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SHORT REPORT

The utility of recruitment incentives in early Alzheimer's disease trials

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Abstract

INTRODUCTION: Amid recent approvals, early Alzheimer's disease (AD) remains an active area of treatment development.

METHODS: We performed a conjoint experiment to compare preferences among 26 patients with mild cognitive impairment for four trial features including designs incorporating active aducanumab-control (vs. placebo), returning tau positron emission tomography (PET) results (vs. no disclosure), remote study partner participation (vs. in person), and increased risk of brain swelling (vs. lower risk). We used a generalized estimating equation to model the utility of factor levels.

RESULTS: Returning tau PET results had the highest utility (est: 0.47; 95% confidence interval [CI]: 0.13, 0.81; $P = 0.007$); remote study partner participation showed a similar trend (est: 0.29; 95% CI: −0.05, 0.63; $P = 0.097$). Trials with active-controlled design (est: 0.01; 95% CI: −0.33, 0.35; $P = 0.956$) did not demonstrate utility and higher risk of brain swelling had negative utility (est: −0.64; 95% CI: −0.99, −0.30; $P < 0.001$).

DISCUSSION: Returning additional biomarker results may increase willingness to enroll in early AD trials.

KEYWORDS
clinical trials, early Alzheimer's disease, recruitment, study design

Highlights

- We compared mild cognitive impairment participant preferences for four trial design features.
- Returning tau positron emission tomography results had the highest utility.
- Remote study partner participation showed a positive, albeit non-significant, trend.
- No utility was observed for an active aducanumab-control design.

1 | BACKGROUND

Slow recruitment to clinical trials threatens the goal of advancing Alzheimer's disease (AD) therapeutics. In fact, few AD trials recruit even one participant per site per month and, more broadly, poor recruitment is among the most common reason for trial failure.[1,2] Early AD trials that enroll participants with mild cognitive impairment (MCI) and mild dementia have unique recruitment challenges, with limited windows of eligibility, the requirement to undergo biomarker testing, and the need to enroll patients with study partners despite some patients being functionally independent.

The US Food and Drug Administration (FDA) granted accelerated approval for the treatment of early AD to the anti-amyloid monoclonal antibodies aducanumab in 2021[3] and lecanemab in 2022[4] followed by the full approval of lecanemab in 2023.[5] These treatments have limited efficacy, inconvenient administration, and risk of serious adverse events such as amyloid-related imaging abnormalities, emphasizing the urgency to continue development of improved treatment options.[6] These approvals, however, have sparked ethical questions, including the appropriateness of placebo controls when ostensibly disease-modifying therapies have entered the clinical arena.[7] Few empirical studies have addressed how trial design features impact enrollment decisions, particularly now that new treatments have been approved.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed existing literature using traditional sources (e.g., PubMed) on early Alzheimer's disease (AD) trials and the impact of design features on enrollment decisions.
2. **Interpretation**: In this conjoint experiment enrolling participants with mild cognitive impairment, returning tau positron emission tomography results had higher utility than remote study partner participation or an active control trial design.
3. **Future directions**: Further studies are needed to examine the feasibility and ethics of placebo-controlled trials as the standard of care for AD patients evolves.

2 | METHODS

We performed a conjoint analysis experiment to compare participant preferences for trial features with competing attributes.[8] Participants were required to be at least 50 years old, able to complete the study in English, and have a diagnosis of MCI. We excluded participants with a diagnosis of dementia, other neurological or psychiatric disorders, and cancer. Study partner participation was optional. We enrolled 6 participants from a previous study[9] who still had a diagnosis of MCI, and 20 participants referred by three dementia specialist clinicians at our institution between May 19, 2022 and December 4, 2023. The study was approved by the University of California Irvine Institutional Review Board. All participants provided informed consent. The structured interviews were performed by one of two trained researchers at the participants' home, on campus, or remotely via Zoom.

