Editorial

The Journal of Prevention of Alzheimer's Disease - JPAD
Volume 7, Number 4, 2020

Establishing a Trial Ready Cohort to Accelerate Alzheimer's Clinical Trial Enrollment and Treatments

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J Prev Alz Dis 2020;4(7):202-203
Published online August 11, 2020, http://dx.doi.org/10.14283/jpad.2020.42

Early detection is critical in our fight to stop or slow Alzheimer's dementia, and even more so to prevent Alzheimer's disease (AD). Current diagnosis of Alzheimer's dementia relies largely on documenting mental decline, at which point, severe cognitive and functional damage has occurred. According to the National Institute on Aging and Alzheimer's Association Research Framework, Alzheimer's disease is defined by its underlying pathologic processes that can be documented by postmortem examination or in vivo by biomarkers. The diagnosis is not based on the clinical consequences of the disease (i.e., symptoms/signs) in this research framework, which shifts the definition of AD in living people from a syndromal to a biological construct (1). The "Framework" is based on research that confirms Alzheimer's disease pathologic changes in the brain begin 15-20 years before the development of symptoms (2). The neuropathologic hallmarks of AD include: amyloid plaques, neurofibrillary tangles (NFTs), Glial responses, and synaptic and neuronal loss. This approach enables a more precise approach to interventional trials where specific pathways can be targeted in the disease process and in the appropriate people. It is hypothesized that during the preclinical period, 10-15 years prior to severe symptoms where fibrillar brain amyloid increases with minimal impact on cognition, that disease-modifying therapy can be most effective (3).

The Anti-Amyloid treatment in Asymptomatic Alzheimer's (A4) Study is examining the effectiveness of solanezumab, a drug targeting beta-amyloid, in over 1,000 symptom-free volunteers whose positron emission tomography (PET) scans show abnormally high levels of beta-amyloid in the brain (4). Enrollment to the A4 study has a 71% screen fail rate for participants, highlighting the difficulties of high cost and patient burden in recruiting eligible participants. Nevertheless, the A4 study demonstrates feasibility as well as the challenges of an early, large, intervention trial to treat AD.

Recruiting individuals in the preclinical stage is especially challenging because the mild nature of symptoms means that individuals do not seek medical care for memory decline. To address this issue, a large number of cognitively normal individuals must be screened with a lengthy and expensive process (including education, behavioral assessment prior to scanning, then scanning and disclosure) in order to fully enroll a prevention trial.

The Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's disease (TRC-PAD) was established to accelerate enrollment of high risk individuals into early stage AD clinical trials (5). TRC-PAD consists of three main elements: the Alzheimer's Prevention Trial (APT) Webstudy, the Site Referral System (SRS) and the Trial Ready Cohort (TRC).

It is projected that 25,000-50,000 participants are needed in the APT Webstudy in order to identify enough eligible participants for the TRC. In addition to local recruitment efforts (media and outreach), TRC-PAD is the first program to leverage existing national registries in order to invite individuals to participate in the APT Webstudy. A referral strategy has been established through partnerships with four national registries, the Alzheimer's Prevention Registry (APR), Alzheimer's Association TrialMatch, the Cleveland Clinic Healthy Brains Registry and the UCI Consent to Contact (C2C) Registry. Currently, these registries are the primary source of participants into the APT Webstudy, on an average of 1,514 per month (6). Successes in recruitment through national registries is in part because participants in registries have already demonstrated an interest in research.

The APT Webstudy obtains demographic, medical and lifestyle information in addition to tracking cognitive performance on a quarterly basis using remote cognitive and functional assessments. To address issues of retention, the APT Webstudy was developed as a user-friendly interface, requiring minimal time commitment, and users are well supported to quickly address any problems that surface. Participant engagement is optimized by allowing users to access results from assessments, receive reminder emails to complete tasks and subscribe to a quarterly newsletter.

Data obtained by the APT Webstudy is used to assess an individual's risk for amyloid elevation in the brain. An adaptive algorithm predicts amyloid positivity in participants and identifies individuals that meet criteria

Received July 2, 2020
Accepted for publication July 2, 2020

to attend in-clinic visits for additional screening for the TRC (7). Machine learning techniques were refined using pre-randomized data of n=4,486 from the A4 study to derive the first cross-sectional predictive models. Variables used in this analysis include demographics, cognitive and functional assessments, and apolipoprotein E (APOE) genotype. This algorithm dramatically improves the accuracy in predicting amyloid positivity, with the greatest improvement when APOE genotype was known. This is intended to reduce burden to trial participants and high cost of screening.

Participants identified by the algorithm as having relatively high risk for amyloid elevation in the brain and are geographically located near TRC-PAD clinical sites are presented to clinical site teams through the SRS. A list of potential participants is provided to TRC sites on a monthly basis and final selections are reviewed manually, with the expectation that this will become increasingly automated. At the in-person visit, additional cognitive assessments are performed, as well as performing APOE genetic testing. With this additional data, participants' risk assessment is updated prior to screening for amyloid burden, either by PET or Cerebrospinal Fluid (CSF) collection. Participants in the APT Webstudy that are not geographically located near a TRC site are provided with the opportunity to obtain a report containing their performance on various assessments as well as an explanation of the assessments that they can review with their healthcare provider.

Design of the informatics architecture for TRC-PAD will allow for longitudinal data from the TRC to inform therapeutic trials and will integrate with the Alzheimer's Treatment Research Institute/Alzheimer's Clinical Trial Consortium (ATRI/ACTC).

The APT Webstudy was officially launched in December 2017 and has consented 30,554 participants with 25 individuals enrolled in the TRC. While exceeding original expectations, the APT Webstudy has not been successful in attracting a diverse group of participants that is representative of the US population (6). Recruitment strategies are being implemented to address this deficiency by creating Spanish language study materials and other community-based approaches.

Continued refinement of the risk assessment will focus on utilizing longitudinal cognitive and functional changes as well as the use of blood-based biomarkers to improve performance of these predictive models (8).

A lot of work remains to be done towards the prevention of Alzheimer's disease and ultimately Alzheimer's dementia. Focusing on the preclinical stage of the disease, where there is low amyloid burden in the brain, may give potential treatments an advantage over the disease. TRC-PAD has developed a framework to enroll a large number of individuals at the early stages of disease, to provide longitudinal cognitive assessments and to predict the elevation of amyloid in the brain. Establishing a cohort of high-risk participants for enrollment into interventional clinical trials ought to fast track the critical treatments needed most. The proof will ultimately be in the ability for TRC-PAD to create a more efficient path towards enrollment into clinical trials, of a population that is in the earliest stages of Alzheimer's disease, and representative of the population in the United States.

Conflict of interests: The author declares there are no conflicts.

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