CLINICAL TRIALS
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An essential resource for managers of clinical trials

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Personalized immunotherapy research leads to more complex clinical trials

It looks at ways to boost patient's immune system

A new approach to personalized medicine is resulting in phase I and phase II clinical trials that rely on extensive, hands-on investigator and clinical research (CR) staff training, and these types of studies are creating both new challenges and opportunities for North American CR sites.

Personalized medicine, including gene therapy, is the wave of the future, says **Anthony T. Dren**, PhD, a consulting professor with the Duke University School of Medicine in Durham, NC. "This is an evolving trend that I think is a very worthwhile approach," Dren says.

The advantage to the personalized immunotherapy or medicine approach is that it should minimize immune reactions since the person is being given a product derived from their own body's cells, Dren notes.

Three clinical trials involving personalized immunotherapy are underway for the testing of new treatments for HIV and cancer. Sponsored by Argos Therapeutics of Durham, NC, the trials involve a much more complex process than the typical therapeutic trial, says **Rafick-Pierre Sékaly**, PhD, a professor in the department of microbiology and immunology, and a Canadian research chair in human immunology at the Université de Montréal in Quebec, Canada. Sékaly is studying the personalized immunotherapy approach in HIV patients.

"It's not like you are just injecting a drug that you're testing," Sékaly says.

This personalized medicine approach follows a trend of the past decade, as investigators and physicians try to find improved and less toxic ways of treating patients through treatment that is geared to the particular landscapes of a patient's own body.

"Personalized medicine is here, and it's just going to become more prevalent," says **Jeffrey Abbey**, MBA, JD, vice president of business development for Argos Therapeutics.

"There are a number of different ways to go about personalized medicine, and a lot of research is looking at it from a genetics perspective," Abbey says.

Clinicians who treat or investigate autoimmunity increasingly are using personalized therapies to treat diabetes and other diseases, Sékaly says.

"I was involved in another protocol involving multiple sclerosis

patients where they were depleted of their whole immune system and were reconstituted with a whole new system, using their own stem cells," Sékaly adds. "And that has been a very promising approach."

Eventually, clinical research into personalized therapies will evolve, but the challenge for clinicians and investigators is to make it a simpler process, he says.

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Editorial Questions

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"Personalized therapies aimed at the immune system will be the way to go," Sékaly says. "It will increasingly enter into the mold of regular therapies." Abbey agrees.

"We believe the best way to help these patients is by helping the patient's immune system to act the way it's supposed to act," Abbey says. "One of the huge advantages of these kinds of approaches is that they have very good safety profiles."

For both cancer and HIV drugs, the existing treatments have multiple side effects, but the early trials with the immunotherapy approach have not shown adverse events to be a significant problem, Abbey adds.

For instance, the process may result in a side effect from the injection of the drug, including some itching and minor discomfort, and it may result in flu-like symptoms with mild temperatures, but that's been about the extent of the adverse events discovered so far, says **Lothar Finke**, MD, chief medical officer and vice president, regulatory affairs, for Argos.

The type of procedures involved in the trials is complex and must be followed precisely, so there are challenges to both participants and investigators. **(See story about how trials are handled, p. 51.)**

For instance, participants have to spend roughly half a day during the collection of their blood cells, and then there are five or six infusions of the vaccine product, Sékaly says.

"One of the biggest difficulties is ensuring that patients will not miss work or be penalized for missing work," Sékaly notes. "So we have tried to adapt the hours and process so it can be the least invasive to their schedule."

For example, the HIV clinical trial will schedule participants in the early morning or late afternoon, whichever is more convenient for them, he adds.

Investigators have to use a process called leukapheresis to harvest about eight billion white blood cells, which are a source of dendritic cells, without putting patients in an anemic state, Sékaly says.

"When we first told the IRB we were going to collect 10 billion white blood cells in HIV patients, we raised eyebrows," Sékaly recalls. "But when a patient undergoes this process, within the next 24 hours his white blood cells might dip slightly but, after 48 hours, everything goes back to normal."

Investigators had to convince IRB members that the process was safe, and it helped that they had safety information from the earlier cancer immunotherapy trials, he adds.

The HIV personalized immunotherapy trial is the first of its kind within the realm of HIV infection, Sékaly says.

"To my mind, as an immunologist, it makes a lot of sense, but for other people it's a concept that is completely new to them," Sékaly says.

Although CR in personalized immunotherapy is difficult for investigators to schedule and is time consuming for participants, if it's proven successful in the HIV trials, it could become an emblem of success in personalized medical research, Sékaly says.

Another challenge in personalized immunotherapy will be the move to phase III trials, which may benefit from different trial designs and methodologies than what is employed by most phase III clinical trials.

