Promoting diversity in clinical trials: insights from planning the ALUMNI AD study in historically underrepresented US populations with early symptomatic Alzheimer's disease

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Summary

Clinical trial participation across disease areas, including Alzheimer's disease (AD), has been biased towards White participants of European ancestry. To support clinical decision-making across diverse populations, we must recognize and address barriers to trial participation. To inform the design of ALUMNI AD, a trial focused on historically underrepresented AD populations, we held advice-seeking fora with key stakeholders to understand barriers and identify potential solutions to maximize trial participation of underrepresented racial and ethnic groups in the US. Strategies identified from this process include: obtaining and implementing recommendations from community stakeholders; establishing a simple and inclusive prescreening and screening process; supporting participants and care partners; identifying and activating community-centric clinical sites; and demonstrating community commitment. While ALUMNI AD did not commence, we hope that our insights could be incorporated into future studies to improve diversity, equity, and inclusion in AD clinical research.

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Keywords: Clinical trial protocol; Diversity, Equity, Inclusion; Underrepresentation; Alzheimer's disease; Social determinants of health

Introduction

Race- and ethnicity-based disparities in clinical research can negatively affect individuals and the healthcare system; differences between drug exposure and response across racial/ethnic groups may impact clinical data, confounding treatment outcomes and expectations in practice.[1] Underrepresentation in clinical research can restrict access to potentially effective treatments for affected groups, despite regulatory approval.[2] Additionally, health disparities can incur substantial societal costs; a US report estimated that alleviating 1% of health disparities through better representation in clinical research would save $60 billion in heart disease management alone.[2]

An important factor of underrepresentation originates from systemic racism, including healthcare disparities and discrimination in clinical practice and research.[2–4] Discriminatory practices, e.g. those exhibited during the Tuskegee Syphilis study, continue to fuel distrust in healthcare in non-White populations, potentially dissuading participation in clinical trials.[2] Here, we will concentrate on modifiable factors that can be addressed to facilitate recruitment of racially and ethnically underrepresented populations (URPs) into clinical trials.

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Sponsor-level barriers to clinical trial representation

The lack of inclusivity in clinical research can bring nuanced logistical and psychological challenges.[1] Despite well-documented racism and discrimination experienced by diverse racial and ethnocultural populations in healthcare, many express interest in clinical trial participation.[2,4] However, they are infrequently invited; sponsors and researchers may carry misconceptions relating to their unwillingness to participate in trials or adhere to treatments.[2,3] Furthermore, there is limited access to clinical trial sites in locations with a high proportion of URPs; such areas often have greater disparities in healthcare infrastructure and inadequate resources to support clinical trials.[1,2,4,5] Clinical site staff do not routinely interact with diverse communities, and there is often a cultural mismatch between the study team, coordinators and participants, along with a lack of culturally and linguistically appropriate resources to support patient education, possibly leading to subpar outreach to, and engagement with URPs.[1,6] This can result in lower health literacy, and reduced awareness of clinical trial participation value and the ethical elements in place to safeguard autonomy and safety (e.g. informed consent), potentially provoking feelings of alienation across URPs, further hindering likelihood of participation.[1,6] Finally, time and resource constraints placed on study participants and care partners can disproportionally affect these communities compared with their White counterparts, due to factors such as conflicting responsibilities (e.g. work and family commitments) or transportation challenges, which can be a compounding factor in the lack of representation.[1,2,4,6,7]

Growing momentum toward health equity and inclusion

While there has been ongoing advocacy and calls to improve representation in clinical trials,[8,9] a renewed momentum was triggered by the disparities in outcomes related to social determinants of health (SDOH) during the COVID-19 pandemic.[10] This captured the attention of key stakeholders, including national organizations and health institutions,[1,5,8,11–13] who are increasingly identifying steps for improving racial and ethnocultural diversity within clinical trials.[2,14,15] For example, the US Food and Drug Administration (FDA) has a dedicated Office of Minority Health and Health Equity providing multilingual resources to educate the public on clinical trial diversity and, as of 2022, advises sponsors to submit a "Race and Ethnicity Diversity Plan" with enrollment plans for URPs.[12,13]

