

Report on the Northeast ALS Consortium (NEALS)

By Amber Dance

Collaboration for a Cure to ALS

Never mind raising a child. It takes a village to stage a high-power clinical trial for neurodegenerative disease. Or rather, make that a global network of dedicated doctors and scientists. In the field of amyotrophic lateral sclerosis (ALS), the [Northeast ALS Consortium](#) (NEALS) is the hands-down largest and hardest-working township in North America. In the 16 years since its inception, NEALS has run 10 drug trials and produced promising data on treatments such as the neuron protector dexamipexole, now in [Phase 3](#). The group is currently completing enrollment of a 600-person, 62-site [Phase 3 study](#) of ceftriaxone, the first compound in ALS to target not neurons, but glia. “Our mission is to get interesting science to patients as quickly as possible,” said Breen Power, the group’s marketing and outreach manager at Massachusetts General Hospital (MGH) in Boston. “When you have an experienced group that is ready to go, you are not inventing the wheel every time.”

Running trials is just one part of what NEALS does. The consortium is a leader in the ongoing search for biomarkers that would speed up trial results. Its [six trial datasets](#) from previous trials and [biological sample repository](#), including cerebrospinal fluid (CSF), blood, and other material, have made NEALS a resource for any scientist with an interest in ALS. Soon, NEALS plans to become a central source of information for people who have the disease, offering an expert hotline, [Webinars](#), patient advocacy training, and a clinical trials database.

Researchers have come to learn that ALS trials cannot succeed without collaborations such as NEALS. There have been treatment trials before, but the sole available medication, riluzole, extends life by only a few months. What is the holdup? In addition to science’s lack of a full understanding of the pathology, ALS is a rare, orphan disease. Although some 5,000 people in the U.S. receive an ALS diagnosis every year, the disease fells most of its victims within five years, so only 20,000-30,000 people have it at any one time. Only some of those people are eligible and willing to participate in clinical trials, making it difficult to achieve a statistically significant group of volunteers. “No one center is going to have enough patients to do even a Phase 2 ALS trial,” said NEALS member Richard Bedlack, who directs the Duke ALS Clinic in Durham, North Carolina. Even at Duke’s comparatively large center, where there are approximately 400 ALS patients, many people decline to sign up for a clinical experiment or are ineligible. Beyond numbers, running a clinical trial requires careful selection of study design, outcome measures, and analysis techniques. Scientists increasingly agree that collaborators must line up their methodologies so that one clinic’s measurements are on par with another’s.

NEALS unites 100 trial-capable ALS clinics in the U.S., Canada, and Europe. Headquartered jointly at MGH and the State University of New York (SUNY) Upstate Medical University in Syracuse, NEALS provides a central coordinating center to handle data and samples, and to ensure that trial designs meet standards set by the Food and Drug Administration (FDA). At SUNY, Jeremy Shefner leads a team that trains and monitors personnel at member clinics to ensure that each site takes the same approach in measuring outcomes, such as lung capacity and muscle strength. From [MGH's Neurology Clinical Trials Unit](#), led by Merit Cudkowicz, NEALS develops protocols, curates databases, and analyzes data. The unit also coordinates grants and contracts for NEALS. "They are a tremendous resource," said Lucie Bruijn of the [ALS Association](#) (ALSA) headquartered in Washington, DC.



Merit Cudkowicz



Jeremy Shefner

Merit Cudkowicz and Jeremy Shefner founded NEALS so academic researchers could have a say in clinical trials. *Image credit: NEALS*

NEALS is one of many collaborative groups in the neurodegeneration arena. For example, the [Alzheimer's Disease Cooperative Study](#) (ADCS) based at the University of California, San Diego, is a National Institute on Aging-funded initiative of nearly 80 North American clinical sites. It has conducted 30 studies on drugs and trial measures (see [ARF Webinar](#)), and in the process has built an infrastructure for publicly funded, highly standardized, multicenter trials, which were previously the province of the pharmaceutical industry. The [Parkinson Study Group](#) and [Huntington Study Group](#) also run collaborative trials.