Immunotherapy studies tend not to be neat fits with the Kaplan-Meier curve, Finke says.

"What happens with the treatment, very often, is below the 50% mark and is a so-called late effect," Finke says.

"In conventional study designs, whatever happens after the median mark is not recognized at all, so the statistics might ignore [positive results] completely," he explains.

There exists different approaches, including a statistical algorithm that recognizes the fact that chemotherapy and immunotherapy act differently, and so you have to apply different statistics to the conventional Kaplan-Meier methodology in order to account for that delay, Finke says.

If the phase II trials show strong positive data, then there will be momentum to carry the research to phase III trials, and these sorts of challenges will be overcome, Finke and Abbey say. ■

Personalized immunotherapy clinical trials in practice

Hands-on training is crucial

As the medical industry increasingly moves toward personalized medicine, there will be challenges for clinical trial sites that adapt to these types of studies.

Experts offer the example of the personalized immunotherapy studies underway for the treatment of cancer and HIV to show how it works.

Below is a nutshell look at personalized immunotherapy in three trials:

A closed-system centrifugation process separates red cells and part of the white blood cells from the monocytes, leaving behind a monocyte-enriched cell preparation, while the other blood ingredients are recirculated into the patient's circulatory system, explains **Lothar Finke**, MD, chief medical officer and vice president, regulatory affairs, for Argos Therapeutics of Durham, NC, which is sponsoring three CTs involving a personalized immunotherapy approach.

Trial participants stay on a leukapheresis machine for nearly four hours while their white blood cells are collected for retrieval of dendritic cells. Patients are monitored in a hospital setting, Sékaly says.

So far, the three trials, including the latest one with HIV patients, have not had any unanticipated problems, says **Rafick-Pierre Sékaly**, PhD, a professor in the department of microbiology and immunology and a Canada research chair in human immunology at the Université de Montréal in Quebec, Canada. Sékaly is studying the personalized immunotherapy approach in HIV patients.

Once the white blood cells are collected, they are carefully labeled and sent to Argos' laboratory in Durham, where they are prepared as a presentation platform for the generation of the patient's individualized anti-viral therapy, which is ultimately filled into vials, frozen, and shipped one by one for every single treatment visit, to the sites, Finke says.

"The fresh cells have to be shipped to us in a very controlled process because these cells are alive, and need to stay alive, and then we culture them into dendritic cells," Finke says.

"We use RNA from the virus or the tumor, which has been amplified previously, so that we can basically take a small sample of RNA virus and make lots of RNA identical to the patient's original material," Finke explains. "Then we put the two together by a process called electroporation, which applies an electric current that gets the RNA into it."

The antigens are expressed under dendritic cells, processed, and then the dendritic cells present these virus- and tumor-specific antigens to the patient's immune system, Finke says.

Further lab work results in a cryopreserved vial that is shipped back to the clinical trial site, one at a time, where it is injected into the patient's skin, Finke adds.

The hopes are that the process will encourage the patient's T-cells to generate memory of the virus or tumor and create more T-cells that can attack the diseased cells, in effect boosting the patient's immune system with his or her own recharged dendritic blood cells, Finke says.

1. The sponsor is cautious when selecting CR sites.

"We are concentrating on sites and physicians who are advocates of, and versed in, immunotherapy," Finke says. "Usually these people have a background in immunotherapy or immunology of cancer and are much more familiar with the procedures that we require than the usual oncologist or urologic surgeon.

Another important prerequisite is that the site has a leukapheresis unit, Finke notes.

"We need to have sites that have good access to that resource," he says.

Sites need to be able to follow relatively strict scheduling and logistics systems to align with manufacturing and treatment shipments, Finke adds.

The first trial included a site that didn't have a leukapheresis unit, so CR staff used a unit at a Red Cross site about 35 minutes away, says **Jeffrey Abbey**, MBA, JD, vice president of business development for Argos Therapeutics.

This site is no longer a part of the research, and all current sites have their own units, Abbey adds.

2. Site training is hands-on and extensive.

In the planning process of the protocol, clinical sites are usually involved in generating details of the protocols, Finke notes.

Once the trials are underway, all sites, and especially new sites unfamiliar with the processes, are visited by an entire team to provide the necessary training.

The training meeting covers the shipment logistics and other information, including these details:

- How do you get the drug?
- What does the container look like?
- How do you unpack the container?
- How is the product injected?
- How does one pack a tumor specimen?
- Where do the Gel packs go?
- Where is the temperature recorder?
- How do you order a pick-up and delivery for Argos?

This training session will take an entire day and include a dry run of the process, and it's required that everyone involved in any part of the clinical trial attend the meeting, Finke says.

The hands-on training has staff use all of the very same materials they would use during the clinical trial. For instance, there are gel packs, temperature recorders, etc.

