



8th CONFERENCE Clinical Trials on Alzheimer's Disease

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At the 8th international conference on Clinical Trials in Alzheimer's Disease Trials (CTAD) on Thursday, researchers from academia and industry grappled with the vexing problems that have led to a series of negative clinical trials.

“Waste is one of the biggest issues that concerns all of biomedical science in the world today,” said Rustam Al-Shahi Salman, Professor of Clinical Neurology at the University of Edinburgh, at a symposium organized to follow up a series of papers published in *The Lancet* last year on increasing value and reducing waste in clinical research. One of the most important issues leading to waste of resources in AD clinical development is lack of recruitment and retention in clinical trials, said Salman. He suggested that future trials should include a “study within a trial” to develop evidence on how to improve recruitment; and also recommended embedding research into everyday clinical practice.

Michael Weiner, M.D., professor of medicine, radiology, psychiatry and neurology at the University of California, San Francisco agreed that poor recruitment substantially slows AD clinical research. In a separate symposium on registries, cohorts, and matching services for AD clinical trials, Weiner said, “We have a huge problem. The single biggest problem is how to get the right people into clinical sites and get them enrolled quickly.”

Four different approaches were described to deal with this challenge. These approaches range from the Alzheimer's Prevention Registry (www.endalznow.org), which requires potential participants to provide little more than an email address to indicate interest in clinical trials; to more intensive programs such as the Alzheimer's Association's Trial Match, which requires participants to provide more detailed personal information; and the Brain Health Registry, in which scores from cognitive games or screening assessments are captured and potentially used to identify individuals experiencing cognitive decline (BrainHealthRegistry.org). The fourth approach, described by Michael Ropacki, Ph.D., of Janssen as a “registry recycling model”, feeds pre-screened participants from a registry managed by Imperial College in London into a trial-ready cohort for upcoming trials (CHARIOT-PRO).

Each of these programs has as a central goal the creation of a large pool of potential participants for clinical trials in order to expedite recruitment. Each is also linked to other studies aimed at addressing other gaps in clinical research or care. For example, the Alzheimer's Prevention Registry recently launched the GeneMatch program, aimed at recruiting people into a study that will require DNA testing so that people can be matched to studies that are recruiting specifically those who are carriers of the ApoE4 gene, which increases their risk of developing AD. TrialMatch will be recruiting U.S. Medicare beneficiaries for the IDEAS study, which is designed to evaluate the clinical utility of amyloid PET imaging. Data from the Brain Health Registry are being used to test an algorithm designed to predict amyloid positivity in cognitively normal older adults, potentially providing a low-cost means of enriching a population with those who might benefit from anti-amyloid therapy. CHARIOT-PRO is already being used in a head-to-head study of different neuropsychological tests to characterize factors that influence cognitive and functional changes.

Another way to increase value is to learn from negative trials. Investigators from Roche Pharmaceutical Research described how even after negative results reported from the SCarlet RoAD trial of gantenerumab led to a termination of that program, post hoc analyses have provided evidence suggesting that a subgroup of fast progressors provided a signal of efficacy. By leveraging data from the Alzheimer's Disease Neuroimaging (ADNI) database, the investigators constructed an AD progression model using baseline scores on the CDR-SB and FAQ, along with hippocampal volume, to predict which subjects would be fast or slow progressors. “We think these results shed positive light on the gantenerumab program and support its continuation with a higher dose,” said Sylvie Retout, Ph.D.

Another gantenerumab substudy presented by Juergen Dukart, Ph.D., showed that fast progressors in the placebo group were much more likely to drop out due to lack of efficacy. Selective loss of these fast progressors in the placebo group may explain the negative primary efficacy analysis, said Dukart.

New findings were also presented at CTAD from several non-pharmacological studies. Yesterday, Miia Kivipelto from the Chronic Disease Prevention Unit of Finland's National Institute for Health and Welfare presented promising results from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER); and today Bruno Vellas, M.D., geriatrician and chair, Gérontopôle and the University of Toulouse showed data suggesting that a multidomain program combined with omega-3 fatty acid supplementation may help slow cognitive decline in older adults, especially those who have mild cognitive impairment (MCI).

Also today, Laura Baker, Ph.D., from Wake Forest Baptist Medical Center described an intervention study showing that a six-month program of aerobic exercise improved brain function and reduced markers of neurodegeneration in adults at risk of AD.

A phase 2 study of another non-pharmacological approach – deep brain stimulation (DBS) -- was presented by Constantine Lyketsos, M.D., of the Johns Hopkins University School of Medicine. DBS has been successfully and safely used in over 100,000 people worldwide with Parkinson's disease and other neurologic conditions. In this study, 42 participants with mild probable AD had DBS leads implanted in their brains. In a blinded manner, stimulation was delivered to only half of the participants; then effects were compared between the "on" and the "off" groups. The study showed that the neurosurgery and DBS appeared safe, and suggested a hint of a clinical benefit and improved blood flow, especially in older participants. A phase 3 pivotal study is being planned, said Lyketsos.