

Review

Modifiable Barriers for Recruitment and Retention of Older Adults Participants from Underrepresented Minorities in Alzheimer's Disease Research

Khushnoo K. Indorewalla^a, Maureen K. O'Connor^{a,b}, Andrew E. Budson^{b,c},
Christina Guess (DiTerlizzi)^b and Jonathan Jackson^{b,d,*}

^a*Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA, USA*

^b*Boston University Alzheimer's Disease Research Center, Department of Neurology, Boston University School of Medicine, Boston, MA, USA*

^c*VA Boston Healthcare System, Boston, MA, USA*

^d*CARE Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

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Abstract. Clinical Alzheimer's disease (AD) trials currently face a critical shortfall of thousands of eligible participants, which inflates the duration and cost of the clinical study as well as threatens the scientific merit of promising clinical interventions. This recruitment crisis is further compounded by the fact that underrepresented and marginalized populations—particularly those identifying as a racial or ethnic minority, those with low socioeconomic status, or living in rural areas—have been historically underrepresented in ongoing AD clinical trials despite overwhelming evidence that such populations are at increased risk for developing dementia. As a result of various recruitment barriers, current AD clinical studies frequently reflect a decreasingly representative segment of the US population, which threatens the overall generalizability of these findings. The current narrative review provides an updated examination and critique of common recruitment barriers and potential solutions, as well as a discussion of theoretical approaches that may address barriers disproportionately experienced by underrepresented communities. AD clinical researchers are encouraged to take purposive action aimed at increasing diversity of enrolled AD clinical trial cohorts by actively identifying and quantifying barriers to research participation—especially recruitment barriers and health disparities that disproportionately prevent underrepresented and marginalized populations from participating in research. Furthermore, researchers are encouraged to closely track which individuals who express interest in AD research ultimately enroll in research studies to examine whether AD research participation is appropriately representative of the intended population for whom these new and novel AD interventions are being designed.

Keywords: Alzheimer's disease, modifiable barriers, recruitment, recruitment interventions, retention, underrepresented minorities

INTRODUCTION

In January 2011, President Barack Obama launched the National Alzheimer's Project Act (NAPA), which established a clear mandate to treat or prevent

*Correspondence to: Jonathan Jackson, PhD, CARE Research Center, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA. Tel.: +1 617 726 3608; E-mail: jjackson31@partners.org.

Alzheimer's disease (AD) by 2025 [1, 2]. In light of the fact that research dollars for AD are now approaching the \$2 billion annual provision proposed by NAPA and potential therapeutic targets have proliferated in recent years, advances in participant recruitment and clinical research design are urgently needed. Clinical AD trials currently face a shortfall of thousands of eligible participants, a number that will rise exponentially as novel and secondary prevention therapies move into Phase II and Phase III stages of research over the next several years [3]. Despite the large and growing need to recruit research participants, the proportion of the US population that participates in research is decreasing. More than one-quarter of US clinical trials fail to enroll a single participant [4] and many ongoing trials are either unsuccessful or slow in recruiting the projected number of participants required for the study [5]. These enrollment difficulties introduce significant delay, cost, and uncertainty in evaluating the scientific merit of promising clinical interventions. Indeed, challenges associated with participant recruitment for ongoing AD clinical studies has been identified as the primary barrier negatively impacting AD clinical research progress [6].

By 2044, it is estimated that almost half of the US population will identify as belonging to a minority group [7]. Racial minorities such as African Americans and Hispanics have been found to have a higher risk of developing AD in comparison to their Caucasian counterparts [8–10], and yet these populations are historically underrepresented in AD clinical research [9, 10]. Unless purposeful action is taken, enrollment into AD clinical research will continue to reflect a shrinking and decreasingly representative segment of the US population. Greater diversity of enrolled cohorts in clinical research trials may improve the generalizability of these studies [11–14], and the efficacy of targeted assessments and therapies for underrepresented populations [15–17]. Underrepresented and marginalized populations—particularly those identifying as a racial or ethnic minority, those with low socioeconomic status or living in rural areas—are at increased risk for developing dementia [16, 18–27], and may potentially provide additional insights into mechanisms of AD and related dementias. Beyond health disparities, these groups face unique barriers such as low health and research literacy, deep mistrust of the academic medical research model, as well as language barriers that prevent their participation in research [2, 28–35]. Moreover, few clinical trial sites have sufficient personnel,

training, or resources to dedicate to minority recruitment. Findings from AD clinical research may be undermined without researchers employing deliberate efforts to include underrepresented populations in ongoing and upcoming research studies [35–37].