During the interview, we read participants educational primers to provide information on MCI, including the use of amyloid and tau biomarkers to distinguish AD; trials, including placebo- versus active-control designs; and aducanumab, including the FDA's accelerated approval, the requirement for phase 4 confirmation of efficacy, and the observed safety profile. For a series of 16 trial scenarios that varied in four pre-selected factors, we asked participants to rate their willingness to participate using a 7-point ordered scale. Each factor included two levels. Three recruitment incentives were included: (1) active-control design with randomization to an investigational anti-amyloid therapy or aducanumab (vs. placebo control), (2) tau positron emission tomography (PET) disclosure (vs. no return of tau PET results), and (3) remote study partner participation (vs. required in-person study partner participation). We included one negative control (5% vs. 25% risk of brain swelling). For each scenario, participants were asked to consider a 2-year trial with monthly study visits testing a new monoclonal antibody against amyloid beta for early AD (including confirmation with amyloid PET). Trial scenarios were presented in random order. Participants were permitted to include a family member or another person to discuss the trial scenarios. While we did not collect data directly from these study partners, if decisions were made in partnership, participants were asked to report their relationship to the person they involved (i.e., spouse, adult child, other).

We used descriptive statistics to characterize the study population and a generalized estimating equations (GEE) model to account for within-subject correlation and assess the utility of the differing factor levels. In our study, utility was defined as the point difference in participants' willingness to participate in trials along the 7-point ordered scale compared to the other factor level. An exchangeable working correlation structure was used for parameter estimation, and robust variance estimates for model coefficient estimates were used for final inference. We present the estimated utility of each scenario indicator along with corresponding 95% confidence interval and *P* value of a test of the null hypothesis of no impact on trial willingness. We ran a separate exploratory model adjusting for age and sex. Given the full FDA approval of lecanemab, we also stratified the responses by those who completed our study before and after the announcement of topline lecanemab results on September 27, 2022.

3 | RESULTS

Twenty-six participants with MCI completed the study, of whom ten enrolled with a study partner (Table 1). Most were male (69%), non-Hispanic White (85%), retired (92%), and married (65%).

In our unadjusted GEE model, returning tau PET results had the highest utility (est: 0.47; 95% confidence interval [CI]: 0.13, 0.81; $P = 0.007$; Figure 1). While not significant, trials with the option

TABLE 1 Study participant characteristics.

Participant characteristics	Total (*N* = 26)
Age, mean (SD)	78.3 (8.2)
Female, *n* (%)	8 (31)
Sexual orientation, *n* (%)	
Heterosexual or straight	23 (88)
Prefer not to answer	3 (12)
Race, *n* (%)	
African American or Black	0 (0)
Asian/Pacific Islander	4 (15)
Native American/Eskimo	0 (0)
White	22 (85)
Other	0 (0)
Hispanic/Latino, *n* (%)	0 (0)
Education, *n* (%)	
Some college	1 (4)
College degree	5 (19)
Some graduate or professional school	4 (15)
Graduate or professional degree	16 (62)
Employment status, *n* (%)	
Full-time employed	1 (4)
Part-time employed	1 (4)
Retired	24 (92)
Marital status, *n* (%)	
Single, never married	1 (4)
Married	17 (65)
Separated	0 (0)
Divorced	4 (15)
Widowed	4 (15)
Primary language, *n* (%)	
English	22 (85)
Other	4 (15)
ADI	
Quintile 1	10 (39)
Quintile 2	11 (42)
Quintile 3	1 (4)
Quintile 4	1 (4)
Quintile 5	3 (12)
Study partner type, *n* (%)	
Spouse or partner	8 (31)
Adult child	1 (4)
Other	1 (4)
No partner	16 (62)
MoCA adjusted total, mean (SD)	20.3 (5.2)

Abbreviations: ADI, Area Deprivation Index; MoCA, Montreal Cognitive Assessment; SD, standard deviation.

for remote study partner participation showed a similar trend (est: 0.29; 95% CI: −0.05, 0.63; $P = 0.097$). No utility was observed for an active control design (est: 0.01; 95% CI: −0.33, 0.35; $P = 0.956$). Higher risk of brain swelling had negative utility and was the strongest predictor among the four trial features (est: −0.64; 95% CI: −0.99, −0.30; $P < 0.001$). In the adjusted model, we found that female participants had higher willingness to participate in trials compared to male participants; no significant differences were observed by age. In our exploratory analysis we observed qualitatively similar trends in responses for subjects interviewed before and after the announcement of the topline results for the phase 3 lecanemab trial (data not shown).