While the typical investigator meeting might be attended by the principal investigator and one or two other people from the CR site, these meetings must be attended by everyone who touches any component of the research, Finke says.

"Sometimes site training takes additional attention, and we have to go through the process again" Finke notes. "But people are enthusiastic and very dedicated, so the training is falling on fertile ground."

Any CR investigator or coordinator who has questions during the trial will be able to reach someone who can help them, he says.

"We've shipped almost 200 samples now, and with one exception, we haven't had any systematic problems," Finke says.

3. Extra attention is paid to identifying and matching material.

"We put a unique identifier system in place that consists of a drug designator, site, and patient number, and samples are made completely anonymous," Finke says. "There are a lot of structures in place to make sure there is no mixing of samples, and that's something the FDA is very concerned about."

Each time there's a change in the trial, it's discussed with the FDA, he adds.

The material sometimes is identified through bar codes, and sometimes there are two people in place to make sure that one compares the number on the vial with the paperwork, which is checked by the other person, Finke explains. ■

Special Report: Network drives trial innovations

[Editor's note: The remaining articles in this issue of Clinical Trials Administrator *are the second part of a special report about how 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 improving data collection. The first part of the series was included in the April 2007 issue.]*

Network encourages close ties to patients

Organizations help with recruitment, study questions

Investigators working in a rare disease field often find that it's an uphill climb to recruit participants, obtain funding, and interest peers in the work.

Now, thanks to the work of the Rare Diseases Clinical Research Network (RDCRN), which is sponsored by the National Institutes of Health (NIH), some of these hurdles have become a little easier to jump.

For example, the RDCRN has helped with patient recruitment by encouraging clinical research sites and patient advocacy groups to work together to promote interest and funding for research.

"When it's clinical research in osteoporosis or hypertension, the recruitment is vastly different than it is in a rare disease," says **Brendan Lee**, MD, PhD, an investigator with the Howard Hughes Medical Institute and a professor in the department of molecular and human genetics at Baylor College of Medicine in Houston, TX. Lee studies urea cycle disorders as part of the network.

"But at the same time, we've found in our region some very motivated families," Lee says. "They are eager to help."

The families have assisted with a web site about the disorder and have supported a patient registry, Lee says.

"Interaction with families, and a partnership with them, is critical," Lee notes. "We work very closely with the primary family support organization, the National Urea Cycle Foundation."

Lee and other investigators describe how they have collaborated with patients, foundations, and families:

• **Rett Syndrome:**

Investigators studying Rett Syndrome, which primarily impacts girls, developed satellite clinics across the country, in conjunction with the International Rett Syndrome Association (IRSA) of Clinton, MD, says **Jane Lane**, RN, BSN, a research nurse manager at the Civitan International Research Center at the University of Alabama, Birmingham.

"The two major centers for Rett Syndrome are in Houston, TX, and here in Birmingham, AL, so we had no problem in drawing patients from south of the Mason-Dixon line," Lane says. "But it's more difficult for families in other regions of the country."

Parents and family members of Rett Syndrome children have been very motivated to assist researchers, says **Alan K. Percy**, MD, professor in pediatrics, neurology, neurobiology, and genetics and associate director of the Civitan International Research Center and medical director of the Sparks Clinic at the University of Alabama.

"We have a very strong working relationship with the International Rett Syndrome Association, and I became scientific director with the association a year ago in January," Percy says.

In order to increase enrollment in Rett Syndrome clinical trials, investigators developed the novel strategy of bringing clinics to various regions of the country, he adds.

Investigators in the rare diseases network worked with the IRSA to establish satellite clinics for the purpose of increasing clinical research enrollment, but also to educate young physicians, therapists, and nurses about Rett Syndrome, in hopes they would start a Rett Syndrome clinic in their area, Lane explains.

For instance, one clinic was established two years ago in Oakland, CA, and it was named the Katie Clinic in honor of a Rett Syndrome patient. Its medical support comes from Oakland Children's Hospital, and the patient's family has been instrumental in supporting the clinic, Lane says.

"In New Jersey, there's a similar clinic in the works, but it's not established yet," Lane says.

The Katie Clinic is full service and provides all ancillary health and therapeutic services, Lane says.

The satellite clinics are held on weekends, and there are close to 70 patients enrolled and seen for follow-up every six months in various locations across the country, Lane says.

The clinic teams consist of physicians, nurses, genetic counselors, and nutritionists, she adds.

"We hope we will have between 75 and 100 children at each clinic," Percy says.

• **Urea cycle disorders:**

Urea cycle disorder organizations are very well organized and have helped investigators with recruitment, Lee notes.

Also, representatives of family support organizations participate at RDCRN teleconferences and meetings, he says.