Efforts to increase recruitment of all populations for AD clinical trials are often mired by several potential obstructions. Often-cited participant factors include their lack of awareness of clinical research or concerns about treatment effectiveness [38] and fear of physical injury [9], as well as mistrust of researchers [9]. These barriers to participation often overlap and differ across cultures and regions, hindering the adoption or implementation of recruitment strategies that adequately address local community concerns. Challenges associated with participant recruitment for ongoing AD clinical studies has been identified as the primary barrier negatively impacting AD clinical research progress [6].

The extant research literature has identified several modifiable factors that negatively impact participant recruitment in ongoing AD clinical trials. Crucially, these are factors that are frequently introduced by research study teams rather than participants themselves. Such barriers include 1) medical and/or psychiatric disturbances [2, 31] that may increase heterogeneity in participant response to the treatment protocol and are therefore often identified as exclusionary criteria in ongoing AD research [39], 2) need for a study partner [2], 3) participant burden [40], 4) unique barriers within primary care settings [2], and 5) difficulty recruiting underrepresented populations [2]. In this narrative review, we offer an updated examination and critique of common barriers to recruitment and potential solutions, as well as discussion of theoretical approaches that may address barriers disproportionately experienced by underrepresented communities.

BARRIERS TO ALZHEIMER'S DISEASE RESEARCH RECRUITMENT

Comorbid medical and/or psychiatric disturbances

Eligibility criteria play a critical role in clinical research as they help define the patient population being investigated [41]. Inclusion and exclusion criteria of a clinical study are often tailored to allow researchers to examine the effectiveness of an experimental intervention in a specific patient population

[41]. Heterogeneity in the research sample may result in confounding variables which may make it difficult to examine the effect of the intervention. Hence, researchers often aim to balance their desire to reduce heterogeneity in the clinical sample against their goal of making their clinical findings generalizable to a larger patient population [41]. In addition to reducing heterogeneity in the clinical sample, exclusion criteria ensure the safety of participants by excluding participants for whom the experimental intervention may be contraindicated [42]. However, employing extensive exclusion criteria, especially in the absence of accompanying rationale for such criteria, can be deeply problematic in that it could result in selection bias such that the sample is not adequately representative of the intended population [42–44]. Such bias may in turn cast uncertainty about the extrapolation of their findings to a more general population [45]. The absence of rigorous studies underscoring the scientific utility of medical comorbidities as exclusion criteria is concerning. Too often clinical researchers rely on longstanding and arbitrary exclusion criteria ‘carried over’ from previous, similar studies [41]. For example, past research has found that cognitive impairment is frequently used as an exclusion criteria in geriatric research; however, a majority of such research offered no rationale in support of using such exclusion criteria [42, 46]. This lack of rationale is especially concerning since such criteria systematically exclude the very participants who are intended to benefit from novel interventions resulting from these AD clinical trials [9]. Indeed, 84.1% of reviewed trials published in high impact medical journals used at least one poorly justified exclusion criteria in their study [42] which could have negatively impacted the study’s overall generalizability. Existing research examining participant recruitment in AD clinical studies fail to identify attrition rate associated with each exclusion criteria, further threatening the trial’s external validity [45].

AD clinical research frequently uses comorbid medical conditions (such as cardiovascular disease) [47] and psychiatric disorders as exclusion criteria [31]. For example, AD clinical trials focused on disease prevention seek to recruit cognitively intact participants who are at higher risk of AD as identified by genetic and biomarker studies [2, 6, 48]. In such studies, researchers often define comorbid medical conditions and cognitive impairment as exclusionary criteria [48]. However, few researchers provide a clear rationale in support of what they consider ‘comorbid medical conditions’ and they often fail