A newer group in ALS is the Pacific ALS Consortium (PAC-10). It combines 10 ALS clinical sites in California and will hold its third annual meeting 4 November 2011 in Lafayette, California. Part of its impetus was the Golden State's support of stem cell research via the California Institute for Regenerative Medicine, said Robert Miller, who directs both PAC-10 and the Forbes Norris MDA/ALS Research Center at the California Pacific Medical Center in San Francisco. "Stem cell trials utilizing those funds must be conducted within California," Miller said; hence, the group is establishing the infrastructure to do so. It will test non-stem cell treatments as well, such as a new palliative for muscle cramps, Miller said. PAC-10 also involves bench researchers and biotech firms. In addition, the group is working to measure and improve quality of care in member clinics.

A large collective such as NEALS makes it possible to work with trial participants who represent subtypes of an already rare disease. There is a

growing realization in all fields of medicine that most treatments work in particular subgroups of patients and not others (see [ARF related news story](#) on [Deng et al., 2011](#)). In ALS, people whose disease arises from mutations in the gene for the enzyme superoxide dismutase 1 (SOD1) form one such subgroup; they represent about 2 percent of people with ALS. Scientists have performed many preclinical studies with mice that overexpress the mutant human SOD1 gene. Yet all treatments that looked good in these mice subsequently made no difference in human trials (see [ARF Webinar](#)). Perhaps those treatments would work in the small population of people with SOD1 mutations? NEALS is currently conducting two clinical trials in this patient group of the molecular protein chaperone [arimoclomol](#) and a [SOD1 antisense agent](#). This same reasoning—that a drug may stand the greatest chance of success in those patients whose mutations led to the mouse models in which the drugs did work—is part of what inspires the current drive to mount secondary prevention trials in people with autosomal-dominant AD, called the [Dominantly Inherited Alzheimer Network](#) (DIAN) and Alzheimer's Prevention Initiative (API) ([Reiman et al., 2010](#)).

Each NEALS trial is funded separately with an approach Shefner describes as “pay-as-you-go.” NEALS itself is a nonprofit organization. Some trials are supported by grants to the consortium, others by companies that contract with NEALS to test a product. Either way, the funding comes through SUNY or MGH, which then distributes it to participating trial centers. Principal investigators working with NEALS can hand off all tasks to the consortium, with NEALS taking care of everything from subject recruitment to results. Alternatively, investigators can run their own trials and tap a few of NEALS’ resources as they see fit. In addition to grants and contracts that are earmarked for specific trials, NEALS has a small budget for maintaining its basic infrastructure, mainly staff and space, sustained by donations from ALSA, the [ALS Therapy Alliance](#), and the ALS Hope Foundation. With a recent anonymous donation of \$480,000, NEALS is now fielding its own grant applications.

Contracting with NEALS can save investigators and drug companies time, said Douglas Kerr at Biogen-Idec in Cambridge, Massachusetts. Biogen engaged NEALS for the Phase 3 dextramipexole study; otherwise, the firm would have had to find a principal investigator and vet potential study sites on its own. In fact, Kerr said, it was the promising results of a [Phase 2 trial](#) conducted by NEALS investigators that prompted Biogen to license the drug from Knopp Biosciences of Pittsburgh, Pennsylvania, where the compound was known as KNS-760704. Dextramipexole is thought to protect neurons by promoting mitochondrial function ([Cheah and Kiernan, 2010](#)). Mitochondria are part of ALS pathology; they are malformed in rodent models of the disease (see [ARF related news story](#) on [Xu et al., 2010](#)), and their DNA is damaged in autopsy samples from people who had ALS (see [ARF related news story](#) on [Keeney et al., 2010](#)).

Cudkowicz and Shefner founded NEALS in 1995 amidst a flurry of excitement and optimism that ALS treatments could be on the way. That

year, the FDA approved riluzole, and pharmaceutical companies rushed to repeat that success. Academic researchers found themselves rather left out of the drug discovery process. They also felt that some of the company trials did not have the best designs, Shefner said. For example, the riluzole trial used survival as an outcome. While that was enough to satisfy the FDA, monitoring survival requires large, long-term studies to discern differences between drug and placebo ([Bensimon et al., 1994](#)). Other outcomes typically measured, such as muscle strength, are tricky to quantify. Some industry teams pursued growth factors as potential treatments but, Shefner said, did not establish beforehand that the medicines could cross the blood-brain barrier. The treatments were ineffective ([ALS CNTF Treatment Study Phase 1-2 Study Group, 1995](#); [The BDNF Study Group, 1999](#); [Lange et al., 1996](#); [Lai et al., 1997](#); [Borasio et al., 1998](#)). Researchers later switched to an intrathecal method of delivering growth factors directly to the nervous system ([Aebischer et al., 1996](#); [Penn et al., 1997](#)), but have not yet succeeded in stalling the disease.

