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Inclusion of Underrepresented Groups in Preclinical Alzheimer Disease Trials—Opportunities Abound

Jennifer J. Manly, PhD; Andrea Gilmore-Bykovskyi, PhD, RN; Kacie D. Deters, PhD

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Author affiliations and article information are listed at the end of this article.

In the search for treatments to delay or halt the progression of Alzheimer disease (AD), researchers see promise in clinical trials that enroll people without cognitive decline who exhibit neuropathology traditionally associated with AD, namely amyloid plaques and tau tangles. The Anti-amyloid Treatment in Asymptomatic Alzheimer trial (A4 study) of an anti–β amyloid (Aβ) monoclonal antibody in older adults with preclinical neuropathological features of AD is the foremost example of this effort.[1] Lead investigators of A4 study set the laudable goal of requiring that at least 20% of people screened for enrollment at each recruitment site would be from minoritized racial and ethnic groups. This objective is a welcome deviation in the AD field, which has underincluded these populations in preclinical and biomarker-based studies, despite the disproportionate burden of AD in minoritized populations.[2] Despite these efforts, the A4 trial fell short of its recruitment goal: 86% of those screened and 88% who remained eligible after initial screening and an amyloid positron emission tomography (PET) scan were non-Hispanic White individuals. As preclinical AD studies continue to expand, trials such as the A4 study present important opportunities to investigate recruitment- and enrollment-based factors relevant to inclusion of minoritized racial and ethnic groups.

The study by Raman et al[3] examined differences in sources of recruitment and eligibility for the A4 trial in North America by race and ethnicity. The authors found differences according to recruitment source, demographic and clinical characteristics, and reasons for exclusion. Unfortunately, due to the lack of equivalent data for those who failed the screening as well as the limited specificity of recruitment data collected at each stage, we cannot draw strong inferences regarding the relative contribution of distinct enrollment-based factors. Study findings shed light on the critical need for community-informed methods for identifying and recruiting minoritized racial and ethnic groups and structured collection and analysis of recruitment data from people who are approached for participation (including people who are not screened), screened (even if they are excluded), and successfully recruited. While Clinical Dementia Rating scores greater than 0 and low Mini-Mental State Examination and Logical Memory scores were the primary reason for excluding participants from minoritized racial and ethnic groups at the initial screening, without data on people who were screened out, we cannot determine whether racial and ethnic differences in the initial screening were the product of well-documented measurement biases in neuropsychological measures, population differences in burden of cognitive impairment, or group variation in amyloid burden.

Participants from minoritized populations who reached the screening phase for the trial were more likely to be recruited from internal sources, described as other studies, community outreach, internal clinic referrals, mailings and/or brochures, referrals by site physicians, and local research registries, whereas White participants were more likely to be recruited from earned media, described as news or other nonpaid content on television or radio, in print, or online. It is unclear whether there was consideration to targeting earned media to minoritized communities or whether the intensity and duration of the recruitment activities influenced recruitment success. Among the subgroup of participants who advanced to the amyloid PET imaging screening visit, participants from minoritized racial and ethnic groups were less likely to meet eligibility criteria, and this difference was reliable in Black and Asian groups. The authors recommend a number of organizational and study design

changes that may address disproportionate exclusion of underrepresented participants, including development of tailored recruitment strategies with targeted funding, selection of sites with diverse teams, and adjusting inclusion criteria for "unique biological or cultural norms."[3]

Raman et al[3] draw attention to the fact that it is acceptable to collect very little relevant information about people who are approached or are screened for eligibility to participate in an AD clinical trial, whether or not they are enrolled. As the authors suggest, adjustments to each stage of the recruitment and enrollment process are needed to achieve better representation, yet absent broader standards for data collection surrounding recruitment-based factors, the field is likely to remain ill-equipped to identify and target specific mechanisms driving exclusion. These gaps can be addressed in future studies through the establishment of standardized common data elements for recruitment- and enrollment-based factors that, if collected at a sufficient level of detail, would facilitate ascertainment of biases at specific prescreening and screening stages. Optimally affixed to individual local sites, these data elements can provide real-time data for investigators regarding effectiveness of and/or systematic variations in their local outreach and recruitment methods (ie, omitting attention to media sources for some groups and not others).

The findings reported by Raman et al[3] also reveal that—as is often the case—prospective participants who were White, well-educated, and well-resourced were centered at each step of the design and execution process of the A4 trial. These conventional research recruitment practices and deeply entrenched norms were associated with the recruitment of participants from minoritized backgrounds. It is a worthy exercise to question the ways these practices do and do not facilitate participation in some groups, but the field can also benefit from reflecting on why the systems and structures of recruitment are so commonly designed around White, resourced populations as a prioritized, referent norm. An example of this ethnocentric approach is seen in the discussion about racial/ethnic differences in the availability and relationship of study partners in the A4 study; namely, more Black and Hispanic people were excluded because they did not have a study partner with whom they had weekly contact. In response, Raman et al recommend future study of "attitudes of multiethnic groups toward the study partner requirement."[3] The conclusion that community attitudes drive group differences in the study partner requirement is based on an assumption of family structure that is centered on White, wealthy, and resourced people. Looking forward, AD researchers should consider other types of study designs or adaptations that can clarify sources of information about daily cognitive and functional status and address the concerns that motivate the study partner requirement.

Engaging minoritized communities in preclinical trials is fundamental to rigorous and equitable AD science, but more considerable challenges will follow. Emerging research shows that even with more substantial participation of older adults from minoritized racial and ethnic backgrounds, ascertainment bias is a serious concern, such that the strength and direction of racial and ethnic differences in cognitive outcomes can vary widely as a result of sampling strategy.[4,5] It is unclear whether screened individuals in the A4 trial are different from the communities that were targeted for recruitment and whether reliance on internal and local channels had a differential influence on representativeness of older adults from minoritized backgrounds. Educational attainment is one example; in the United States, 42% of Asian adults older than 65 years have a college degree, but this is lower in White (35%), Black (25%), and Hispanic (18%) populations.[6] Regardless of racial/ethnic background, the average person screened for the A4 trial had a college degree; therefore, it can be surmised that the Black and Hispanic people who were screened had disproportionately higher socioeconomic status than the general population of Black and Hispanic people, while the White and Asian older adults who were screened were more representative of their peers.

Placing the Raman et al[3] study and the A4 trial in a broader context, we need to consider the lasting implications of engaging underrepresented communities to recruit for a research trial and then deeming most willing people ineligible. To learn from each other, narrow widespread disparities in AD, and accelerate toward our 2025 goal of reducing the impact of AD in the United States, harmonization and standardization of recruitment data are needed, but if the foundation of that standard continues to be Whiteness, AD research will continue to be dramatically less inclusive than the disease itself.

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Corresponding Author: Jennifer J. Manly, PhD, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Irving Medical Center, 630 W 168th St, P&S Box 16, New York, NY 10032 (jjm71@cumc.columbia.edu).

Author Affiliations: Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Irving Medical Center, New York, New York (Manly); School of Nursing, University of Wisconsin–Madison, Madison (Gilmore-Bykovskyi); Department of Neuroscience, University of California San Diego, La Jolla (Deters).

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