to objectively define ‘cognitive impairment’ for the purpose of their research study. As a result, less than 30% of patients diagnosed with AD are eligible to participate in ongoing clinical studies [6, 31, 39, 49]. Indeed, past research has found that applying an exclusion criterion of “significant” medical and psychiatric comorbidities such as hypertension, cardiovascular disease (CVD), stroke history, depression, and substance use would exclude approximately 94.8% of participants listed in a clinical registry for an AD trial [42, 50]. While there is important reason to exclude participants with a history of stroke or severe mental illness due to possible adverse reactions to treatment protocols, it may be problematic when researchers fail to objectively define what they consider to be clinically significant levels of depression or substance use. Undoubtedly, a single occurrence of mild depression, or remote history of occasional substance use (e.g., alcohol or marijuana) several years prior to research participation should not be used as an exclusionary criterion. The above-mentioned statistic is also especially concerning in light of the evidence that CVD is frequently associated with AD [47, 51] and a significant proportion of AD patients present with vascular abnormalities [47]. Because vascular comorbidities are a part of AD disease presentation, using such comorbidities as exclusion criteria in ongoing AD clinical trials could invariably result in erroneously screening out potential participants. Vascular comorbidities may also be a part of AD pathophysiology among different ethnic and racial groups. Past research has found an increased prevalence of CVD and cardiovascular risk factors among African Americans [52, 53], which has been related to higher incidence of AD in this population when compared to the non-Hispanic White population [52]. Hence, the use of vascular comorbidities as exclusion criteria disproportionately excludes African Americans from ongoing AD clinical research in comparison to their non-Hispanic White counterparts [42, 50]. As such, the clinical trial’s choice of eligibility criteria may unwittingly predetermine the racial composition of the study sample [54, 33], thereby resulting in sampling bias [54]. At an aggregate level, such bias obscures the true effectiveness of the experimental intervention in its intended population.

Given that overuse of exclusion criteria [42] may result in sampling bias, there is a need for greater transparency in the process of determining appropriate eligibility criteria [41], with awareness of how these criteria interfere with the clinical utility

of research findings [46]. Clinical researchers are encouraged to carefully examine the rationale underlying specific exclusion criteria, with the aim of revising eligibility criteria lacking scientific merit [41]. As such, poorly justified, ethically and/or scientifically suspect exclusion criteria (such as those which unwittingly influence the racial and/or socio-economic composition of the study sample) must be eliminated in an effort to increase external validity of the findings [45]. Indeed, AD clinical trials may benefit from development of a theoretical framework aimed at helping researchers examine how, why, and whether specific exclusion criteria may be appropriate for a study [55]. Recent work by Li and colleagues suggests a balance between eligibility criteria and safety to expand access to trials in AD [56]. Clinical studies should also provide detailed information on the number of potential participants excluded as a result of implementing such criteria [57]. Lastly, efforts must be made to eliminate exclusion criteria (such as vascular comorbidities associated with AD) which have been found to inequitably impact different racial groups and exclude large proportions of affected patients from AD clinical trials.

NEED FOR THE RECRUITMENT OF A STUDY PARTNER

AD research often necessitates the enrollment of dyads, the participant diagnosed with, or at risk of, AD as well as a study partner who is able to accurately report on the participant's ability to carry out basic and instrumental activities of daily living [2]. AD clinical trials have historically focused on recruiting spouses as study partners [2, 30, 58]. As a result, approximately two-thirds of study partners enrolled in AD research are often spouses [2, 10, 59]. This disproportionately high participation of spousal dyads is striking given that older adults without spouses comprise a majority of the population of potential participants. Furthermore, there is a recent increase in the number of older adults who reside alone [2, 60] and have limited access to study partners [31]. As a result, potentially eligible research participants may be excluded from ongoing studies due to their inability to identify a study partner [10].

As a representative example, adult children comprise a large proportion of caregivers to patients diagnosed with AD [8, 10]. Approximately 50% of participants who identified as being primary caregivers reported being caregivers to their parent(s)

diagnosed with dementia, and approximately 25% of all dementia caregivers are "sandwich generation caregivers" [8], providing assistance to their elderly parents as well as taking care of children under 18 years of age [8]. Ongoing clinical trials that fail to minimize research participation burden experienced by these adult children caregivers are often unsuccessful in recruiting them as study partners for such trials. As a result, they unwittingly exclude a large pool of potential participant dyads [30]. This exclusion is particularly problematic considering that underrepresented participants are particularly likely to enroll in clinical AD trials along with non-spousal study partners [10].

Adult children are also intricately involved in the potential participant's decision to enroll in AD clinical trials [10, 61, 62]. Caregivers who view intervention protocols used in ongoing AD trials as beneficial for patients may play a crucial role in decision-making surrounding the participant's decision to enroll in such studies [62–64]. Alternatively, the decision not to participate in an AD clinical study is frequently made by the older adult's caregiver unilaterally as they may hold less favorable attitude towards research, question the effectiveness of the intervention, fear potential side-effects, and wish to avoid increasing the patient's medical burden [9, 10, 62].