Underrepresentation in Alzheimer's disease (AD) clinical research

In the US, AD has a disproportionately high prevalence, incidence, and cumulative risk in non-White (Black or African American, Hispanic or Latino, and American Indian or Alaska Native) populations compared with White populations, with cases of AD among minority groups projected to more than double by 2030.[16,17] However, in AD clinical research, participants are not representative of real-world epidemiology,[16–18] with approximately 95% of participants being White.[18] This limits the understanding of AD pathogenesis, creates challenges for data generalizability, and compounds health inequities.[9,19] Although generalizability may be addressed with statistical methods (e.g. reweighting estimators),[20] it remains critical to address barriers to participation in AD trials. Previously recognized barriers specific to AD trial recruitment include comorbidities and/or psychiatric conditions, failure to meet cognitive inclusion criteria, strict care partner requirements, participant and care partner burden, cultural beliefs and/or practices leading to late diagnosis, and lack of or limited awareness of primary care settings where AD is diagnosed,[19,21] especially in early symptomatic stages.[22]

This article aims to share insights from designing a protocol for ALUMNI AD, a dedicated study in US racial and ethnic URPs with early symptomatic AD, and highlight insight-based focus strategies for advancing inclusivity in AD research.

Rationale for ALUMNI AD

ALUMNI AD was a planned phase 3b open-label study, evaluating the effects of gantenerumab, an anti-amyloid monoclonal antibody, in early symptomatic AD. Whereas the previous phase 3 GRADUATE I and II studies of gantenerumab comprised a mostly non-Hispanic White patient population,[23,24] the purpose of ALUMNI AD was to evaluate gantenerumab in US URPs (Black or African American, Asian or Asian American, Native American or Alaska Native, Native Hawaiian or Other Pacific Islander, Hispanic or Latinx) to inform clinical decision making. The objectives, endpoints and study design of ALUMNI AD are shown in Supplementary Fig. S1.

We envisioned this study as an opportunity to address modifiable barriers to the lack of representation in AD trials identified through stakeholder input and trials dedicated to improving representation in other disease areas.[1] However, because the GRADUATE studies did not meet their primary endpoints,[23] ALUMNI AD was not initiated. Nonetheless, the development of this study has highlighted key focus strategies aiming to increase participation of traditionally URPs for future trials in AD and other disease areas.

Engagement with experts in AD

The study protocol development process involved collaboration with multiple external stakeholders,

chosen according to their Diversity, Equity, and Inclusion (DEI) expertise and/or interest in understanding the challenges across diverse AD communities. Stakeholders had a balanced sex ratio, diverse training backgrounds, and experience in various settings and geographies across the US. Every historically URP listed in the inclusion criteria of the study was represented across these stakeholders. Advice-seeking engagements were held to establish best practices in protocol design, recruitment and retention, community outreach, and building trust with the targeted population (Fig. 1).

Strategies to address barriers to AD trial participation

The following modifications were incorporated into the ALUMNI AD study design and implementation to address identified barriers to recruitment (Fig. 2): 1) including a simple, location-flexible prescreening period; 2) improving the screening process (including modifying the study eligibility criteria, without compromising safety); 3) improving site access; 4) upskilling site capabilities; 5) developing a companion document for study participants; and 6) providing additional support for participants and care partners. An

		TAE	CRRA	SC	Key takeaway
Protocol Design*	Entry criteria	✓	✓		Consider population-specific comorbidities and social determinants of health when defining entry criteria
	Screening	✓	✓	✓	Optimize facilities and staffing for screening activities to reduce burden on participants and care partners; follow up with participants shortly after prescreening and main screening to help them navigate the next steps
	Treatment period		✓	✓	Time commitment to many clinical studies is significant, and navigating through the participant journey can be confusing and intimidating for participants and care partners. Provide support for participants and care partners to maximize retention throughout the treatment period
	Outcome measures	✓	✓		Biological markers are important outcome measures, but need to be clinically meaningful; participants may demonstrate fear and mistrust of outcomes measures and safety throughout the study
	ICF		✓		ICFs are designed with the intent to inform participants and care partners on study details and requirements ensuring that they have the adequate information to decide whether they want to participate in the study, but ICFs are often overwhelming for participants and care partners
Community Engagement	Recruitment and retention	✓	✓	✓	Providing services to develop a sense of community Leveraging existing relationships with communities Developing culturally relevant educational opportunities and tools Demonstrating a commitment to participants beyond the clinical trial will promote recruitment and retention
	Community outreach		✓	✓	
	Educational materials	✓	✓	✓	

