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WHITE PAPER

Strategies to streamline Alzheimer's disease trials

July 2024

In this white paper, we discuss strategies for AD clinical trials to:

- Overcome slow recruitment
- Improve enrollment and retention
- Reach a representative sample of people with AD

Introduction

Alzheimer's disease (AD) is a complex disease with multiple risk factors, which can also complicate clinical trials for new therapies. The need for large sample sizes, long trial durations to capture disease progression, and intricate eligibility criteria mean that clinical trials for AD therapeutics often take longer and are more expensive than trials for other conditions.[1] In fact, it takes approximately 13 years for an AD therapy to progress from preclinical studies to regulatory review.[2]

That's why it's particularly exciting that, after almost 20 years of no new drug approvals, therapies such as ADUHELM®, LEQEMBI®, and Kisunla™, all disease-modifying drugs (DMDs), have made it from the lab to market. In addition, 76% of the 164 trials assessing 127 drugs for AD listed in clinicaltrials.gov are DMDs.[2] The future looks bright for AD treatments.

However, AD drug development is still considered to be higher risk in terms of both clinical and commercial success than other therapeutic areas, which might explain why there are fewer trials and fewer drugs listed on clinicaltrials.gov now than in 2023 and previous years.[2] Strategies to overcome challenges in recruitment, enrollment, retention, and data collection in AD trials are needed to streamline clinical trials and ensure we can get new treatments to the people who need them.

~13 years

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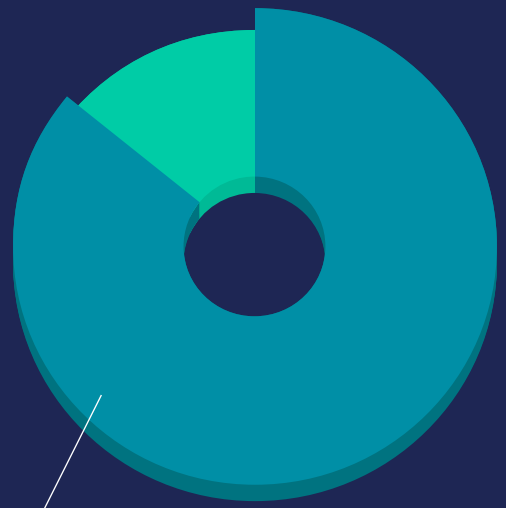

86% of potentially eligible people for an AD trial never make it to the healthcare system for AD symptoms

THE PROBLEM

Recruitment is often slow

Slow recruitment in AD trials is a commonly reported barrier to clinical trial completion. Much of this is associated with a lack of awareness about AD and its symptoms as well as about clinical trials. Memory loss and other cognitive impairments are considered a normal part of aging, meaning that they are often not discussed with family members or physicians until the symptoms are pronounced. At the same time, many people fear a dementia or AD diagnosis and might initially avoid discussing their concerns. It's estimated that only 14% of people who could be eligible for an AD clinical trial ever even reach the healthcare system for symptoms related to AD.[3] This not only delays healthcare but also means that individuals who do present to clinical trials have more severe disease.

Many AD diagnoses occur after the individual is experiencing observable symptoms, which might mean they are ineligible for studies of DMDs. Even if they are, a lack of awareness of clinical trials in general, about specific AD trials, and about who is eligible to participate limit exposure to research opportunities. For example, being able to offer their patients clinical research opportunities was viewed as a benefit of early diagnosis by <40% of primary care physicians (PCPs) in a recent survey.[4]

Mike and Susan O'Brien became involved in AD clinical research only after seeing a neurologist at JEM Research Institute, a Headlands Research site.

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THE SOLUTION

Strategies to improve recruitment

Education for individuals, communities, and healthcare professionals is an important first step to improving recruitment. At Headlands Research, we've found success in conducting lunch and learns with physician groups as well as educational sessions within the community, such as at community centers and local health fairs. We establish bidirectional communication channels, inviting members of the community and healthcare professionals to contact our sites with questions about ongoing trials.

These avenues provide opportunities to seek feedback about barriers to participation such as transportation, site hours, and compensation in order to strategize about how to overcome those barriers.