Factors negatively impacting the recruitment of non-spousal study partners also result in slower accrual of participants and limit generalizability of promising findings [10] therefore making it crucial to identify, measure, and successfully mitigate these barriers. Non-spousal study partners are more likely to experience increased opportunity costs such as lost wages or reduced time for other familial responsibilities [10]. Over half of these caregivers are actively employed in the workforce [65] and must also balance providing care to their aging parents while taking care of their minor children [8]. These limitations make it inherently difficult for adult caregivers to participate in ongoing AD clinical trials.

Efforts to mitigate these barriers—such as accommodating the study partner's work schedules in the form of shorter clinic visits, options to schedule evening or weekend visits, availability of in-home visits, and allowing remote participation by study partners [10, 62, 66–68] may facilitate recruitment of non-spousal dyads. Additionally, efforts to reimburse out-of-pocket costs (i.e., cost of fuel, parking fees, etc.) as well as modest compensation of the non-spousal study partner's time may also mitigate their

persistent lack of representation in AD clinical trials [10, 67]. Furthermore, providing patients and their caregivers frequent opportunities to ask clarifying questions to staff members [32, 63] stagger and reiterate important trial information, as well as discuss the risks and benefits associated with participation in the clinical trial may also increase participant recruitment [61] by allowing adult caregivers to gather more information about the AD clinical trial. Caregivers may be more willing to encourage and support patient participation if they have greater knowledge about the clinical trial. Lastly, AD clinical trials may increase caregiver participation in ongoing research by providing them with supportive services (such as psychological support, counseling services, and/or support groups) aimed at reducing caregiver fatigue and promoting their psychological wellbeing.

PARTICIPANT BURDEN

Patients diagnosed with AD may be motivated to participate in research studies due to their desire in advancing research [62, 67]; however, participant burden in the form of potential physical risk, logistical inconvenience, and opportunity costs may deter their subsequent enrollment in ongoing AD clinical trials. Past studies have identified potential for risk to the participant's physical health as a significant deterrent to their participation in ongoing studies [9, 10, 62, 69–71] and have found that the patient's willingness to participate in clinical studies decreases as the level of risk associated with participation increases [62]. Individuals may worry about the potential side-effects associated with the experimental intervention, which may increase their reluctance in enrolling for available clinical trials. Family members may discourage a patient from participating in clinical trials if they question the effectiveness of the intervention or wish to avoid increasing the patient's medical burden [10] resulting from greater frequency of medical appointments. Furthermore, negative social/emotional implications of labelling an individual with a specific neurodegenerative disorder, typically required for participation in a clinical trial, may also reduce their willingness to enroll in ongoing studies [62]. For example, a patient may be comfortable with a diagnosis of "dementia" but not with the label "Alzheimer's disease" required for the trial. More recently, the potential increased risk of COVID-19 infection associated with multiple trips to the clinical trial site may

also shift participant willingness to participate in person and thus the perception of an increased burden [66].

In addition to potential health risks, structural and logistical challenges such as demanding medical appointments [62, 70–72], lengthy study durations spanning multiple years [61], requirement to undergo repeated diagnostic and/or neurocognitive evaluations [2, 69, 70], health insurance issues [70], lack of adequate transportation to and from the medical facility [40, 62, 67, 69, 71, 73], and high costs involved in transportation [67, 69, 73] may further burden the participant and deter them from enrolling in ongoing clinical trials. Finally, economic constraints [72] and opportunity costs in the form of lost wages, coupled with lack of any financial compensation for their time [67] may also negatively impact recruitment efforts. A recent analysis by Rios-Romenets and colleagues [74] suggests nearly half of prospective, high-risk participants decline participation, largely due to factors related to study burden, including the protocol itself, as well as travel and work burden.

In order to address participant burden, clinical researchers may consider providing extensive psychoeducation, engagement, and additional incentives for AD clinical trials. In general, this approach is captured by focused effort on delivering a strong return of value to participants—a critical design criteria for all but the most privileged prospective participants [75]. Such efforts may increase patient knowledge of the clinical trial and eliminate any uncertainty surrounding potential risks or side-effects of participation [71]. Clinical researchers must also prioritize patient health and safety by frequently monitoring their physical and psychological health and promptly addressing any side-effects experienced by the patient [71]. Additionally, positive views about the trial brought on by psychoeducation around the patient's potential to directly benefit from participation [61, 62, 67], learn more about their clinical condition [62], and advance AD research [9, 62] may help mitigate some potential burden associated with enrolling in clinical trials and facilitate research participation. Finally, providing flexible appointment times and locations (evening or weekend appointments, as well as in-home appointments) [67, 71], financial compensation commensurate with opportunity costs such as lost work wages or need for child, elder, or spousal care [67, 71], and adequate transportation to and from medical appointments [67, 71, 73] may further alleviate participant burden and facilitate research participation.