Urea cycle disorders are a group of genetic conditions that affect the body's ability to handle nitrogen, mostly from protein food intake, but also nitrogen created within the body, Lee explains.

"Patients with urea cycle disorders have a block in the enzymatic and transporter proteins that affect the ability to convert this nitrogen into urea," Lee says. "The excess nitrogen travels around as ammonia, and it can lead to coma and death."

One thing researchers are learning from the network involvement is that many patients present later in life in a nonclassical fashion, he notes.

"The classical presentation is often a newborn who becomes comatose, develops seizures, and dies, often with the diagnosis of Reye syndrome," Lee says.

Recent research suggests that patients sometimes have partial blockage in their ability to convert nitrogen from protein, and they could be asymptomatic clinically until following a stress event, such as eating too much protein or a viral illness, Lee explains.

Collaboration with patients, families and advocacy groups has been very helpful, he says.

"I'm a pediatrician and a geneticist, and I think we have more to learn from families than we do from each other," Lee says. "It's how families present with their own clinical problems that points us in the direction we need to take in research."

For example, in one urea cycle protocol, investigators became aware that patients were having significant liver disease, Lee explains.

Some patients had pediatric hypertension, and while the evidence was all anecdotal, it encouraged researchers to ask whether the excess argininosuccinic acid being made in patients with this specific urea cycle problem was toxic to the liver, Lee says.

"We give patients amino acids to make more precursors to get rid of the nitrogen that builds up in their bodies, and we think it's very effective," Lee says. "But we wondered whether the treatment itself could have the unwanted side effect of impacting the liver by making more of this acid."

Since patients raised questions about the liver disease, researchers were able to address this issue with possible research projects, he says.

• **Angelman, Rett & Prader-Willi Syndromes:**

Other researchers involved in the rare diseases network noted ways patients and families have impacted their research and, occasionally, even study design.

For example, investigators working in the Angelman, Rett & Prader-Willi Syndrome Consortium have discovered new areas of investigation because of the input from families, says **Steve Skinner**, MD, a senior clinical geneticist and associate director, and director of clinical services at the Greenwood Genetic Center in Greenwood, SC.

"I think it's important to have families involved in designing research," Skinner says. "The trials are going to benefit them and help them."

While researchers have a scientific interest in the rare diseases, the families live with the conditions and know what's most important to their own lives, he notes.

"They're also very powerful advocates for fundraising, awareness, and political organization," Skinner says. "They can do a lot more than we can as individual investigators, so it's a very good partnership."

Rett Syndrome families convinced researchers to investigate the seemingly high incidence of gall bladder disease among young patients, Skinner says.

"We didn't know about this until families pointed it out to us, and so we did an incidence study and confirmed it," he says.

While basic science and animal studies are very important, one of the goals of the NIH is to do translational research from basic science to what will benefit patients, Skinner says.

"One of the NIH's goals with these grants is to do something that will benefit patients and their lives," Skinner explains. "So we're starting out with natural history studies because many of these diseases don't have a good baseline of what is the norm and what you can expect to see developmentally, as well as what problems you can expect."

Once these natural histories are complete, investigators will design an intervention trial to see if they can make a difference in patients' lives through better quality of life or survival rates, he adds.

• **Lung Diseases:**

The Lung Disease Consortium has worked closely with the Alpha-1 Foundation of Miami, FL, which is named after the disease of Alpha-1 Antitrypsin Deficiency, says **Charlie Strange**, MD, professor of pulmonary and critical care medicine at the Medical University of South Carolina in Charleston.

"The Alpha-1 Foundation has set up significant infrastructure to support research and run the Alpha-1 registry of more than 3,000 individuals," Strange says.

All 3,000 people have agreed to be involved in research if the right protocol comes their way.

"In this way, new drugs and new therapies that may have had a hard time enrolling patients with a rare disease have an almost instant way of enrolling people," Strange explains. "We can enroll a clinical trial in a heartbeat, and there are significant advantages to come to the FDA with a shorter review time."

The Alpha-1 Foundation has also set up an infrastructure of clinical resource centers, as well as a DNA and tissue bank. When a new patient is diagnosed, they are invited to donate blood/tissue to the DNA tissue bank, Strange says.

Alpha-1 patients sit at research meetings and discuss options of investigation, he adds.

The Lung Disease Consortium also works with other foundations and advocacy groups, and some of these have been established by the consortium and Alpha-1 in recent years, Strange says.

Alpha-1 Foundation also has a health care arm

called Alpha Net, which is a foundation that has spun off large amounts of money to support Alpha-1 research, including $28 million in research over the past few years, Strange says.

"With this rare disease, that amount is rather significant, and it helps tide over seasoned and young investigators," he adds.