Fig. 1: Seeking input and advice from multiple stakeholders throughout the ALUMNI AD design process, through 15 advice-seeking events, held from May to December 2022. An external party recorded the contributions from stakeholders and developed a clinical trial strategy document based on the outcomes of the discussions held during these advice-seeking activities. *The Genentech External Council for Advancing Inclusive Research, comprising expert clinicians, academic researchers, and patient advocates across several therapeutic areas who are working towards new standards and principles for inclusive research at Genentech, Inc., were also consulted to inform protocol design. AD, Alzheimer's disease; CRRA, Community Research Recruitment Accelerator on Aging; ICF, informed consent form; SC, study coordinator; TAE, therapy area expert; US, United States.

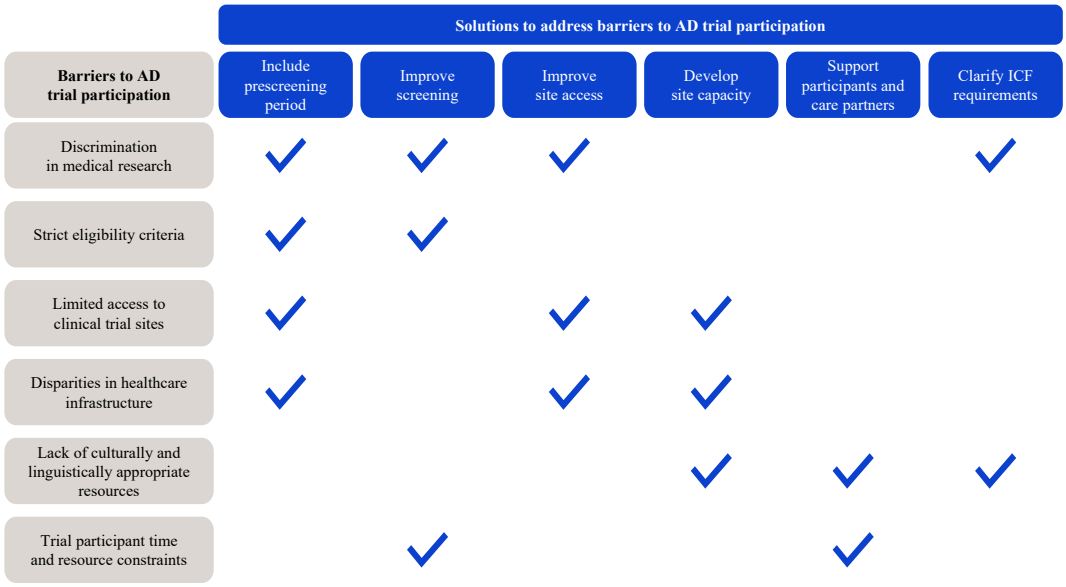

Fig. 2: Summary of barriers to, and solutions designed to improve, AD trial participation in historically underrepresented US populations for ALUMNI AD. AD, Alzheimer's disease; ICF, informed consent form; US, United States.

overview of the rationale for each modification made and the planned actions is shown in Table 1.

Focus strategy #1: Listen to and implement recommendations from community stakeholders to the maximum extent possible

Building trust with underrepresented communities was foundational in our efforts, achieved through the identification of key US stakeholders and collaboration with community partners who currently serve and engage these communities. These entities have existing infrastructure/mechanisms to assist with healthcare needs and social support navigation. Continued engagement and advice-seeking from community members, including partnering with contract research organizations, organizing community advisory boards, and validating study recruitment and support strategies with communities, is common amongst studies aiming to improve clinical trial representation[1,2,5,7,14,25,26]; e.g. the Diversity Task Force and Engagement Core to improve recruitment across the Alzheimer's Disease Neuroimaging Initiative (ADNI) studies.[5,25]

During the design of ALUMNI AD, effectively engaging with these communities was critical. We found that it was paramount to include stakeholders early in conceptualizing the trial design, including potential participants, their care partners, and experts with combined knowledge in AD and principles of inclusive research, while ensuring diverse representation across stakeholder groups. Their input was vital to aspects related to increasing community engagement, e.g. study protocols, informed consent forms (ICFs), and culturally appropriate patient and caregiver support and resources (Fig. 1).