Cudkowicz and Shefner wanted a piece of the action. “We thought we would have more say if we were working as a group,” Cudkowicz told ARF. They teamed up with seven other New England clinics. The consortium started out with trials of two drugs: the anti-convulsant topiramate ([Cudkowicz et al., 2003](#)) and creatine, a mitochondrial pore stabilizer ([Shefner et al., 2004](#)) and neuroprotective agent ([Beal, 2011](#)). They had to stick with some imperfect outcomes, such as muscle measurements and survival, but also added the ALS Functional Rating Scale. This is a measure of how well a person performs daily tasks, such as getting dressed, and is still commonly used today. Neither treatment worked, although NEALS researchers now believe the creatine dose was too low and are trying it again in a [new trial](#).

Since then, the group has outgrown its Northeastern roots and become the force behind many top ALS trials in the U.S. As a testament to NEALS’ success, Shefner expects some 200 attendees at [this year’s annual meeting](#) 26-28 October 2011 in Clearwater Beach, Florida.

In ALS Trials, One Design Does Not Fit All

Stephen Stokes has had amyotrophic lateral sclerosis (ALS) for two years. For the 47-year-old Boston resident, joining a clinical trial with even a sliver of a possibility that the drug would slow his disease was a no brainer. However, choosing the right trial was anything but. Trials vary not only in the drug they test, but also in the study design and what impact it might have on a participant’s activities. Stokes told ARF that he agonized over his options. Part of the dilemma was that one trial he considered would have required a jugular intravenous line, rendering swimming and showering difficult. Part of it was that any large trial came with the risk of being assigned to the placebo group. In the end, Stokes decided to enroll in the [Phase 3 trial](#) of dexpramipexole (formerly known as KNS-760704). The drug, he hopes, will protect the motor neurons under attack in his

spinal cord. The dexamipexole study is one of several run by the [Northeast ALS Consortium](#) (NEALS).

Since 1995, NEALS has united clinicians around the common goal of bringing potential medicines to people like Stokes by mounting large, multicenter clinical trials. However, it is not clear what is the best way to run a clinical trial for ALS. The NEALS team has experimented with many trial designs and a variety of outcome measures. “I do not necessarily think that we know what the best approach to ALS trials is,” said NEALS member Richard Bedlack, who directs the Duke ALS Clinic in Durham, North Carolina. Bedlack commended the consortium for not being “stuck in its ways.” The overall trend is toward leaner, more efficient trials, added Robert Miller, who directs the Forbes Norris MDA/ALS Research Center at the California Pacific Medical Center in San Francisco. It is no small issue: Poor design choices can make it difficult to recruit participants or result in invalid or insufficiently powered data. The worst outcome is not a negative trial, but an uninformative one from which scientists cannot learn.

As the behemoth in the ALS clinical trials field, NEALS has the opportunity to test-run trial designs as it experiments with different drugs. Currently, NEALS is testing several study designs in trials. They include the Phase 3 dexamipexole study, a multiphase study of [ceftriaxone](#) to clear excitotoxic glutamate from synapses, and a [Phase 2 trial](#) comparing the mitochondrial booster creatine to the inflammation regulator tamoxifen. Earlier in the clinical pipeline, they include a [Phase 1 trial](#) with stem cell therapy (one of the first of its kind; see [ARF related news story](#)). Targeting select subpopulations, the designs include a [Phase 1 trial](#) of an antisense nucleic acid to reduce levels of the mutant enzyme superoxide dismutase 1 (SOD1), and a [Phase 2/3 study](#) examining arimoclochol to prevent protein aggregation ([Cudkowicz et al., 2008](#)). In the past, NEALS has also tested [lithium](#), which ended up being ineffective; sodium phenylbutyrate, which proved safe (the study was not designed to examine clinical efficacy; [Cudkowicz et al., 2008](#)); celecoxib, which was ineffective ([Cudkowicz et al., 2006](#)); coenzyme Q, deemed safe (the study was not designed to examine clinical efficacy; [Ferrante et al., 2005](#)); topiramate, which gave no benefit ([Cudkowicz et al., 2003](#)); and a compound, [CK-2017357](#), that activates skeletal muscle in an attempt to relieve the weakness that characterizes ALS, which appeared promising in a Phase 2 study.