• **Neurologic channelopathies:**

Investigators working in the area of neurologic channelopathies have sat at meetings with the president of the Periodic Paralysis Association of Tracy, CA, says **Richard J. Barohn**, MD, chair and professor in the department of neurology at the University of Kansas Medical Center in Kansas City, KS.

"The association's president has been at RDCRN meetings twice a year, and he's had significant input in these protocols," Barohn says. "We've had more patients' input for this research than we have through other research studies I've been involved in."

Some of the patient input has helped investigators decide how much testing patients can tolerate, Barohn says.

"At one time, we thought about having patients spend a night in the hospital, and we decided not to do that based on input from patient groups," Barohn says. "We decided to do all of the testing in an outpatient clinic and squeeze as much [information] as we can in one day."

• **Genetic diseases of mucociliary clearance:**

Research sites studying genetic diseases of mucociliary clearance have worked closely with the Primary Ciliary Dyskinesia (PCD) Foundation of Phoenix, AZ, which has served as a sounding board, says **Susan Minnix**, RN, BSN, a research nurse coordinator at the University of North Carolina at Chapel Hill.

"Some investigators have presented at the PCD Foundation, and we keep them abreast of what we're doing," Minnix says. "We've listened to their input and questions."

Patients with PCD have a genetic sinus pulmonary disease, characterized by chronic otitis media and a history of neonatal respiratory distress, Minnix explains.

Half of the patients have reversed organs with their heart and stomach reversed, and most of them are born full term with lungs full of fluid, resulting in pneumonia or collapsed lungs, she adds.

The clinical research site opened a year ago, and so far more than 100 patients have been recruited, Minnix says.

"We have two studies going on, including the rare diseases of the airways, which is a cross-sectional comparison of clinical features," Minnix says. "And another study is a longitudinal study of participants, seeing what happens to their lungs over five years." ■

New and improved data collection methods

General research could benefit, as well

Clinical research sites involved in the Rare Diseases Clinical Research Network (RDCRN) have numerous advantages from the collaborative work, including the ability to access a data and technology coordinating center (DTCC).

The network, created through National Institutes of Health (NIH) funding, has a DTCC charged with developing a scalable information systems approach to collecting data from many different types of disorders in research settings, says **Jeff Krischer**, PhD, head of the DTCC at the University of South Florida in Tampa, FL.

The goal is to incorporate into the system data standards across studies, diseases, and sites, Krischer says.

CR sites collect data from their natural history studies and treatment trials and send these to the DTCC.

"We all use the same format and form and went through numerous meetings and phone calls to come to a consensus of what data was important, how to score it, and how to conduct interviews and exams," says **Steve Skinner**, MD, a senior clinical geneticist and associate director and director of clinical services at the Greenwood Genetic Center in Greenwood, SC.

The DTCC has helped sites navigate the web site and use the database and tools, says **Susan Minnix**, RN, BSN, research nurse coordinator at the University of North Carolina at Chapel Hill.

"They can post same-time meetings and have your screen come up with whomever is presenting them," Minnix says. "So they educated us about what those tools are."

The key is for the DTCC to be consistent with the NIH roadmap, which includes making data available to the larger research community, Krischer says.

"The larger research community could benefit from the studies we have underway as well," Krischer says. "In the application of data standards, we not only review in terms of applicability to the

disease settings we have, but participate in future refinement to make sure they are robust enough to address other clinical research issues."

The DTCC developed the approach with the consideration that the center is supporting 10 research consortia, which represent more than 55 medical institutions in eight countries, he says.

"So the data technology and capture systems have to be robust enough to support studies being done in such diverse settings," he says.

Some of the ways the DTCC has captured data is through interactive voice response systems to collect patient reported outcomes, and information is captured on-line from various types of imaging data, such as MRIs, etc., Krischer says.

Another innovative approach is the patient contact registry, in which individuals who are interested in participating in clinical research can register and be contacted when new trials are open, Krischer explains.

"That's a very valuable resource that we hope will stimulate more rapid accrual to studies," he says. "More than 3,000 individuals are enrolled in that registry, representing a valuable resource for researchers to draw upon."

Most of the DTCC systems are built around Web-based data capture and management, Krischer says.

"We can also receive data from paper forms that are scanned and computer read," he explains. "We use those in special settings where it is more appropriate than data entry on a computer."

At the RDCRN site at the University of Alabama, Birmingham, research information was collected on a regular form and faxed to the DTCC, rather than hand-entered, says **Jane Lane**, RN, BSN, a research nurse manager at the Civitan International Research Center, at the University of Alabama, Birmingham.

"We wanted to get information entered in a timely fashion, and we were backlogged because we'd collected so much data before the data center was ready to accept it," Lane recalls.

"This process greatly streamlined things for us, so that we could come back from the clinic and fax data there," Lane adds.