Focus strategy #2: Establish a simple and inclusive prescreening and screening process

Eligibility criteria and associated screening assessments in clinical studies are critical to ensure participant safety and scientific validity, but may disproportionately exclude URPs due to historical bias towards White participants.[1,21] In ALUMNI AD, the inclusion of a prescreening assessment and targeted, study-appropriate modification of the entry criteria were key aspects of tailoring the study protocol to the target population.

Due to systemic racism across medical research, access, and eligibility criteria, certain populations tend to be excluded before screening or disproportionately fail screening procedures.[21] To optimize recruitment, the study protocol included a digital prescreening assessment that aimed to overcome geographic hurdles to participation and decrease the burden on patients and study staff, utilizing simple, rapid, yet validated testing methods to exclude ineligible individuals before initiating full study enrollment requirements. These digital assessments also captured functional biomarkers and could be performed in flexible and remote settings, meeting participants in areas close to home and central to their community.

Moreover, partners such as the Global Alzheimer's Platform Foundation (GAP) had planned to use a mobile medical vehicle, equipped to perform prescreening tests, as well as provide recruitment, awareness, and

Study element	Insights	Planned modifications
Prescreening	**Findings from literature:** Due to systemic racism across medical research, access, and eligibility criteria, URPs tend to be excluded before the screening process or disproportionately fail screening procedures.[21]	1 Recruit participants for ALUMNI AD not only in the clinic, but also through community outreach events and mobile stations 2 Administer prescreening assessments in a flexible community setting (e.g. at local pharmacies or health fairs) or clinical site 3 Include prescreening period with accessible assessments to exclude cognitively normal individuals and individuals less likely to be amyloid PET-positive, thus decreasing patient and site burden by only advancing participants with a greater likelihood of eligibility • Conduct digital cognitive tests that include both cognitive assessments (four tests assessing psychomotor function, attention, visual learning, and working memory), and functional biomarkers (e.g. eye, speech and language tracking) • If cognitive test results are suggestive of cognitive impairment, individuals to undergo blood-based biomarker tests (Elecsys® β-Amyloid [1–42])
Screening*	**Findings from literature:** A disproportionate number of individuals from historically URPs fail to meet inclusion criteria on cognitive or functional screening measures. The reasons for this are not always clear, but one explanation is that commonly used thresholds may not be appropriate across patient populations.[21] **Stakeholder input:** Factors such as common comorbidities, patterns in AD presentation (e.g. amyloid load, ARIA), socioeconomic status, language, and education should be considered for each reported race/ethnicity to minimize screening failure for potential participants in these populations.	1 Use cognitive and functional assessments that had normative data or adjusted cut-off points for the targeted populations to define inclusion criteria for ALUMNI AD 2 Utilize validated instruments with lower training burden on site staff and less patient administration time
Screening*	**Findings from literature:** Cut-off values in some laboratory tests disproportionately exclude certain participant groups. Notably, folic acid deficiency has been shown to have a higher prevalence in American Indian or Alaska Native and African American populations; vitamin B12 deficiency is more prevalent in people of Asian descent; and the reference limits of thyrotropin tend to be lower for Black Americans compared with White or Mexican Americans.[27,28]	1 Patients with evidence of folic acid deficiency or vitamin B12 deficiency, and those with abnormal thyroid function as indicated by abnormal laboratory tests, could be eligible for inclusion, based on the treating physician's judgment • These changes were considered appropriate given the primary endpoint of the study (change in brain amyloid load) and the lack of impact on participants' safety • No changes were made to exclusion criteria associated with the risk of ARIA or other areas that may compromise participant safety
Screening*	**Stakeholder input:** Flexibility in care partner participation is important, as the precise role of a care partner may vary within and between participants of a trial.	1 Do not restrict participants to a single care partner 2 Allow care partners to not attend every visit 3 Provide more flexibility in the level of interaction between care partners and participants
Access to clinical sites	**Findings from literature:** Access to clinical sites for historically URPs is a key barrier to clinical trial participation, which is augmented by disparities in healthcare infrastructure across different communities.[1]	1 Use a geomapping tool synergistically with a site selection survey to prioritize sites with existing capacity, infrastructure, and high levels of community engagement, that were in close vicinity to counties with the highest prevalence of underrepresented patients with AD • The National Alzheimer's Disease Index™ (NADEX) was a geomapping tool developed by UsAgainstAlzheimer's and funded partially by Genentech, and aimed to visualize and analyze Alzheimer's statistics by geography and by demographics. The tool enables identification of counties across the US with the highest and lowest Alzheimer's prevalence by race and ethnicity, through analyzing Medicare data.[29] 2 Preference for sites that already had resources or events directed to engaging with underrepresented communities 3 Connect traditional research sites with community service institutions if participants lived in more remote areas
Site capabilities and capacity	**Stakeholder input:** Upskilling site capabilities is crucial to increase access of more diverse populations to clinical trials. Collaboration with community partners and training investigational site staff is critical for building site capacity and overcoming disparities in health care infrastructure.	1 Partner with trial optimization partners who can provide programs on cultural insight training for all of those at study sites 2 Increase the capacity of safety net providers, including FQHC† 3 Optimize the process of qualifying raters to perform cognitive testing
Informed consent form (ICF)	**Stakeholder input:** Despite the importance of participants and care partners receiving adequate information for participation in a clinical trial, they often report feeling overwhelmed and struggle to comprehend the information in patient-facing materials.	1 Create a two-page document for patients and care partners structured similarly to the ICF, summarizing important high-level particulars about the trial, and providing information on participation requirements, in a simple and direct manner
Expanded support and resources for study participants and partners	**Stakeholder input:** In AD clinical research, recruitment and retention can be impacted by the burden of treatment, transportation to clinical sites, and scheduling assessments placed on participants and care partners.	1 Offer respite care services for care partners beyond transportation, e.g. additional time to run errands and meal provision 2 Work with care partners with special circumstances to accommodate their lifestyle