Establishing referral pathways for PCPs and other healthcare professionals to provide their patients with opportunities to undergo free cognitive assessments can be an effective way to recruit participants. Advertising these assessments at local health fairs and community sessions improves public awareness. After screening, eligible individuals can be easily matched with available clinical trials, presented with the trial information, and given the choice to participate — increasing recruitment rates while benefiting public health.

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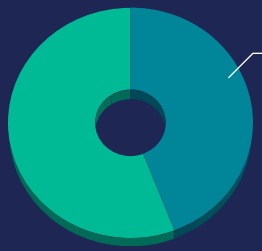
THE PROBLEM

Screen failures result in slow enrollment, and burdensome study procedures compromise retention

Screen failure rates for mild AD trials reach an average of 44%,[1] extending trial timelines and adding considerable cost. Screening procedures such as neurocognitive testing, imaging (MRI and PET), and CSF testing are time-consuming and expensive, representing 50% to 70% of the total per-participant costs.[1]



44%
average screen failure rate for AD trials

In addition, strict eligibility criteria that exclude individuals with comorbid conditions limit the population from which to enroll. This is especially true given that older adults represent the majority of individuals with AD and often have other conditions such as cardiovascular disease and diabetes and use a higher number of prescription medications — all of which are typical exclusion criteria.

Other barriers to participation and retention include long study visits, logistical barriers such as distance to study sites and transportation challenges, and a misunderstanding about the risks associated with participating. Research participation can be burdensome for both the individual with AD and their caregivers or family members, especially as most studies require that a support person be present during the visits.

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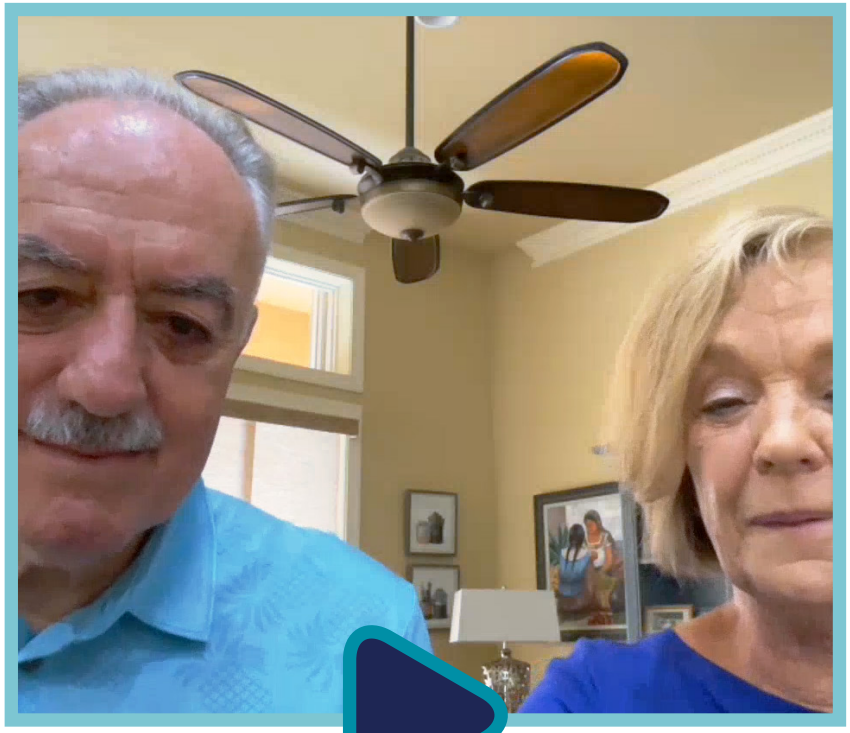
THE SOLUTION

Strategies to improve enrollment and retention

Considering broadening the eligibility criteria to include individuals with comorbid conditions or high prescription drug use might require more planning to discern between drug-related cardiovascular events, for example, but would allow greater participation, especially from under-represented populations such as racial/ethnic minorities.

Offering wrap-around services such as support groups for both the individual with AD and their caregiver can help them feel like they're part of a community, more than just a research subject. This not only enriches the research experience but also encourages word-of-mouth referrals to others within their social groups.



Mike and Suzanne shared their positive research experience with others within their community.

