Editorial

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

Accelerating Preclinical Alzheimer's Clinical Trials through a Trial-Ready Cohort with Diverse Representation

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J Prev Alz Dis 2020;4(7):204-205
Published online August 11, 2020, http://dx.doi.org/10.14283/jpad.2020.43

Alzheimer's disease (AD) treatment and prevention research has reached a tipping point. Federal funding in the US for AD study has increased exponentially over the past several years. Public and private institutions, including the Alzheimer's Association, are advocating for diversifying discovery work on novel biomarkers and treatment targets. Early career and established researchers have joined force in the quest for an effective early therapy for AD. What the field critically needs is a platform to recruit a large number of study participants to accelerate this research effort. The ideal platform should be scalable and cost-effective, allowing efficient testing of multiple new treatments simultaneously. The Trial-Ready Cohort for Preclinical/prodromal Alzheimer's Disease (TRC-PAD) project may help address this critical need.

The TRC-PAD project is a monumental step forward in speeding up recruitment for the burgeoning number of preclinical and prodromal AD clinical trials. As introduced by Aisen et al. (1), the TRC-PAD project is motivated by current conceptualization that disease-modifying strategies are likely most effective and best evaluated at the earliest/preclinical stage of AD. Recruitment of individuals during the preclinical AD stage is challenging given the high screen fail rate and high cost of AD biomarker tests. TRC-PAD demonstrated the feasibility of a number of innovative recruitment and screening methodologies to overcome this challenge to identify individuals at higher AD risk through successive stages of assessment. The use of online registries and unsupervised remote digital assessment has proved to be a cost-effective way to reach a large number of potential participants for preclinical AD trials, yielding an impressive enrollment in the initial phase of the project (2). The development of a brain amyloid risk prediction algorithm based on the A4 study data and its application in prioritizing individuals most likely to be amyloid positive, thereby improving TRC-PAD screening efficiency, is an elegant exemple of cross-project collaboration (3). Further, the advance of cloud-based informatics architecture underlying TRC-PAD supports further adaptation of this risk algorithm based on longitudinal cognitive assessment (4), as well as future addition of new plasma amyloid and tau biomarkers that show promise in differentiating high-risk but cognitively normal individuals (5, 6). Together, these innovations have provided a scalable mechanism to support growth in biomarker risk assessment and data analytics, as well as surges in interests in response to major media report or recruitment effort. The next milestone is to show that this platform can actually reduce the screen fail rate and shorten recruitment time when the first preclinical/prodromal AD drug trials start to enroll participants from the TRC-PAD cohort.

One major challenge in this early stage of the TRC-PAD project is diversity recruitment. Most participants enrolled to-date are white and highly educated, which may reflect a selection bias for individuals who are motivated to join clinical trials through online registries and those with internet access given the web-based study design (7). It is commendable that the TRC-PAD project team plans to improve accessibility to diverse and underserved groups by providing a Spanish language version of study materials and by adapting digital cognitive tests to be compatible with smart phones which black and Latino populations may be more likely to use to access the internet. These efforts will be most impactful for the field if the TRC-PAD team leverages this opportunity and experience to identify and generate empirically derived diversity recruitment strategies for broader dissemination.

Evidence-based recruitment and retention of underrepresented populations is a highlighted need in the National Strategy for Research Recruitment and Participation in Alzheimer's and Related Dementia Clinical Research (8) and aligns well with diversity initiatives being pursued by the ADNI and POINTER trials. Prospective studies with a clearly defined recruitment strategy with standardized outcome measurement will strengthen the evidence for and enable the adoption of successful recruitment practices (9). The TRC-PAD project is well positioned to contribute to the recruitment science of diverse and underserved populations, as the team is now planning to invest in engaging a more representative cohort. For instance, they may consider prospectively defining a few strategies

Received July 28, 2020
Accepted for publication July 29, 2020

to present the Spanish version APT webstudy to the Latino population, and systematically compare the measured outcomes such as participant exposure and new enrollment across the different approaches.

Importantly, a comprehensive understanding of different cultural perspectives in aging and dementia is essential to engage members of diverse racial/ethnic backgrounds. For example, some black Americans may consider cognitive decline and dementia as inevitable with aging, while some Latino individuals may attribute dementia as a consequence of having lived a hard life as opposed to a pathological entity that requires medical treatment (10). Variability exists within groups, however, and some cultural perspectives may apply across racial/ethnic groups. Adhering to top-down assumptions, that minority populations have inadequate awareness of cognitive changes and require education on what constitutes cognitive decline, may not be the most effective way to engage underserved and diverse communities. Rather, AD researchers should adopt a bottom-up approach to understand how these populations conceptualize aging, cognitive decline, and dementia, and allow members of those communities to inform researchers of their needs, concerns, and barriers to research participation. Deeper understanding of diverse sociocultural values and beliefs may inform trial design that better match their specific needs.

In that regard, the TRC-PAD project has demonstrated goodwill in giving back to the participants by providing assessment feedback, but it should also consider the difference in values and needs across diverse groups. While study feedback may be valued by a majority of participants, it is unclear if the same feature also has a similar appeal to different racial/ethnic groups, especially in the context of health disparity. For instance, the TRC-PAD APT webstudy has an online dashboard for participants to track the changes in cognitive performance and concerns, which is very informative for those who value self-care and self-monitoring. The platform also allows participants to generate a summary report from the quarterly online assessment to facilitate bridging with primary care, which is helpful only if the participants already have a good working relationship with their primary care providers. Consultation with community advisory boards, as well as qualitative studies on the values and needs of racial/ethnic groups will be helpful to inform the best way of optimizing engagement. Ultimately, a more diverse and representative trial-ready cohort will enhance the generalizability of any effective preclinical AD treatment.

Acknowledgement & Funding: Athene Lee PhD is partially supported by Institutional Development Award Number U54GM115677 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds Advance Clinical and Translational Research (Advance-CTR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest: Dr. Lee is one of the institutional site PIs of the TRC-PAD study (Butler Hospital site). Dr. Salloway reports grants, personal fees and non-financial support from Biogen and Lilly, grants and personal fees from Eisai and Avid, personal fees and non-financial support from Novartis and Roche, and personal fees from Genentech, outside the submitted work. Dr. Correia has nothing to disclose.

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