Clinical Trials Consortium Succeeds ADCS, Focuses on Prevention

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The National Institute on Aging has awarded $70 million over five years to establish a new flagship clinical trials network, the Alzheimer's Clinical Trials Consortium (ACTC). This network of 35 sites will provide the expertise and infrastructure to facilitate multicenter trials of AD interventions, said Reisa Sperling of Brigham and Women's Hospital, Boston. Sperling leads ACTC along with Paul Aisen of the San Diego-based Alzheimer Therapeutic Research Institute (ATRI) at the University of Southern California, Los Angeles, and Ron Petersen of the Mayo Clinic in Rochester, Minnesota. The consortium's key goal will be to speed up trials by streamlining recruitment and startup protocols. Its leaders will emphasize prevention studies and work on improving inclusion and outcome measures for people at preclinical disease stages, Sperling said.

- An NIA grant will create a next-generation clinical trials network, ACTC.
- ACTC seeks to accelerate recruitment and heighten efficiency.
- ACTC will collaborate with existing networks such as GAP Net and ADCS.

Researchers in the field hailed the news as a step forward for AD trials. Currently, the field lacks the capacity and participants to run as many trials as are needed, noted John Dwyer, who leads the Global Alzheimer's Platform Foundation based in Washington, D.C. "With the approval of the ACTC, the NIA has added a lot of resources and leadership to the fight," Dwyer told Alzforum.

The NIA award supplants the institute's previous support for the Alzheimer's Disease Cooperative Study. NIA founded this trial network in 1991 as part of an agreement with the University of California, San Diego. Two years ago ADCS became embroiled in an ugly dispute when Aisen, then its director, departed UCSD for USC (Jul 2015 news). A lawsuit between UCSD and USC is still ongoing. The final ADCS NIA grant runs out at the end of this year. Its new director, Howard Feldman, noted that ADCS will not disband but will seek other financial support to continue running trials (Jan 2016 news).

ACTC will differ from the ADCS model in several ways. It reflects a paradigm shift toward the preclinical phase of AD with its greater emphasis on community outreach, efficiency, and centralized protocols, Sperling said (see also Dec 2017 conference news). In addition, trials will have their own funding, separate from the ACTC grant. This approach helps ACTC access a company's prime investigational AD drugs, whereas ADCS had largely funded off-patent or repurposed drugs whose sponsors were not developing them for Alzheimer's. Sponsors must submit R01 applications directly to NIH, instead of consortium leaders selecting projects to undertake, as was the case in ADCS. "That may increase the diversity of projects we will support," Sperling predicted. She expects to see a variety of trial designs in addition to prevention approaches, from smaller proof-of-concept studies to late-stage trials of

behavior-modifying drugs or combination therapies. Calls for proposals will go out in the spring, with the first trials expected to start in late 2018 or early 2019.

With trials bringing their own funding, most of the NIA ACTC award will go toward creating infrastructure. In this context, "infrastructure" refers to the centralized core facilities as well as the personnel, expertise, and protocols at each site. The three principal investigators will split key responsibilities. Aisen will lead the coordinating center, which will be housed at ATRI. The center will oversee the data management and much of the day-to-day operations of the trials. Sperling and colleagues at the Brigham will spearhead innovations in recruitment strategies as well as cognitive and PET outcome measures, while Petersen will co-chair the cognitive work and lead the MRI core. The consortium also encourages input from site investigators. ACTC may add additional sites as funding allows.

Wanted: Faster, Cheaper Trials

The researchers particularly want to accelerate trial recruitment and attract more diverse participants. Slow and sometimes incomplete enrollment has been the Achilles heel of AD trials, and the challenge has become even greater now that researchers are seeking people at preclinical stages, who do not know they have the disease (Nov 2013 news series). The ACTC grant will fund an outreach coordinator at each site who will establish relationships with the surrounding community to inform people about trial opportunities. These outreach coordinators will particularly concentrate on engaging members of minority groups, such as African-Americans and Latinos, who historically have been underrepresented in AD trials. The barriers to trial participation vary by geographic region and different ethnic groups, Sperling noted, adding, "It's important to build local relationships."