4 | DISCUSSION

The landscape of AD research is transforming due to the emergence of amyloid-lowering treatments.[6] This study is among the first to offer empirical data on factors that may impact willingness to participate in trials among likely candidates for these treatments. We observed no significant difference in participant willingness to enroll in an active aducanumab-controlled trial over a placebo-controlled trial. Instead, participants were more willing to enroll in trials that returned tau PET results than ones that did not. The option of having remote study partner participation showed a similar, albeit non-significant, trend toward increased willingness. We observed a decrease in participant willingness to enroll in trial scenarios that described an increased risk of brain swelling, confirming the validity of our approach.

Most trials now disclose amyloid results to participants as part of determining eligibility, but disclosure of tau PET results is infrequent. Our findings align with previous studies that find most participants with MCI express strong interest in receiving both amyloid and tau biomarker results.[10] Despite limited literature on the impact of tau disclosure, studies on amyloid disclosure have reported participants perceived benefits[11] such as personal utility, including using the information to instruct modifying behaviors and adjusting plans for the future.[12] We measured willingness to participate in trials, which may not translate directly to actual enrollment decisions (enroll vs. not enroll). We note, however, that the sizes of the negative effect of higher safety risk and the positive effect of tau biomarker disclosure were comparable, lending credibility to the idea that tau biomarker disclosure could meaningfully sway participants' decisions.

The approval of the anti-amyloid antibodies has prompted an ongoing discourse on ethical considerations for future AD trial designs, particularly regarding the use of placebo.[7] Determining whether and when placebo becomes unethical for use in trials of new treatments requires routine but complex assessments. For placebo to be unethical, a new standard of care must be achieved. Standard of care is evidenced by effectiveness in real-world clinical practice but also demonstrated harm from withholding therapy. For anti-amyloid treatments, this hinges on demonstration of disease modification.[7,13] Short of a new standard of care, trial feasibility contributes to ethical considerations—including whether participants are willing to enroll in trials that include randomization to placebo. Our study suggests that, at present, the use