Doing it this way did make things more stressful for the DTCC staff, she notes.

"If we didn't write correctly, they might have to hand-check it," Lane adds.

The DTCC has automated systems for data quality control and monitoring, including adverse event monitoring in all studies, Krischer says.

"It can be distributed to the appropriate medical review officers for review electronically," Krischer says.

"We have a system in which we can monitor them in terms of our review and analysis, as it pertains to the safety of the ongoing study," he says.

"It's a continuing process," Krischer adds. "As we open new studies, there are new study requirements."

For example, the DTCC added a system by which we can track distribution of investigational agents, links to research pharmacies at participating sites, manage distribution of study drugs, and replenish it so dispensing of study drug can occur, Krischer describes.

"We make sure there are adequate supplies, and we make sure we can do the statistical component and that the study operating characteristics are maintained throughout," he says. "We have the ability to track biological samples collected by studies, whether they are going to repositories or tissue banks, and we can link samples and data generated as well." ■

Researchers have more training opportunities

NIH wants next research generation trained

When the National Institutes of Health (NIH) established the Rare Diseases Clinical Research Network (RDCRN) in 2003 with $51 million in grant funding over five years, one of the NIH's stated goals was to train the next generation of investigators.

Investigators working within the RDCRN have found these goals attainable, largely because of the network's ability to improve research infrastructure and the additional funding available for hiring young physicians/investigators.

"Everyone wants young investigators in their field," says **Charlie Strange**, MD, professor of pulmonary and critical care medicine at the Medical University of South Carolina (MUSC) in Charleston.

Strange has a rare disease fellow who is working on a project involving Alpha-1 Antitrypsin Deficiency, under Strange's guidance.

One of the big focuses of the neurologic channelopathies consortium is training junior neurologists who are neophytes in the study of rare diseases, says **Richard J. Barohn**, MD, chair and professor in the department of neurology at the University of Kansas Medical Center in Kansas City, KS.

"We hope this experience will stimulate them to stay in the field and do research into rare neuropathies," Barohn says. "At each site we have a young neurologist and a senior investigator."

A big portion of the consortium's grant has been designated for training this next generation of young neurologists, he notes.

"At monthly conference calls, we try to have young neurologists lead the discussion and give data from their site," Barohn says. "I think our project is the only one that is doing that actively."

Barohn is training his second young neurologist since the network was formed, and some of the sites have as many as three young neurologists, he notes.

Some of the young neurologists come up with their own independent grant funding, and this helps to keep them active in the field, Barohn adds.

The young neurologists are post-fellowship doctors, and some of them are junior assistant professors in academics. They can spend half of their time on the RDCRN project, which gives them time to interact with patients and families, doing detailed physical exams, and participating in monthly network conferences, Barohn explains.

RDCRN sites, such as MUSC's, which are part of the lung disease consortium, are finding funds from either NIH grants or foundations to start projects with the purpose of developing pilot data for young investigators, Strange explains.

"We want to launch them into a career that has lots of investigator support," Strange says. "The grant actually pays for independent fellows to train in rare disease research, to establish these [rare diseases] foundations, and to provide for some small clinical trials in each of the clinical areas."

Bright young physicians have lots of career paths open to them, so the hope is that RDCRN sites will obtain enough funding to train them in rare disease research, which will keep them in the business of being good clinical researchers rather than have them steered toward the more lucrative private practice medicine, Strange says.

"Based on philanthropic funds, we've been able to support specific fellowships within the network," says **Brendan Lee**, MD, PhD, an investigator with the Howard Hughes Medical Institute and a professor in the department of molecular and human genetics at Baylor College of Medicine in Houston, TX. Lee studies urea cycle disorders as part of the network.

"It's a strength of our network — the ability to supplement NIH funds," Lee adds. "One of the fellows we funded here is leaving and taking a faculty position to be a rare disease physician, so I know this process works."

One of the investigators involved in the RDCRN says he personally has benefited from the training and mentoring opportunities provided by the network.

"I've been more involved in clinical evaluations and not so much in research," says **Steve Skinner**, MD, a senior clinical geneticist and associate director and director of clinical services at the Greenwood Genetic Center in Greenwood, SC.

"I've spent a good bit of time with Rett Syndrome research, being trained by investigators in Alabama and Houston," Skinner says.

"This is an ideal model," Skinner says. "I have not actually been involved in this extensive degree of clinical research before, so I have learned to walk through the IRB process with institutions, and I'm learning data analysis and how to conduct clinical trials because all of that is included in our training." ■

Attention to details when improving recruitment

Know your subject's wants and needs

Even for research professionals for whom clinical trial recruitment is fun, the nuances can be challenging.