Filling ALS trials is hard, in part because both doctors and patients can shy away from joining trials, Bedlack said. Doctors are concerned that trials will increase their workload. NEALS addresses this in that its established infrastructure makes participation easier for doctors. Many patients are reluctant because they worry that being in a trial will cost them time and money; some even fear they will become helpless “guinea pigs” at the mercy of scientists, Bedlack said. The last concern is unfounded—a person cannot participate in a trial without giving informed consent—but the general specter of the abusive scientist persists in some people’s minds.

Even though new treatments cannot reach FDA approval without ALS patients participating in trials, only 10 percent of people with the disease sign up ([Bedlack et al., 2008](#)). That number seems respectable compared to other fields; a recent study suggested that less than 1 percent of people with cancer join trials ([Al-Refaie et al., 2011](#)). However, the overwhelmingly larger number of cancer patients still enables many more treatment trials in cancer than in ALS. What's more, those people with ALS who do enroll represent only a sliver of the spectrum of the ALS population. Data from a recent study suggest that people in trials are younger and took longer to diagnose than people with ALS overall. People in trials were also more likely to be men and to have spinal onset of the disease ([Chiò et al., 2011](#)).

Stokes, an environmental consultant, carefully reviewed his options before joining the dextramipexole study. He calls the decision process “double Russian roulette”: First, he had to bet on which drug was most likely to succeed; second, he had to hope he would wind up in the active compound, not the placebo, arm of the study. “The psychological consequences of that can never be understated,” he said. “It might all be for nothing. It is kind of a form of cruelty, I think.”

Trial designers try to heed the concerns of people like Stokes without sacrificing the science. For example, NEALS researchers testing lithium two years ago needed to recruit participants who were willing to risk receiving the placebo, even though the drug was already available for bipolar disorder and people with ALS could easily get it off-label. Those eager to obtain lithium were tempted to do so by a small previous study that had suggested the medicine could prolong survival in ALS (see [ARF related news story](#) on [Fornai et al., 2008](#)), but the claim had not been rigorously tested. People with ALS have so little time that for them, a stay on placebo is particularly costly.

To attract participants, NEALS used a “time to event” trial design, promising that anyone on placebo whose condition significantly worsened would be automatically switched to the lithium arm. Worsening by six points or more on the ALS Functional Rating Scale, a measure of daily activities such as preparing food, was considered an “event” and reason to switch. To obtain an answer quickly, NEALS preset checkpoints to examine the data, rather than wait until the end of the trial. The team planned the first checkpoint to occur once 84 participants had joined; the second was planned for six months after that, or once 55 events had occurred; and the third was intended to occur after 100 events. As it turned out, the study did not make it past the first checkpoint. At that time, the investigators saw that not only was there no benefit to lithium, but the medication might have done harm. They were able to halt the trial and announce their results within just eight months (see [ARF related news story](#) on [Aggarwal et al., 2010](#)). This, then, is an example of a negative trial that is nonetheless successful because it was informative.

About the placebo arm that so frequently troubles patients, Miller said it might be possible to eliminate it altogether from Phase 2 studies. Miller heads another trial team, the Western ALS (WALS) consortium, which also tested lithium in a recent Phase 2 trial. WALS compared data obtained from 107 people who took lithium during the trial to published data on 249 placebo control subjects from six previous ALS trials of other drugs (NEALS' lithium, creatine, and celecoxib trials; WALS' minocycline trial; [Gordon et al., 2007](#); [Kaufmann et al., 2009](#) on coenzyme Q; and [Miller et al., 2007](#) on TCH346). Like NEALS, WALS found no evidence for a benefit from lithium ([Miller et al., 2011](#)). Although placebo groups are required for Phase 3 trials, Miller believes that smaller screens and Phase 2 trials could proceed without them, using these kinds of historical controls instead. For this approach to work, he noted that researchers must make sure the new participants and old controls match on clinical features. In addition, outcomes for placebo-group people must have remained constant since the historical studies. (Over time, outcomes in people with ALS have improved due to better symptom management; see [Qureshi et al., 2009](#).)