BARRIERS IN PRIMARY CARE SETTINGS

AD is increasingly diagnosed and managed in primary care clinics as opposed to specialty memory clinics, particularly for populations underrepresented in AD research [61, 76–79]. Older adults experiencing memory concerns often first relay these concerns to their primary care providers during routine outpatient appointments [2]. As such, AD researchers looking to improve participant recruitment for their clinical trials would benefit from cultivating a working relationship with community-based primary care providers in order to receive appropriate patient referrals from them [73]. However, community providers may be unaware of ongoing AD clinical trials [2] as well as potential treatment interventions available to their patients as a result of their participation in such clinical trials. Lack of communication between community providers and researchers may limit the provider's understanding of the study and its potential to benefit their patients [69]. This breakdown in communication can negatively impact a provider's willingness to assist with patient recruitment [69]. Furthermore, poor communication in conjunction with absence of any formal recruitment training for referring providers may cause them to lack confidence in their ability to explain the study to potential participants [61]. Time constraints experienced by providers working in busy community clinics may also decrease their engagement in ongoing clinical research [73]. Provider engagement may also be thwarted by their fear of losing patients to medical research sites [73, 80]. Absence of research initiatives being embedded in the clinic culture of AD patient care [61] may make it difficult for medical providers to successfully identify potential participants and refer them to AD clinical trials they may be eligible for.

Potential efforts to mitigate these barriers may include direct outreach through in-person meetings with medical providers at primary care clinics [81–84] in an effort to provide detailed information about the study, address any concerns identified by the provider [69, 73], and communicate ongoing progress of the study [73]. Engaging medical providers by providing tailored returns of value at the primary care setting may also be warranted, such as CME education programs, patient education materials [73], or research opportunities [85]. These opportunities may also prove to be helpful in motivating physicians to refer appropriate patients to ongoing clinical trials.

Furthermore, researchers would benefit from highlighting potential experimental treatment options the patient may be able to pursue, as such expansion of treatment interventions may add greater value to the existing patient-provider relationship [73]. Respect for and design of this existing relationship and efforts to foster a non-competitive, mutually supportive working relationship with the provider may also increase provider engagement with ongoing recruitment efforts as a clinician champion [73, 86, 87]. This relationship may be further bolstered by employing supportive research infrastructure in primary care settings such as research coordinators, research support staff, and patient navigators to assist with recruitment and enrollment activity in outpatient community clinics where providers see their patients. Such supportive infrastructure would ensure that recruitment activities do not encroach on the provider's direct patient care activities and may further increase their willingness to engage in recruitment efforts [73]. Lastly, AD research recruitment could potentially be facilitated by requesting a patient's consent to be contacted for eligible research initiatives when they seek medical care at the clinic [61].

PARTICIPATION BY UNDERREPRESENTED POPULATIONS

Despite substantial efforts to include ethnically and racially diverse individuals in ongoing AD research, their enrollment in clinical trials have been low. Nearly three decades following the passage of the National Institute of Health (NIH) Revitalization Act in 1993, their underrepresentation in AD clinical trials remains an unfortunate reality [9, 52, 70, 73]. For example, African American and Hispanic participants comprise well under 10% of the Alzheimer's Disease Neuroimaging Initiative's (ADNI) research sample in 2012 [52, 88] despite evidence of higher prevalence and incidence of AD in these populations [52, 89, 90]. Existing research has also demonstrated a difference in AD pathophysiology between African American and Caucasian populations, which may unwittingly result in underdiagnosis of AD among African Americans [91, 92]. The exclusion of such populations from ongoing AD research undermines the generalizability of research findings to broader patient populations. Equally concerning is the fact that several ethnic and racial populations, such as American Indians/Alaska Natives as well as Pacific Islanders, are frequently minimally represented (or

entirely absent) in AD clinical research [9, 88]. This complex set of barriers stem, in part, from the lack of a clear definition in terms of what participant diversity in AD research should encompass. Although some recent efforts have focused on increasing ethnic and racial diversity among AD clinical trial participants, few studies have focused their attention on recruiting socioeconomically diverse [9] or rural participants. Indeed, very little effort has been made in recruiting diverse populations apart from African-American racial and, less frequently, Latinx ethnic minorities. Furthermore, few studies have made efforts to recruit participants with differing educational attainment.

