don't have a patient population, so there's no sense in our participating in this and wasting everyone's time,'" Chilton says.

If the study will work and the clinical trial agreement is signed, then the sponsor will send a feasibility questionnaire to the site, and this will be completed by Chilton and investigators, she says.

"No agreement is fully signed off until the budget and everything is agreed upon," Chilton notes. "If the budget is a lot of work then there's no sense in doing the study."

With about 18 years of experience, Chilton has a pretty good idea about what items should be captured in a budget and how to make sure nothing is forgotten.

"We look at the clinical research forms (CRFs) that will need to be filled out to see how time-consuming they'll be and what the reimbursement is," Chilton says. "If they're detailed and time-consuming, then we make sure appropriate budget is there for each visit."

Chilton's other budgeting tips include these:

- Add in the cost of storing records in a secure area for the required time;
- Check with other departments to determine which procedures are standard of care and which are not, and then make certain an accurate price is in the budget for the procedures that will be billed to the study;
- Put in a facility fee for study participant visits;
- Use current, standard prices when possible,

and have these mapped out in advance by having each department keep a fee list;

• Include pharmacy storage and drug preparation fees;

• Add in an upfront fee for the physician investigator's and clinical research associate's time;

"I try to be as complete as possible in the budget," Chilton says. "Then if the sponsor does balk at some items, we have to go back and renegotiate."

Most sponsors don't have a problem dealing with a thorough and accurate budget, she notes.

Once a site's budget is complete, it should be reviewed by the institution's legal department, and then it's sent to the sponsor, Chilton says.

Some sites will save time by working on the budget at the same time other steps are being taken, such as submitting a protocol for IRB approval, she says.

While the IRB process can take a couple of months, Chilton typically works with a contact person in the IRB office to make certain all of the documents are in place and all questions are answered.

Next, after the clinical trial agreement is signed, the sponsor might want to perform a site initiation visit to see the answers to these questions:

• Where will samples be stored?

• Is this a good facility to work with?

• Is this a secure facility?

"Then once you come back with an IRB approval, and you do a study start-up visit, the next step is to meet with staff and train them on the pertinent details of the protocol," Chilton says.

It's also important to develop a good relationship with the site monitor, and this is why it's important to have a consistent monitor, Chilton says.

"It's really tough when monitors keep changing," she adds. "So if you can continue to talk with the same people, it makes the work flow much easier."

Chilton often will comment to the monitor at the first visit, "We hope we'll see you again."

Sometimes the monitors don't know whether they'll be the person returning to the site, but often they'll try to be consistent, she adds.

Another tip for dealing with monitors is to maintain contact with them and call them back in a reasonable amount of time, Chilton suggests.

"If I have any questions, I'll go to the monitor first before going to the company because they're the person you're supposed to go to," she adds.

"Monitors would much rather have the phone calls than to have something go drastically wrong," Chilton says. "So you need to keep that line of communication open."

When something unplanned happens in a study, it's important to document it and let the site monitor and sponsor know what has happened, Chilton says.

"If you have a deviation, contact the company right away and say, 'We're sorry this happened,'" she says.

For example, the weather might be bad and a participant could not make it to the site for a scheduled visit, Chilton says.

"It's not a big deal, but you should document why this little deviation happened," she adds.

It's essential to keep up on the documentation to avoid the appearance of problems or violations, she notes.

"The monitor will come in and go through charts, making sure that what's on case report forms matches what's documented, and if there are any deviations, the monitor will look at the notes about these," Chilton explains.

If a site has missed an item, then the monitor will ask about it and the sponsor will send the site a data clarification form.

"So you will go back through the chart and see how to clarify what they're asking for and see if there's documentation for clarifying it," Chilton says. "We have a doctor/investigator review all data clarification forms and sign off on them before they're sent back to the company."

Once a study closes to new patients and there are no more follow-ups to be done, then the monitor will return, collect all data, and do a study close-out visit to make certain the site's regulatory binder and the sponsor's regulatory binder match with updates on all IRB correspondence and serious adverse event (SAE) reports, she explains.

"If the study is permanently closed and there will be no more follow-up, then that's the last visit with the monitor," Chilton says. "You've looked at all the patient case report forms and all data questions are answered."

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Then the sponsor will tell the site how long to store the information, and that is the end of it.

Except, this also is a good time to look for more studies, Chilton suggests.

"At this point you might say, 'If you have another study you think we'd be interested in, we'd be very happy to take a look at it and see if we have the patient population for it,'" she says. "Or you might say, 'Keep us in mind if something comes up with regard to this disease area."

The best way to develop a good, long-term relationship with a sponsor is to produce good studies with minimal violations and deviations, Chilton says.

But it's also important to stay in contact with the company. When a site is approached about a study that won't work with its patient population, it's important for clinical trial administrators to let the sponsor know the site is still interested in working with the sponsor, even if the site is unable to do a certain study at that moment, she says. ■

CE/CME *questions*

11. One of the diseases being studied as part of the National Institutes of Health's Rare Diseases Clinical Research Network is Rett syndrome. Which of the following is not a characteristic of Rett syndrome?
A. The infants are normal at birth and have normal development for the first six to 18 months of life and then they start to have regression and lose skills.
B. It is a neurodevelopment disorder that predominantly affects females.
C. It results in large heads, feet, and hands.
D. People with Rett syndrome have significant motor and balance problems.

12. According to NIH guidance, which of the following is an action likely to be considered a change in scope in a research project and will require NIH awarding office prior approval?
A. Change in the specific aims approved at the time of the award.
B. Any change from the approved use of animals or human subjects.
C. Shift of the research emphasis from one disease area to another.
D. All of the above

13. One advantage of using a flexible and adaptable clinical trial design is which of the following?
A. It is easier to do with regard to timing and methodology.
B. It could help improve investigators' and sponsors' understanding of the drug and disease, especially in certain patient populations.
C. It is already being done extensively in Europe and Asia.
D. All of the above

14. Which of the following would be good study budgeting tips?
A. Add in the cost of storing records in a secure area for the required time.
B. Use current, standard prices, when possible and have these mapped out in advance by having each department keep a fee list.
C. Put in a facility fee for study participant visits.
D. All of the above

Answers: 11. (c); 12. (d); 13. (b); 14. (d)