*Although ALUMNI AD did not commence, we had performed modeling and basic statistical calculations to estimate the potential effect of modifying the screening criteria on recruitment during the protocol development. †FQHC are federally funded nonprofit health centers or clinics that serve medically underserved areas and populations. For ALUMNI AD, collaboration was planned with specific FQHCs that had dedicated memory clinics, to invite patients to participate in a clinical trial as well as help them to partner with local sites to facilitate a referral network for patients interested in participation.
AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; FQHC, federally qualified health centers; ICF, informed consent form; PET, positron emission tomography; URP, underrepresented population; US, United States.

***Table 1*: Overview of the insights gathered and subsequent planned modifications to elements of the ALUMNI AD study, as identified through input from external stakeholders and current literature.**

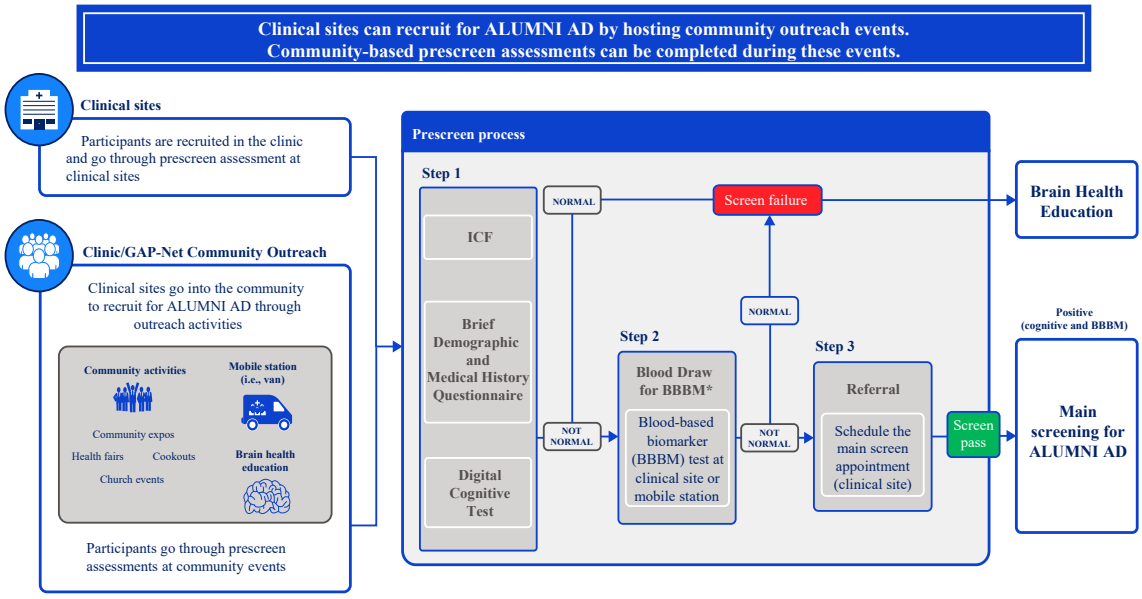

Fig. 3: Prescreening strategy for ALUMNI AD. *In individuals suspected of cognitive decline via digital test results, a positive BBBM indicates a greater chance that the impairment seen is due to AD and not other causes. AD, Alzheimer's disease; BBBM, blood-based biomarker; GAP, Global Alzheimer's Platform; ICF, informed consent form.

education services (Fig. 3). This focus on prescreening at the community level, as recommended by external stakeholders, would have allowed for more direct engagement with potential participants who are not on existing electronic databases, while also creating opportunities to build trust with and provide resources to URPs. Our approach was similar to that proposed by the ADNI4 research group to enable URP recruitment via a culturally informed digital marketing and social media campaign utilizing locally site-branded websites, digital prescreening assessments, and community navigators to provide tangible support to URPs.[25]

For ALUMNI AD, we aimed to include prescreening and screening criteria specific to AD clinical trials to maintain or improve scientific validity without compromising participant safety. This expands upon the study design modifications (e.g. reducing comorbidities-related exclusion criteria) previously suggested in the literature.