For its part, NEALS is pursuing placebo-free results in its Phase 2 trial of tamoxifen and creatine. In this “selection design” trial, participants will receive either creatine or one of two tamoxifen doses. (NEALS has tested creatine before and the drug provided no benefit, but researchers now suspect that the doses used in the previous trial were too low; [Shefner et al., 2004](#)). Why combine the two drugs in one trial? It is a fast way to get results when you are not sure if either drug warrants a large trial, said NEALS co-founder Jeremy Shefner of the State University of New York (SUNY) Upstate Medical University in Syracuse. Selection design allows researchers to obtain maximum data on different drugs from a small number of patients, 60 in this study. In the current trial, investigators are looking for one arm to provide 20 percent benefit over the other two on the ALS Functional Rating Scale. The winner is the drug, or dose, worth pursuing further. If no clear winner emerges, then the results will not help the team decide whether to drop or continue to study either drug.

Right now, one of NEALS' highest-profile projects is the 62-site, 600-person ceftriaxone trial. The “adaptive design” study allows the researchers to modify their plans based on early data coming from the trial, and flows seamlessly from Phase 1, to 2, to 3, eliminating downtime among trials (for more on adaptive designs, see [ARF related news story](#)). The researchers have completed the first two phases, examining ceftriaxone uptake into the cerebrospinal fluid and drug safety; now they aim to discover if the drug fights ALS. The original participants can stay on for further phases, and the team added more participants at each stage. The results of the study are expected in the fall of 2012.

For dexamipexole, NEALS took a different approach to Phase 2 trial design. The study divided 100 participants into four groups, one placebo and three different drug doses. Participants swallowed their assigned pills for 12 weeks, after which they took a break from treatment so the doctors could determine whether any unpleasant side effects or any improvements

in their ALS Functional Rating Scale score or lung capacity disappeared once the drug was discontinued. Then, the researchers re-randomized people to one of two drug doses for another 24 weeks. At some point during that period—timing was blinded to the subjects—people received placebo for four weeks.

This novel study design allowed the researchers to examine multiple doses and assess potential efficacy at the same time as they made sure the drug was safe and tolerable. Plus, the multiple doses and two randomizations increased the chance that any one participant would receive active medication at some point in the trial, increasing the appeal to potential volunteers. The research team found that in both the first and second run, the drug slowed down the disease in a dose-dependent manner. If the current Phase 3 trial confirms that the drug works, the earlier trial “might end up being the new model for Phase 2,” Cudkowicz said.

Like Cudkowicz, Stokes and 799 other patients are hanging on the results of the Phase 3 study. Stokes takes his pill morning and night, and is disappointed that he has not noticed any difference in his condition. Even unpleasant side effects would be welcome, he said, if it meant he might be on the active drug that could potentially keep him alive longer. In the end it is that hope, more than anything that trial designers do, that sells the idea of joining a study. Many other participants are further motivated by the desire to help future patients.

Desperately Seeking ALS Biomarkers

Researchers studying amyotrophic lateral sclerosis (ALS) have plenty of drug ideas to try, but a great problem in figuring out if they work or not. Right now there are no good tests to detect the disease or measure its progression. “This field has been screaming out for biomarkers,” said Robert Miller of the California Pacific Medical Center in San Francisco, who leads the Western ALS Consortium and is a member of the [Northeast ALS Consortium](#) (NEALS). A coalition of more than 140 ALS investigators at 100 sites, NEALS has been hunting for good biomarkers for the better part of a decade. It is running projects on fluid proteins and metabolites, as well as new tests to quantify muscle function.

The creeping paralysis that marks ALS can first make itself known with a stumble, fingers skittering across the keyboard, or slurred words. Of course, many diseases could cause these symptoms; doctors must eliminate all other possibilities even as ALS spreads from one body part to the next. It can take a year just to diagnose ALS. This means that people starting clinical trials are already well into the process of spinal cord neurodegeneration—when it may be too late for drugs to make a big difference.

Another problem for trials is that scientists have no good way to quantify disease progression, and thus no obvious method to determine whether a drug is slowing it down. The muscle strength and breathing tests used in

many trials often yield variable results. Even survival is not entirely reliable as a measure of a drug's effectiveness; How long people with ALS live depends on many factors, including whether they receive supportive therapy such as a tracheostomy (see [ARF related news story](#) on [Gordon et al., 2009](#)). Plus, using death as an endpoint requires large, lengthy trials. Neither researchers nor people with ALS want to wait around for this result.