"Every site should develop an effective recruitment and retention strategy for each trial," says **Bryce Bartruff**, RN, PhD, senior clinical project leader at Sanofi-Aventis in Malvern, PA. Bartruff runs two clinical trials and has extensive experience in the healthcare/pharmaceutical industry. Bartruff was a scheduled speaker at the 2007 Association of Clinical Research Professionals (ACRP) Global Conference and Exhibition, held April 20-24, 2007, in Seattle, WA.

During the flirtation stage of finding matches between sites and studies, it's easy for investigators to say they could enroll patients.

But it's a whole different issue to actually put down their strategies on paper, Bartruff notes.

"It's also important for each pharmaceutical company or clinical research organization (CRO) to have a recruitment strategy for each clinical trial," he says. "This way they'll understand who the patient is and the various characteristics of patients, as well as what will attract patients to the trial."

The sponsor and CRO should think through why patients want to participate in a trial, and they should share this information with the recruitment sites, Bartruff advises.

Unfortunately, most recruitment strategies are put in place when there already is a problem, he adds.

Bartruff offers these suggestions for designing a recruitment strategy:

1. Describe what the patient will look like.

Here's an example: "I put together a strategy for a trial involving people who are obese," Bartruff says. "Taking that into consideration, we would look at the cultural and social significance of these individuals wanting to participate in the trial."

In other trials, the patients might be diabetic, where their weight or age is a problem, or getting the right medication is an issue, Bartruff says.

"Do they want a free physical or medication?" he says. "We need to recognize what it is they're looking for."

The idea is to analyze the make-up of participants and recognize what motivates them to participate.

This same strategy applies to retaining patients.

For instance, in a clinical trial involving obese participants, a CR site might give them diet tips, a pedometer, or information about support groups, Bartruff says.

"We need to sit in front of the patient and look at the world from his perspective," he adds.

It's also important to ask and find answers to these kinds of questions: "If we're doing a study on deep vein thrombosis, why does the patient want to take our medication when there already is a standard of care?" Bartruff says.

2. Where do you find these patients?

"In some instances, you want to run an ad in the paper, or the investigator will want to look in his personal database," Bartruff says.

In other cases, including the above example of patients with deep vein thrombosis, the only place to find them is in the hospital, he adds.

For DVT, an investigator might need to check with the orthopedics department because a lot of people who have knee surgery have DVT, Bartruff says.

In the case of a study involving obese subjects, investigators might check with Weight Watchers groups, or if the subjects are athletes, the track might be the place to start, he says.

"You go where they hang out," Bartruff says.

"Or you could have a physician look in his database for potential subjects," Bartruff says. "A doctor's database will show patients' body mass index and other characteristics."

3. Understand why people will volunteer for research.

Bartruff lists these seven reasons why people volunteer for research:

- they desire to contribute to the future health of others;
- they will receive free medication that they couldn't otherwise afford;
- sometimes they realize they have this disease and are scared and are looking for any help they can find;
- some people want to do something that makes them feel special;
- a lot of patients will participate in research to please their doctors;
- sometimes, people will do it because they like the attention they receive from the research staff; and, unfortunately,
- some people do it because they need the money, Bartruff says. "This is not supposed to be a draw, but it happens."

Bartruff lists these eight reasons why people do not volunteer for research:

- they're concerned they may end up taking the placebo;
- they're afraid of the side effects or risks involved with participation with a new compound;
- they're concerned about inadequate treatment and a failure to respond to study treatment;
- they don't understand what is expected of them;
- they have transportation issues, and this is a big reason why people don't volunteer, Bartruff notes;
- some people also believe they don't have the time to participate;
- in some trials, there are complex procedures that would require people having to go through more than they're willing to do, such as a monthly colonoscopy; and
- some people fear having adverse events.

4. Find out what issues might impact participation by a patient, and address these.

It's up to the clinical trial staff to provide thorough informed consent that explains all of the expectations and potential risks and benefits of the proposed research, Bartruff says.

"Spend lots and lots of time with them so they fully understand what they're involved in and how important it is," Bartruff says. "If they fully understand, then they'll stay for the entire trial."

For example, explain that a participant might be placed on placebo, but they will be closely watched, and if anything happens to compromise their health, then the CR staff will step in to make sure they're well taken care of, he says.

"If someone is on a hypertension study and the person's blood pressure goes up very high, then he or she will be rotated out of the clinical trial," Bartruff offers as an example. "Reassure the patient up front that, 'Yes indeed, things may happen, but we're here and watching very closely."

If the obstacle involves transportation, then there are a variety of ways to handle this.

"I'm working on a trial right now, and I'm going to visit a site where the study coordinator said she goes to some of the patient's homes to give them their weekly injections," Bartruff says. "I've worked on clinical trials where they send a car service to the patient's house and pick them up to take them to the doctor's office."