[5] The ALUMNI AD screening process included the use of simpler and shorter validated assessments, modified cut-off values in certain laboratory parameters compared with the GRADUATE studies, and collection of information that would allow correlations to be drawn between SDOH and participants' outcomes. This study also included a longer rescreening period, such that patients who were interested in joining the trial but did not initially meet the eligibility criteria had the opportunity to rescreen. Key differences in the eligibility criteria for the GRADUATE studies (NCT03444870; NCT03443973) and ALUMNI AD are summarized in Supplementary Table S1.

Focus strategy #3: Support participants and care partners during the recruitment and treatment periods

It is crucial to understand the participation burden on patients and care partners and provide support to help them overcome structural barriers on a case-by-case basis. The ELEVATUM (NCT05224102) and CHIMES (NCT04377555) trials provided support for participants to address the financial burden and time commitment that patients could be facing.[1] For ALUMNI AD, given the nature of AD presentation, we planned to provide additional support and resources beyond financial reimbursement to alleviate participant and care partner burden, e.g. respite care services for care partners. When arranging respite care and potential partner agencies, we were advised to involve community members in the decision-making process to ensure appropriate services are offered.

Another consideration, as identified from stakeholder input and in literature,[1,7,30] was to promote better understanding of ICF content (e.g. patient and participant clinical trial rights). Thus, we aimed to develop a companion document to the ICF, providing information on participation requirements and study details in a simple and direct manner.

Finally, it was important to introduce flexibility in care partner involvement, both in terms of defining a care partner and in the level of interaction with the patient. In ALUMNI AD, participants would not have been restricted to a single care partner and care partners would not have needed to attend every visit.

Focus strategy #4: Identify and activate community-centric clinical sites

Training investigational site staff is a key focus area for improving access to clinical trials, which in turn can help overcome disparities in healthcare infrastructure.[1,2,7,30] Rather than providing generic DEI training, we aimed to collaborate with community partners to optimize training and resources (e.g. through community connectors that would provide concierge-level service with direct support to each site).