Beyond health disparities in AD itself and with associated comorbidities, underrepresented groups broadly face unique barriers preventing their participation in research that include 1) low health and research literacy; 2) poor or inconsistent relationships between their communities and researchers; 3) deep mistrust of the academic medical research model; 4) lack of cultural competency and representation among research faculty and staff; 5) language barriers; and 6) inclusion/exclusion criteria and clinical trial design that disproportionately bar individuals from some communities from taking part in research [2, 28–33]. These barriers to participation differ but often overlap across cultures and regions, hindering the adoption and implementation of recruitment strategies that adequately address local community concerns. The above-mentioned challenges to recruitment of AD research run the risk of delaying invaluable treatment advances, threaten the validity of the study, negatively impact generalization of the research findings, and creating disparities in disease treatment [31].

In addition to previously examined physical, psychological, and logistical burdens experienced by research participants, recruitment of diverse populations in AD clinical trials are further limited by mistrust [9, 93], fear of exploitation [70, 93], history of racism in research [9, 94], as well as cultural beliefs surrounding illness [91, 94], and medical procedures associated with AD research [94]. African American research participants, whose barriers to AD research participation are the best documented, have frequently cited their mistrust of the medical community as a significant barrier to AD research participation [9, 70, 93] as they fear that researchers may deliberately withhold pertinent information from them as well as expose them to unnecessary research risks [93]. Historical evidence of past medical abuse as well as unethical treatments of ethnically and racially

diverse participants has further cemented this sense of mistrust, and participants frequently feel that researchers may use them as “guinea pigs” in their effort to obtain meaningful findings from their clinical trial [93]. Lastly, cultural beliefs held by various ethnic and racial groups may influence their decision to participate in ongoing clinical trials [93, 94]. For example, African American participants who view memory loss or dementia as a natural course of aging may be hesitant or unwilling to participate in research aimed at delaying disease onset or progression [93]. In a similar vein, cultural beliefs held by various Asian racial groups with regard to maintaining the integrity of the human body upon the individual’s demise may affect their willingness in agreeing to brain donations after their death [94].

Despite the central importance of adequate and representative study populations to advance scientific understanding, most research recruitment to date is performed ad-hoc, with focus on previously recruited participant populations, with little-to-no sustained engagement or trust from community or clinician partners, and with no dedicated resources. The few publications on recruitment best practices in aging and AD largely reflect idiosyncratic efforts or offer theoretical suggestions that are not empirically feasible. One of the most prominent consequences of this lack of engagement and recruitment infrastructure in AD research is a persistent difficulty in successfully recruiting diverse participants from underrepresented communities [70]. Hence, in order to mitigate above-mentioned barriers, researchers are encouraged to employ broad-based strategies aimed at increasing participation by underrepresented populations in AD research, such as appealing to participants currently enrolled in other ongoing AD research, increasing referrals from hospital and/or university-affiliated as well as community-based clinics, as well as educating physicians on appropriate referrals [31]. Researchers would benefit from utilizing interactive in-person efforts to establish rapport with members of diverse communities, focused primarily on awareness-raising and engagement efforts, rather than direct recruitment activities [93]. Engaging potential research participants in easily accessible, community-based locations may also help communicate genuine interest and concern for the individual, which could help reduce their mistrust of the researcher [93]. Recruitment efforts focused on engaging key community stakeholders such as community leaders and church pastors to disseminate accurate information about ongoing AD clinical trials

among community members may also be beneficial in mitigating the community's mistrust of researchers and increase participation by ethnically and racially diverse populations [70, 73]. Use of existing trusted networks (such as churches and other faith communities) to advertise ongoing recruitment efforts as well as highlighting the relevance of the clinical trial to the community's health needs would further instill a sense of trust among community members and motivate them to enroll for such studies [70]. Efforts to increase research participation in underrepresented communities necessitates that ongoing challenges in appropriately seeking informed consent for AD research participation be continually refined and addressed in efforts to make it applicable to underrepresented populations. In addition to building strong relationships with key community stakeholders, the development of patient organizations and/or advocacy groups specifically designed to meet the unique needs of underrepresented populations may also be a novel approach in addressing recruitment barriers in this population. Furthermore, employing full-time community outreach coordinators with congruent racial identities and language abilities [9, 33] in efforts to educate and enroll potential participants as well as disseminate research findings within the community [73] would also facilitate AD research participation among diverse community members. Such efforts could help eliminate their fear of exploitation by cultivating a trusted relationship with researchers characterized by reciprocity whereby participants may benefit from their enrollment in ongoing research studies [33]. Lastly, researchers must be mindful of structuring their clinical trial in the broader context of AD management, such that they provide underrepresented populations with continued access to care beyond the designated clinical trial period. In order to do so, researchers may need to consider novel approaches such as an open-label period for drugs/interventions that are found to be efficacious in symptom management.