Sometimes, sites will provide a taxi service, he adds.

"If you're paying $13,000 for each patient, then to spend $25-$30 per patient to pick them up is nothing," Bartruff says. "I worked on a Parkinson's disease trial once and transportation was very important, so they used lots of car services."

Time can be an issue when participants are not adequately informed about how long each visit might last.

"As you go through the informed consent process, you need to tell patients that it's not just 20 minutes where they'll be checked over, given medicine, and sent home," Bartruff says. "Maybe they'll be there for eight hours."

Sometimes, patients have signed informed consent documents and are enrolled in the trial, only to drop out when they learn a long visit is coming up, he notes.

"Well, they should have known about it, as well as all of the complex procedures ahead of time," Bartruff says. "You need to get their buy-in at the very beginning."

5. Make participants feel important.

"One of the most important aspects of recruitment is the ability of the study coordinator and the investigator to make the potential subject feel special," Bartruff says. "Give them lots of attention and sincerely care about them."

Some people in the industry downplay the importance of TLC, but Bartruff says it's the most important thing research professionals can do.

"I call it the personal touch, where a patient will say, 'I like these people, and I want to be in the clinical trial so I can hang out with them,'" he says.

"One of the statements I use is, 'It's the little things that count,'" Bartruff says. "Touch their arm, look in their eyes."

These strategies should continue at every visit.

"There is power in a smile, using good listening skills, making sure the visit is convenient for them and making sure they only wait a few minutes before someone says, 'Janet, you're here — come on in,'" Bartruff says.

Also, trial sites can help prevent participants from having trial fatigue by providing some nice touches, such as wellness kits, holiday cards, newsletters, personal notes from the study staff, and phone calls when it's been a long time between visits, he suggests.

It's for these reasons, all having to do with the patients' happiness with their participation, that Bartruff recommends hiring people who have good people skills.

"If you have the opportunity to hire someone with great experience versus a person with a great personality who is smart, pick the person with the great personality," Bartruff says. "They can learn the operations."

6. Use repeat participants when possible, and develop referral sources.

Patients who've already participated in a clinical trial are good candidates for future trials, Bartruff says.

"You've already educated them about research, and they know what's to be expected," he explains. "They've had a good relationship with you, and it's extremely inexpensive to just make a phone call to them and ask if they'd like to be in another clinical trial."

Investigators can easily go through their own databases to find potential subjects.

"Find the right people to refer patients" Bartruff advises.

"If you need patients with blood clots, then find out who is the first person to identify these patients, whether it's the emergency room doctor, ultrasound department, nurse on the floor, and go out and make an alliance with those referring partners to get them on board," he says.

It may require some basic public relations skills.

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"Say you're looking for patients with deep vein thrombosis, and they're all going through the ultrasound department to be seen, then take coffee or candy to the ultrasound department," Bartruff says. "Have a chat with them, and get them on your side."

Bartruff has seen principal investigators visit potential referral sources with trays from Starbucks, and his study coordinator will do the same thing.

"Everybody can do it," he says. "It's just connecting with people and letting them know if there are any exciting clinical trials."

Once an investigator has identified the patients he or she would like to recruit, then it's time to visit the physician and ask for the referrals, he adds.

The same strategy can apply to developing resources in the emergency department or pharmacy department.

"When you go to one of these referring partners, help them understand the science of your study," Bartruff advises. "For example, if this clinical trial could make a change in the way we view the standard of care of patients, then most people in the hospital will want to be a part of it."

The other key component to developing referral sources is to be consistent in your contact with them.

"There is no silver bullet — it's plain hard work," Bartruff says. ■

CE/CME *questions*

15. True or False: According to early trials involving personalized immunotherapy research, there have been numerous serious adverse events.
A. True
B. False

16. In which way have families and patients with rare diseases assisted rare disease investigators involved with the National Institutes of Health's Rare Diseases Clinical Research Network?
A. They helped with protocol questions.
B. They've raised research funds through foundations.
C. They've attended investigator meetings and encouraged people with the diseases to join a registry in which they will be notified about upcoming clinical trials.
D. All of the above

17. Why has the rare diseases network focused on training and mentoring young investigators?
A. The NIH required all sites to hire young investigators as fellows and to train them in research of rare diseases.
B. This was one of the NIH's goals for the rare disease network, and established investigators believe training and mentoring young physicians is the best way to encourage them to become researchers of rare diseases.
C. Both A and B
D. None of the above

18. Which of the following is not a reason why people will refuse to participate in a clinical trial?
A. They have transportation issue.
B. They don't have the time to participate.
C. They fear having adverse event.
D. They are scared and are looking for any help they can find.

Answers: 15. (b); 16. (d); 17. (b); 18. (d)