To facilitate recruitment for prevention trials, a separate initiative will create trial-ready cohorts of cognitively unimpaired people. ACTC researchers will develop algorithms based on factors such as age, sex, education, genetics, and cognitive tests to help them predict which people are likeliest to have brain amyloid. The effort will draw on existing data, including the 4,500 PET scans performed in the A4 secondary prevention study. Later, the algorithms may incorporate blood tests (Dec 2017 conference news) or polygenic risk scores as those become available (Dec 2017 conference news). Researchers hope such prescreening will lower the screen failure rate for PET scans, currently a high cost for prevention studies.

Other innovations in ACTC aim at slashing startup time by standardizing protocols. All the participating institutions will use a centralized Institutional Review Board and a master contract template, so these documents will not have to be created from scratch each time. These administrative regulatory requirements are some of the most time-consuming steps in ramping up trials, Sperling noted.

Gleaning Maximum Information from Each Study

ACTC leaders also want to extract better data from trials. They hope to develop new imaging paradigms and more sensitive cognitive tests for assessing preclinical populations. Dorene Rentz and colleagues at Brigham and Women's Hospital will build on previous innovations in computerized testing (Dec 2014 conference news; Dec 2017 conference news).

In addition, ACTC will use centralized tissue banking, bioinformatics, and imaging cores, and will establish a neuropathology autopsy unit. Participants will be asked to consent to brain donation, even if

they die years after the trial. “That way, we can learn as much as possible from people who were in trials,” Sperling said.

Despite high hopes for the new consortium, it can run only a fraction of the trials needed to tackle Alzheimer’s disease, Feldman said. NIA expects ACTC to undertake five to seven trials during its initial five years, leaving plenty of room for other trial networks.

Dwyer noted that GAP Net, a worldwide trials network headquartered in the U.S., will work closely with ACTC (Aug 2016 conference news; Aug 2016 conference news). The majority of the ACTC sites are also in GAP Net, and the same investigators and personnel will work on trials for both networks. In particular, GAP will share strategies for improving recruitment and minority outreach with ACTC, Dwyer said. He expects the two initiatives to share data, as well.

That said, GAP Net will also establish its own bailiwick. With 59 sites, GAP Net is larger and includes many private commercial sites in addition to academic institutions. GAP will undertake a broader spectrum of projects than ACTC, including observational studies, non-therapeutic interventions such as exercise, and late-stage trials. “Our mandate is to try to improve the clinical trial environment for all therapeutic trials,” Dwyer said. GAP offers fewer services than ACTC; for example, it does not collect biospecimens or capture electronic data. Instead, its role is to facilitate studies for sponsors, accelerating recruitment and improving site performance, Dwyer said. The network expects to kick off its first two to four trials in 2018.

For its part, ADCS also plans to carve out its own niche. Feldman wants to concentrate on running proof-of-concept trials for new compounds to help expand the realm of clinical targets for AD beyond Aβ and tau. He is also interested in developing treatments for symptomatic disease. “We would like to create more options across a diverse pipeline of opportunities,” Feldman told Alzforum. The ADCS is finishing up seven trials funded under the NIA grant or through other partnerships such as UC Cures. ADCS also has new projects in development that Feldman expects will provide some of its infrastructure funding for the immediate future, such as a collaboration with Biohaven Pharmaceuticals to test its glutamate-modulating drug trigriluzole in mild to moderate AD (see press release).

Feldman also expects to collaborate with ACTC and GAP Net. The ADCS website lists 103 participating clinical sites, many of which overlap with the other networks. Some of the larger sites, such as Brigham’s, may run trials from all three networks. Another example is Butler Hospital in Providence, Rhode Island. “We are members of ACTC, ADCS, and GAP to meet the National Plan goal of breakthrough treatments by 2025 and the development of combination treatments for AD,” said its leader, Steve Salloway.

Feldman believes all the networks have a role to play. He noted that the infrastructure needed to coordinate multicenter trials represents a rare and precious resource. “The ADCS is an established brand, and it can make a unique contribution,” he said.—Madolyn Bowman Rogers