Furthermore, we sought to identify sites with existing connections and resources to support local communities based on learnings from past trials dedicated to historically URPs,[1] and by using a novel geomapping tool (the National Alzheimer's Disease Index™ [NADEX]; developed by UsAgainstAlzheimer's and funded partially by Genentech), assistance from the field medical teams, and a site selection survey. This would be supported by helping more centers and raters become qualified, increasing the number of potential sites. This community-focused approach used existing infrastructure and relationships, rather than simply providing transport and monetary support to facilitate participant access.

Focus strategy #5: Demonstrate community commitment and holistic support

Recommendations highlighted that community outreach should focus on building new, and leveraging existing relationships, while dispelling mistrust in clinical trials. In line with stakeholder input, others have proposed activities e.g. health literacy and programs developed to address areas of health inequities to enable community outreach and awareness.[7]

ALUMNI AD aimed to offer support in collaboration with community partners as informed by the communities themselves, for instance through community outreach events and mobile stations planned in the context of recruitment, whereby multilingual brain health education (e.g. a brain game training exercise) would be provided, regardless of whether individuals met the prescreening criteria. This would tackle the lack of culturally and linguistically appropriate resources and educate participants on ways to positively impact their brain health, as well as build trust and encourage wider engagement.

Future considerations

For completed studies, it would be advisable to report and disseminate race and ethnicity data and ensure the study results are communicated in layperson summaries in multiple languages.[1] Furthermore, on study conclusion, it is recommended to continue building rapport with the communities, for instance through communicating the impact of their participation on the study outcomes, once results are published.[7,30]

A limitation of this research is that ALUMNI AD did not commence, and despite statistical modeling performed to predict the potential impact on recruitment, there are no clinical data to inform whether the proposed methodology would yield positive results once implemented. Furthermore, as our insights are based on consulting with US communities, it is important to discuss proposed solutions with representatives from local communities due to varying needs, preferences, and feasibility. Finally, the open-label design and expected sample size of ALUMNI AD would not have been sufficiently powered to draw conclusions for subgroups within this study or for comparisons with the GRADUATE populations, and the results of this study would need to be interpreted in the context of those from the GRADUATE trials.

Conclusions

Based on the ALUMNI AD protocol development experience, we have identified several strategies to drive participation of traditionally underrepresented racial and ethnic populations in AD clinical research. We envisage our insights on the development of an inclusive protocol being used as an initial guiding point to improve participation not only with regards to race and ethnicity, but of all people in groups frequently underrepresented in clinical research. Improving inclusivity in healthcare research remains a key challenge but it is becoming increasingly attainable through combined efforts.

Contributors

AWB and SSA conceptualized the study. All authors were involved in the development of the study protocol, the interpretation of key learnings from the study design process to propose techniques likely to increase DEI in future clinical trials, and the decision to publish these findings. AWB and SSA drafted the manuscript and all authors reviewed, edited, and approved the final manuscript for submission and publication.

Data sharing statement

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. The study protocol and the recommendations received to inform the study design are available from the corresponding author upon reasonable request.

Declaration of interests

AWB, HL, BA, GAR, RG, and SSA are employees of Genentech, Inc. and shareholders of F. Hoffmann-La Roche Ltd. SAB, JNH and MG are consultants for Genentech, Inc. SM has received consulting fees from Alzheimer's Clinical Trials Consortium (ACTC), Alzheimer's Therapeutic Research Institute (ATRI) and Genentech, Inc. MWP has received a Foundation award for Outreach from Alzheimer's Foundation of America; consulting fees from Eisai, Eli Lilly, and Genentech, Inc.; support for attending meetings and/or travel from Eli Lilly; is a member of the Board of Directors for Alzheimer's Foundation of America and AG Rhodes Nursing and Rehabilitation; and has provided approval for and reviewed CME training sessions for accreditation for the Commission on Continuing Professional Development, American Academy of Family Physicians. JEM has received funding from National Institute of Aging, Alzheimer's Association, Eisai, GHR Foundation, Eli Lilly, Cerevel Therapeutics LLC, GSK Research & Development Limited, Merck Sharp

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102693.

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