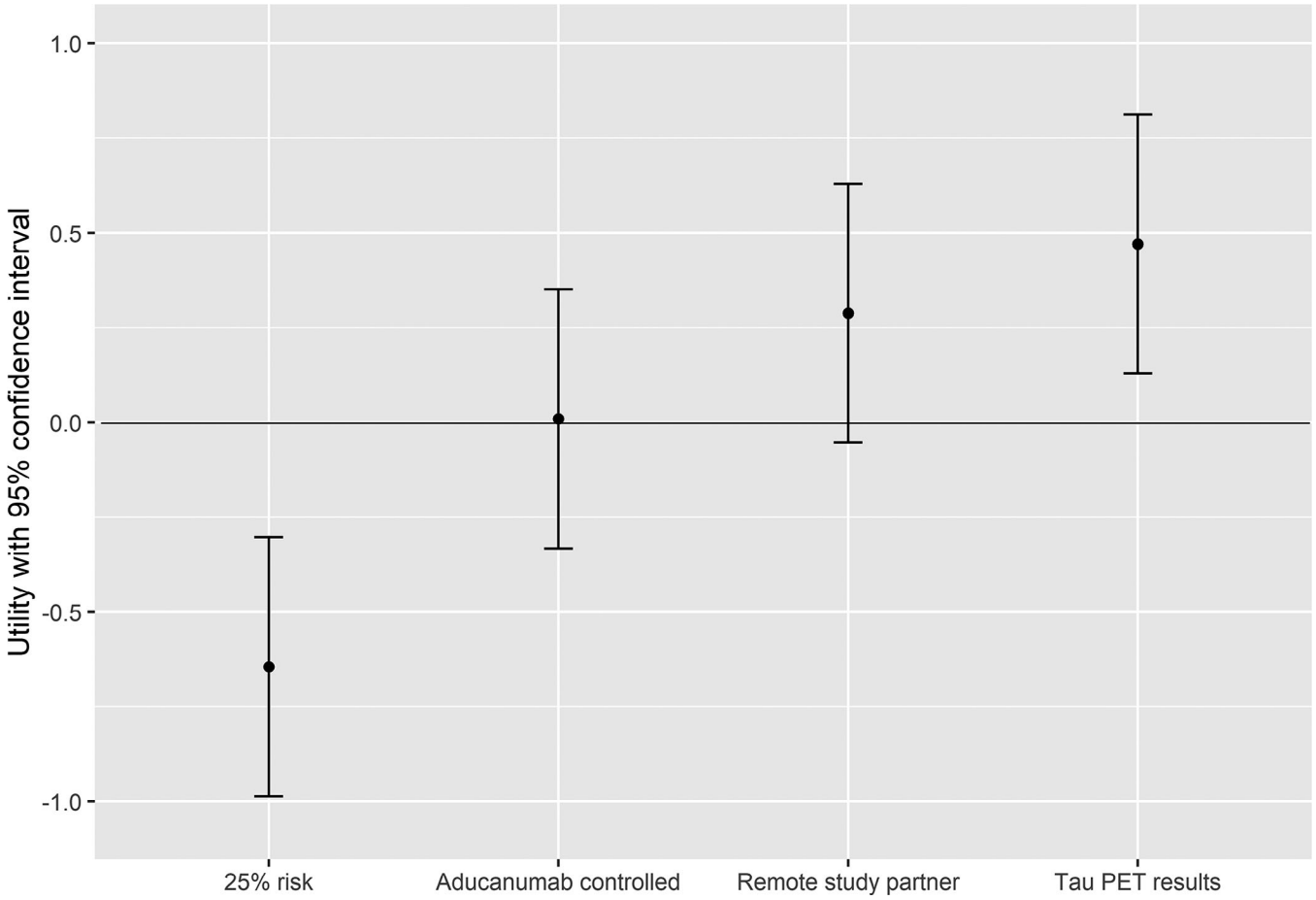

FIGURE 1 Utility of three recruitment incentives (active-controlled design, tau positron emission tomography [PET] disclosure, remote study partner participation) and one negative control (higher risk of brain swelling).

of placebo in early AD trials may be feasible, as no preference was observed for an active- compared to a placebo-controlled design. As the quality of evidence supporting new treatments as "disease modifying" improves and the use of these drugs in clinical practice increases, participant preferences in trial design may change.

The approval of aducanumab was controversial[14,15] and lecanemab received full FDA approval[5] during our data collection period. This may have affected participants' attitudes toward trials with aducanumab as an active control.[16] While we observed no clear differences before and after the announcement of topline lecanemab results, our small sample size is a key limitation and future research must seek to more thoroughly understand the implications of specific choices of active control therapies. To reduce participant burden, we provided the option to enroll in person or virtually. There may have been subtle differences in the level of participant engagement between the two modes of administration. Other limitations included that our sample was not representative of the larger disease-suffering population or the local population in Orange County, California, where the data were collected. In particular, it will be important to understand how trial design features affect decisions among sub-populations consistently underrepresented in AD trials.[17]

5 | CONCLUSION

Patients with MCI may be more willing to enroll in early AD trials that disclose both tau and amyloid PET results. Returning biomarker results may have a greater impact on participant enrollment decisions than would use of active-controlled designs.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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