In the absence of validated biomarkers for ALS, NEALS currently uses a combination of outcome measures, including lung capacity, muscle strength, and the ALS Functional Rating Scale, which scores a person based on day-to-day activities such as getting dressed. NEALS also uses motor unit number estimation (MUNE), a tool to assess muscle function in an axonal-loss disease. MUNE measures the number of functioning motor units, which include the motor neuron and the muscle it innervates. Electrophysiologists calculate MUNE based on nerve responses, recorded with surface electrodes, to stimuli. NEALS co-founder Jeremy Shefner of the State University of New York (SUNY) Upstate Medical University in Syracuse is evaluating and improving MUNE for the consortium's studies.

NEALS has applied MUNE in some studies, such as a trial of celecoxib ([Shefner et al., 2007](#)), but previous results were wildly variable and fraught with artifacts ([Shefner, 2009](#)). In a new study of MUNE methods, published in July, Shefner and colleagues were able to obtain more stable results by measuring activity at multiple points along a nerve ([Shefner et al., 2011](#)). People with ALS declined by an average of 9 percent on MUNE each month. This rapid drop makes MUNE a powerful tool to use in ALS Phase 2 trials, said Merit Cudkowicz, Shefner's NEALS co-founder at the Massachusetts General Hospital (MGH) in Boston.

NEALS is also investigating the value of two other measures of muscle health and strength in ALS trials. The group recently [completed a trial](#) to evaluate the ATLAS (Accurate Test of Limb Isometric Strength) device. Developed by Patricia Andres of MGH-East in Charlestown, Massachusetts, ATLAS consists of a chair mounted to a frame and looks a bit like a home gym. People sit in the chair, and the device measures the force they exert when flexing different muscle groups. In a study recently accepted for publication in *Muscle & Nerve*, Cudkowicz and colleagues report that the device was convenient and precise in experiments with 20 healthy people and 10 with ALS.



Using new devices such as the Accurate Test of Limb Strength (ATLIS), shown, may help clinicians better track the progression of ALS and any benefits from treatment. *Image credit: NEALS*

In addition, NEALS is collaborating with Seward Rutkove of the Beth Israel Deaconess Medical Center in Boston. Rutkove developed a handheld device that measures electrical impedance myography—in other words, how well electrical current travels through muscle (see [ARF related news story](#); [Rutkove, 2009](#)).

Once a diagnosis of ALS is confirmed, MUNE, ATLAS, and the impedance device could turn out to be sufficiently sensitive measures to monitor disease progression during a clinical trial, Cudkowicz said. These measures are noninvasive and relatively portable. They are not specific for ALS pathology, but rather for motor unit degeneration; therefore, they could also serve research into other diseases. For example, researchers are using MUNE as an outcome measure in a [trial for spinal muscular atrophy](#). The NEALS ATLAS study was sponsored in part by the Muscular Dystrophy Association based in Tucson, Arizona.

In the hunt for ALS-specific measures, Robert Bowser of the Barrow Neurological Institute in Phoenix, Arizona, has led NEALS' molecular biomarker program for the better part of a decade. Much of the effort has been devoted to screening for protein markers, using mass spectrometry, in cerebrospinal fluid samples from ALS patients and healthy control donors. Promising candidates, Bowser said, include neurofilament, an important axonal component ([Mendonça et al., 2011](#)); inflammatory molecules such as complement component C3 ([Goldknopf et al., 2006](#)); and other proteins such as cystatin C ([Wilson et al., 2010](#)). (For an in-depth review on fluid biomarkers in neurodegenerative diseases, see [Olsson et al., 2011](#).)

Now, researchers must verify those markers in large groups of people with and without the disease ([Ryberg et al., 2010](#)). Adding to the challenge, some diseases mimic ALS. Whereas ALS, by definition, affects both upper and lower motor neurons, it can be confused with similar conditions that affect only upper motor neurons, such as primary lateral sclerosis or hereditary spastic paraplegia, or only lower motor neurons, such as progressive muscular atrophy. In one [NEALS study](#), the consortium collected samples from nearly 250 people with and without motor neuron disease to identify a marker that helps distinguish ALS from its mimics. Thus far, a combination of the phosphorylated neurofilament heavy chain and C3 best distinguishes ALS from these similar conditions. In a recent study, this pair correctly identified 87.3 percent of people with ALS among a population of 71 people with ALS, 40 healthy subjects, and 52 people with varied diseases including ALS mimics, multiple sclerosis, and other kinds of neurodegeneration ([Ganesalingam et al., 2011](#)).