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THE PROBLEM

Representativeness is often lacking in AD clinical trials

Only about one-half of trials in a recent systematic review of AD clinical trials reported the participants' race. For those that did, only 2% of participants were Black or Hispanic.[5] In a systematic review of 101 clinical trials of DMDs for AD,[6] the authors reported that a median 94.7% of participants across the trials were White, which remained consistent for studies conducted from 2001 to 2019. Further, studies fail to report the efficacy, safety, or tolerability of the treatment by race.[5] However, recent findings regarding differences in imaging and tau levels between racial and ethnic groups[7,8] suggest that the etiology of cognitive impairment might differ by group and should be considered when designing studies.

Because other health conditions could complicate the analysis in AD trials, many studies exclude people with conditions such as psychiatric illness (78.2% of studies), cardiovascular disease (71.3% of studies), cerebrovascular disease (68.3% studies), and diabetes (22.7% of studies).[6] Not only are many of these diseases comorbid in older individuals but they are also more prevalent in non-White individuals and can be important risk factors for AD.

Cognitive test performance is strongly predicted by educational quality, particularly in Black individuals,[9] but this association is rarely considered when interpreting cognitive test results in the clinical research setting. In other words, our current cognitive tests and testing environments may not perform equally across races. For example, Black participants in a study in the United States performed the poorest on cognitive testing if they lived in the South and attended a desegregated school in their early education.[10]

Geographic location of AD trials also limits accessibility. Data collected at large medical institutions tend not to be inclusive, partially because of their location within urban areas.[11]

THE SOLUTION

Strategies for reaching a representative sample

As these data demonstrate, a representative sample of AD research participants involves not only race/ethnicity[12] but also comorbid conditions and social determinants of health (SDoH) such as socioeconomic status, education, and residential area.

Successful ways to reach a broader population include engaging with communities to determine the barriers to participation as well as including participants with common comorbid conditions. More inclusive recruiting practices resulted in approximately 25% of the randomized participants in the Phase 3 confirmatory study of lecanemab for early AD who were Black and Hispanic, and the eligibility criteria allowed a broad range of comorbidities/comedications, such as hypertension, diabetes, heart disease, obesity, renal disease, and anticoagulants.[13]

In addition, are there ways to increase awareness of the trial and make it easier to participate? Strategies could include educating physicians in geographic AD hot spots about research opportunities and the referral pathway; locating sites in these hot spots; planning appointments outside of work hours, especially if a caregiver needs to be present; and considering remote, home, or community-based visits when possible.[14]

Mistrust of healthcare professionals and research is a key reason many people don't actively engage with their care, including research. To overcome this barrier, employ research staff who are representative of the community, hold focus groups to understand cultural or other barriers to recruitment and enrollment, engage with community groups to spread the word about the research and its benefits, locate research sites within the communities, disseminate findings to participants and the larger community at local events, and report demographic characteristics in press releases and publications so the public has insight into research that represents them.

CONCLUSION

Streamlined recruitment, enrollment, and retention can accelerate clinical trial timelines and reach a representative sample

Because AD clinical trials often need to demonstrate beneficial effects on cognitive, behavioral, and functional endpoints for regulatory approval, long treatment periods and large sample sizes are typically required to detect a clinically meaningful change. For DMDs, demonstrating a treatment's ability to slow disease progression can also require years. However, fostering relationships that encourage referrals, minimizing screen failures, and creating a positive research experience can shorten trial timelines through faster recruitment and enrollment and by minimizing drop-outs throughout the study. In addition, meeting people where they are in terms of readiness to participate in research as well as understanding physical barriers to participation can help ensure we meet our goal of greater representativeness in AD research and, at the same time, aid with recruitment and retention.

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Headlands Research is a multinational integrated clinical trial site organization with a mission to improve lives by advancing innovative medical therapies. Its network of sites focuses on large-volume recruitment and retention of diverse, inclusive populations through its extensive site databases and physician partnerships. With key opinion leaders, experienced principal investigators and site staff, and a broad range of therapeutic area expertise, the sites deliver meaningful participant experiences, operational excellence, and the highest quality data. To date, Headlands Research has successfully supported more than 5,000 clinical trials. Additional information about the company is available at www.headlandsresearch.com.

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