Although the fields of aging and AD have advanced multiple frameworks and even reviews on engagement and recruitment of underrepresented minorities [2, 6, 17, 28–31, 33, 68, 95–105], these investigations have several key limitations. For example, many treatments of engagement and recruitment focus on specific communities and populations, with unclear implication of whether a given method might be replicated in new setting or should be modified (and how specifically a method might be modified). Additionally, protocols of action remain underspecified

relative to standard research design, and also lack common ontology, metrics, data, outcomes across studies. Indeed, common terms like *engagement*, *outreach*, and *recruitment* are not consistently or precisely defined within aging and AD research, much less harmonized with engagement and recruitment science outside of the field. Lastly, very few investigations present comparative effectiveness design or even a framework for comparison (although see Rasouly et al. [106], which is outside of aging and AD).

CALL TO ACTION AIMED AT IMPROVING ENROLLMENT IN AD CLINICAL TRIALS

Unless purposeful action is taken to address these disparities in research recruitment, enrollment in AD clinical research will continue to reflect a shrinking and decreasingly representative segment of the US population. Existing health disparities in aging and AD may be compounded without comprehensive and deliberate intent to include underrepresented populations in ongoing and upcoming research studies [35–37]. At present, despite newly available resources such as the National Institute on Aging's Alzheimer's and Dementia Outreach, Recruitment and Engagement (ADORE) platform, individual research sites for ongoing AD clinical trials differ widely in their recruitment strengths, challenges, infrastructure, and goals. A dearth of peer-reviewed research on the optimization of recruitment tactics further exacerbates this variation. It is therefore imperative to develop strong, replicable research on recruitment/engagement plans for AD research to address this problem. There is a clear need to build an infrastructure of research recruitment that proposes detailed protocols to adequately address this heterogeneity.

There is a need to identify effect sizes, testable theoretical foundations, identification of subfields, outcomes beyond screening and enrollment, and a de-confounding of interventional approaches from charismatic individuals who may themselves drive recruitment—separate from even the most carefully considered of methods. Practically speaking, these limitations serve as a set of collective *researcher* barriers for engagement and recruitment, preventing study teams from applying or even identifying relevant literature and resources to improve site-specific practices. Given the urgency of needed

Table 1

Current barriers to Alzheimer's Disease (AD) research recruitment as well as potential solutions aimed at mitigating these barriers