The proteome is not the only hunting ground for biomarkers; small metabolites might flag ALS as well. NEALS is collaborating with Metabolon Inc. of Research Triangle Park, North Carolina, to seek metabolic markers of ALS in blood, and expects to publish results shortly, Bowser said (see [ARF related news story](#)).

At a 12 September 2011 joint workshop between NEALS and the [ALS Association](#) (ALSA), researchers met at Massachusetts General Hospital in Boston to discuss biomarker progress. "There is still work to be done," noted Lucie Bruijn, ALSA chief scientist, in an e-mail to ARF. "As a community, we have done a good job of standardizing CSF and plasma collections, and are now working toward standardizing imaging techniques among centers." Researchers are starting to use magnetic resonance

imaging and positron emission tomography to examine degeneration of nerve fibers, for example, in the brains and spinal cords of people with ALS (see [ARF related news story](#)). Standardizing methods for CSF collection, biomarker measurements, and imaging has also been a crucial issue in Alzheimer's research (see [ARF related news story](#)). It is a focus of the [Alzheimer's Disease Neuroimaging Initiative](#) (ADNI), a longitudinal study in its seventh year of collecting and analyzing blood and urine samples, plus brain images, from 800-plus people with Alzheimer's (see [ARF related news story](#)), as well as of a quality control initiative in which some 70 labs from around the world participate (see [ARF related news story](#)). Like ADNI and other studies, NEALS is starting to collect samples longitudinally to hunt for markers that track disease progression.

Many researchers expect there will not be one biomarker for ALS, but many. Several may work well in concert (see [ARF related news story](#) on [Steinacker et al., 2011](#)). In addition, Bowser suggested that researchers might want to use different biomarkers, depending on a drug's action. If the medicine affects inflammation, then molecules in that pathway make the most sense; but an entirely different set of biomarkers could be preferable to monitor the efficacy of drugs protecting mitochondria, for example.

Sharing Among ALS Researchers and Participants

In the world of neurodegenerative disease trials, no researcher can afford to be an island. Willing participants—particularly with a rare disease such as amyotrophic lateral sclerosis (ALS)—are scattered so sparsely across the country that any one clinic cannot hope to recruit sufficient numbers. “The scientific community in general is increasingly realizing that it is all about collaboration,” said Michael Benatar at the University of Miami Miller School of Medicine. Benatar is one of more than 140 ALS investigators who are members of the [Northeast ALS Consortium](#) (NEALS).

NEALS was founded so that researchers, working together, could complete more and better clinical studies than they could alone. From the start, anyone with an interest in ALS, and a trial-capable clinic, has been welcome to join. Because NEALS has spread beyond its New England roots—there are now member sites across the U.S. and in Canada and Europe—some members joke that the “NE” actually stands for “Non-Exclusive.” But the sharing does not stop there. Scientists can access [six datasets](#) from past trials and obtain biofluid samples from [NEALS' growing repository](#). Non-members pay a \$1,000 administrative fee for these resources.

NEALS' newest initiative is to share its expertise with patients. With recruiting trial volunteers a big challenge in the field, NEALS hopes that educating people with ALS about the process of clinical research will inspire them to participate. This year's [annual NEALS meeting](#), to be held 26-28 October 2011 in Clearwater Beach, Florida, convenes not just

doctors and scientists, but also 10 patient-caregiver pairs. These 20 people will attend the inaugural Clinical Research Learning Institute, a one and a half-day retreat where clinical researchers will teach them the ins and outs of clinical trials. They will address questions such as these: Why does the research take so long? What rules do scientists have to follow? NEALS is co-developing the program with the [ALS Research Group](#)—another consortium dedicated to improving patient education and care, as well as supporting research—and the retreat is sponsored by the [ALS Association](#).

After the retreat, the 20 participants can share what they have learned with the larger ALS community, serving as informal ambassadors to promote trial participation. “We are trying to generate a buzz,” said Richard Bedlack, who heads the ALS Research Group and the Duke ALS Clinic in Durham, North Carolina. These NEALS ambassadors might write letters to the editor and lobby Congress, he said. They might also blog, or participate in support groups, and point their peers to NEALS as a source of information, added Breen Power, NEALS’ marketing and outreach manager at Massachusetts General Hospital (MGH) in Boston. Merit Cudkowicz, NEALS’ co-founder at the hospital, said she is also looking forward to hearing from people with ALS about what keeps them from joining trials.

In November, the NEALS website will launch an updated version intended to serve as an information hub for patients, Power said. Recently, the consortium defined a position for an “ALS Trial Expert.” This new hire will get up to date on all trials, serve as a patient liaison to companies testing ALS treatments, and as a go-to person for patients’ questions. Once trained, this person will answer the group’s new trials expert hotline, 877-458-0631, or alstrials@partners.org, replacing a clinical research fellow who is a NEALS member at MGH. “The lines have been pretty busy,” Power wrote in an e-mail to ARF. “We have been getting great feedback [from patients who call in].”

Explaining trial rules to patients and helping them understand their options are new aspects of NEALS. The consortium already has a track record of sharing information among ALS investigators, such as for [de-identified data](#) from past NEALS trials of topiramate, celecoxib, creatine, coenzyme Q10, lithium, and arimoclomol.

Researchers reanalyze data from these past trials, which are available subject to approval by a NEALS committee, to yield new results. For example, Cudkowicz and colleagues plumbed placebo numbers to discover that people with ALS today are living longer than they did in the past. However, muscle strength, lung capacity, and ability to perform daily activities have remained unchanged over the past decade. The researchers concluded that the increased survival is due to intensive symptom management in the later stages of disease—for example, ventilation and feeding tubes—while the underlying disease course has not slowed ([Qureshi et al., 2009](#)).

Some members of the same team also mined the archived records to discover factors that might help determine a patient's prognosis. People with ALS who took aspirin, who had low blood chloride levels, or high blood bicarbonate levels died sooner than average. Those who took calcium supplements fared better than others who did not ([Qureshi et al., 2008](#)). Given the effects of aspirin, the study authors suggested that researchers should continue to study the impact of neuroinflammation in ALS. The immune response appears to be a key player in the disease. Although its role—as both protector and mediator of damage—remains far from clear (e.g., see [ARF related news story](#) and [ARF news story](#) on [Chiu et al., 2009](#)), scientists are already pursuing treatment options related to inflammation (see [ARF related news story](#) on [Lincecum et al., 2010](#) and [ARF Webinar](#)).

The next step, Cudkowicz said, is to convince companies to share their data, too. This is a project called PRO-ACT, for Pooled Resource Open-Access ALS Clinical Trials database. Unlike the six individual datasets currently shared by NEALS, PRO-ACT will unite records from several trials into one pooled database. Spearheading this collaborative project is Melanie Leitner of the Cambridge, Massachusetts-based nonprofit [Prize4Life](#). Prize4Life's mission is to stimulate ALS research by offering prizes for achievements such as the discovery of biomarkers and treatments (see [ARF related news story](#) and [ARF related news story](#)), as well as by developing initiatives such as the [ALSGene](#) database. (Prize4Life collaborates with ARF on ALSGene and also funds this reporter's position.)

With PRO-ACT, Leitner and NEALS' director of systems Alex Sherman will design a data management system to merge and house raw data from Phase 2 and 3 industry trials, together with the NEALS datasets. Leitner estimated the database will contain 5,000-10,000 unique patient records. PRO-ACT's integrated database can be used for “identifying new biomarkers, providing insight into the natural history of the disease, as well as potentially providing insights into the design and interpretation of future clinical trials,” she wrote in an e-mail to ARF. Obtaining the placebo numbers alone could be helpful, Cudkowicz said. The [ALS Therapy Alliance](#) provided a grant to Prize4Life to support the PRO-ACT project.

In addition to the past trials database, researchers can also apply for access to a collection of more than 4,000 vials of biological samples—serum, plasma, whole blood, cerebrospinal fluid, urine, and DNA—collected as part of NEALS studies ([Sherman et al., 2011](#)). Collection, processing, and storage of the samples—many of which stem from NEALS' biomarker efforts—are standardized. Many of the samples are stored at [Mass General's Neurology Clinical Trials Unit](#), while others are scattered in labs across the country.

Part of NEALS' spirit is to support newcomers. “I came into the field almost a decade ago; I did not have a mentor,” Bedlack recalled. “NEALS

was incredibly welcoming to a new, enthusiastic, but rather naïve investigator.” Like so many NEALS members, Bedlack received personal mentoring from Cudkowicz and NEALS' co-founder Jeremy Shefner of the State University of New York (SUNY) Upstate Medical University in Syracuse. Bedlack, who credits their advice for advancing his career, now tries to “pay it forward” by mentoring other researchers. Working with ALS doctors and scientists has been a career highlight, Bedlack said: “I am inspired every day in this field.”