Barriers to Alzheimer's disease research recruitment	Potential solutions to address current recruitment barriers
<i>Comorbid medical and/or psychiatric disturbances</i>	
Reliance on arbitrary exclusion criteria without adequate accompanying rationale for the same [43–46]	Greater transparency in the process of determining appropriate eligibility criteria [43]; revision of exclusion criteria that lack scientific merit [43, 47]; provide detailed information on number of excluded participants as a result of adopting each exclusion criteria [60]
Use of cardiovascular disease (CVD) as an exclusion criterion for AD recruitment, which may erroneously screen out potential participants [44, 52]	Greater awareness of how this criterion interferes with clinical utility of research findings [48]; balance between eligibility criteria and safety in expanding access to AD trials [59]
<i>Need for recruitment of a study partner</i>	
Focus on recruitment of spouses as study partners [2, 10, 61–63]	Increased efforts to recruit non-spousal study partners (e.g., adult children caregivers) by addressing specific barriers impacting participation from this population [8, 10]
Increased opportunity costs such lost wages, time off work, reduced availability for other familial responsibilities [10, 69]	Accommodate caregiver's work schedule by providing shorter visits, options for evening and/or weekend visits, increasing availability of in-home visits, developing opportunities for remote participation [10, 66, 70–72]; reimbursement of out-of-pocket costs [10, 71]; providing modest monetary compensation [10, 71]
Caregivers lacking favorable attitudes towards research, fear of potential side-effects, and wish to avoid increasing patient's burden [9, 10, 66]	Provide frequent opportunities to ask clarifying questions [67, 73]; frequent opportunities to discuss risk and benefits of research participation [65]
<i>Participant burden</i>	
Fear of potential physical risk and adverse side-effects [9, 10, 66, 74–76]	Extensive psychoeducation aimed at increasing patient knowledge and eliminating uncertainty [76]; researchers should prioritize patient health and safety [76]; delivering a strong return of value to participants [80]
Logistical inconvenience, opportunity costs (e.g., lost wages, lack of financial compensation) [9, 10, 66, 74–76]; need for frequent medical appointments [10]; lengthy study durations [65]; requirement to undergo repeated diagnostic evaluations [2, 74, 75]; lack of health insurance [75]; lack of adequate transportation [42, 66, 71, 76, 78]	Provide flexible appointment times/locations [71, 76]; financial compensation commensurate with opportunity costs [71, 76]; convenient transportation to and from medical appointments [71, 76, 78]
<i>Barriers in primary care settings</i>	
AD frequently being diagnosed in primary care settings as opposed to specialty clinics [65, 81–84]	Cultivate a working relationship with community-based primary care providers [78]
Community-based providers being unaware of ongoing AD clinical trials [2]; lack of communication between community providers and researchers [74]; absence of formal training for referring providers [65]; time constraints experienced by community-based medical providers [78]; fear of losing patients to medical research sites [78, 85]	Direct outreach to community-based providers through in-person meetings [86–89]; providing detailed information regarding the clinical study [74, 78]; educating community providers on appropriate referrals [40]; increasing engagement from providers by offering tailored return of value programs such as CME education and research opportunities [78, 90]; fostering a non-competitive, mutually-supportive working relationship [78, 91, 92]; providing supportive research infrastructure to reduce burden on community-based providers [65, 78]
<i>Participation by underrepresented populations</i>	
Lack of adequate representation by ethnically/racially diverse populations [9, 54, 93–95], socially diverse populations [9], and rural populations [9]	Appealing to racially-ethnically diverse participants currently enrolled in ongoing research [40]; increasing referral from hospital and community-based clinics [40]; educating physicians on appropriate referrals [40]
Unique barriers preventing participation such as mistrust [9, 75, 98]; fear of exploitation [75, 98]; history of racism in research [9, 99]; cultural beliefs surrounding illness [96] as well as medical procedures [98, 99]	Establishing rapport with members of diverse communities [98]; Engaging potential research participants in easily accessible, community-based locations [98]; engaging key community stakeholders [75, 78]; use of existing trusted networks to advertise recruitment efforts [75]; employing full-time community outreach coordinators with congruent racial identities and language abilities [9, 57, 78]

advancements in precision research engagement and recruitment, there is a clear need for a kind of precision engagement and recruitment, founded on theoretical mechanisms that are specific, testable, modifiable, and, critically, transferable between sites without a loss of efficacy. Without critical developments in operationalization and measurement of engagement and recruitment activities, and deliberate intent to include underrepresented populations in research studies, we risk misunderstanding—or worse, exacerbating—existing disparities in AD. Indeed, recent work by Gleason and colleagues [107] demonstrated that recruitment bias confounds with racial identity in determining AD risk in large datasets such as the National Alzheimer's Clinical Consortium repository, suggesting that our largest, most crucial resources already inaccurately estimate racial disparities in AD. Inclusion of underrepresented populations in AD research, if only for the sake of accurate estimation of dementia risk, is a promising frontier that requires advanced understanding of effective recruitment and engagement mechanisms. Lastly, addressing current barriers for recruitment of underrepresented populations in AD research may provide us with a much-needed framework to address similar barriers in low/middle income countries around the world. Future research aimed at increasing recruitment efforts in AD clinical trials must adopt a cross-cultural and cross-national approach to address these recruitment barriers in a global context.

CONCLUSION

Difficulty in participant recruitment runs the risk of delaying treatment delivery [108] by inflating the duration and cost of the clinical study [6, 108] and has the potential to threaten the external validity of research findings [108]. Rather than accept these barriers as omnipresent, we encourage clinical research sites to individually identify and quantify barriers to research participation and develop novel recruitment interventions to address them, and to share new knowledge from these efforts so that best practices can be disseminated widely. We recommend closely tracking the conversion rate of individuals expressing interest in AD research to those who enroll in research studies according to a proposed participant journey funnel, determining whether the subset moving closer to research participation is random, or at minimum appropriately representative. In this way,

AD research teams may be more fully empowered to understand where recruitment barriers are particularly acute within their research workflow, and may accordingly deploy more relevant and timely engagement, recruitment, and retention activities.

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