



Common Mistakes in Recruiting for Alzheimer's Disease Clinical Trials:

A Strategic Framework for Optimization

Executive Summary

The landscape of Alzheimer's disease (AD) research has reached a critical inflection point. While scientific breakthroughs are accelerating, the operational framework for clinical trials remains burdened by inefficiencies. Currently, AD trials face several challenges including protracted enrollment timelines, site-level bottlenecks, and staggering screen-failure rates up to 88% (Schaeffer Center, 2020).

These failures are not merely administrative hurdles; they represent a significant drain on capital and a delay in developing therapies. The high cost of biomarker confirmation, in addition to intensive resource requirements of traditional site-based screening, have made the status quo unsustainable, particularly as the industry shifts its focus toward prodromal and preclinical populations.

Addressing the Screening Gap

As the field moves into earlier disease stages, the ability to identify the right patient at the right time is a scientific necessity. This whitepaper identifies the most prevalent flaws in modern AD recruitment strategies and offers an evidence-based framework for optimization.

By integrating digital cognitive assessments (DCAs), blood-based biomarkers (BBMs), and decentralized screening methodologies, sponsors can reduce site burden, lower costs, and accelerate timelines.

1. Underestimating Participant Burden in Pre-Symptomatic and Prodromal Populations



The Challenge

The AD research paradigm has shifted decisively toward the earliest stages of disease progression, focusing on preclinical and prodromal populations. However, this strategic pivot introduces a profound recruitment paradox: the target participants for these trials are often asymptomatic and do not yet perceive themselves as patients. Because they lack noticeable cognitive impairment, they do not present at memory clinics or seek specialist care, leading to diagnostic delays of up to two years in many healthcare systems (Gauthier et al., 2021). For drug development programs, this creates a significant gap, where low prevalence in the general population and a lack of patient self-referral make traditional, site-based recruitment models increasingly ineffective.

Furthermore, traditional trial designs often fail to account for the lifestyle of a cognitively intact participant. Unlike patients in later stages of the disease, these individuals are typically professionally active, socially engaged, and logistically independent. Requiring extensive, multi-hour, in-person assessments creates a significant participation burden. When a trial's operational requirements conflict with demanding careers and family responsibilities, high attrition rates and poor enrollment velocity become inevitable.



Mitigation Strategy

Trial designs must be recalibrated to align with the reality of pre-symptomatic recruitment:



Abbreviated assessments

Implement brief, mobile-optimized cognitive tasks that require minutes rather than hours. Speech-based assessments, for example, can capture cognitive performance through natural conversation or structured tasks lasting 5-10 minutes.



Flexible scheduling

Enable assessments at times convenient for participants rather than rigid clinic hours. Remote platforms allow for assessments to be completed when participants are available and can focus.



Reduced visit frequency

Leverage remote assessments to maintain engagement without requiring physical presence, reserving site visits for essential procedures only.

Success in recruiting asymptomatic populations is directly proportional to the seamlessness of the study's integration into their daily lives.

2. Overloading the Recruitment Funnel with Low-Probability Candidates



The Challenge

Amyloid PET imaging and CSF biomarker analysis represent the gold standard for AD pathology confirmation but carry substantial costs ranging from \$1,250-\$8,000 per participant (Schaeffer Center, 2020).

When individuals with low pre-test probability proceed to confirmatory testing, the combination of high screen-failure rates and expensive procedures creates unsustainable financial and operational burdens.

Additionally, site PET capacity often represents a bottleneck, with scan appointment availability limiting speed of recruitment even when appropriate candidates are identified.



Mitigation Strategy

A staged screening approach incorporating enrichment tools substantially improves efficiency:



Digital cognitive assessments (DCAs)

Deploy sensitive, scalable cognitive evaluations as an initial screening tier. These assessments identify individuals with cognitive performance patterns consistent with AD pathology, enriching the pool before costly procedures. For example, the Speech Biomarker for Cognition (SB-C) assessment rules out candidates for better patient stratification. (Tröger et al., 2022)



Blood-based biomarkers (BBMs)

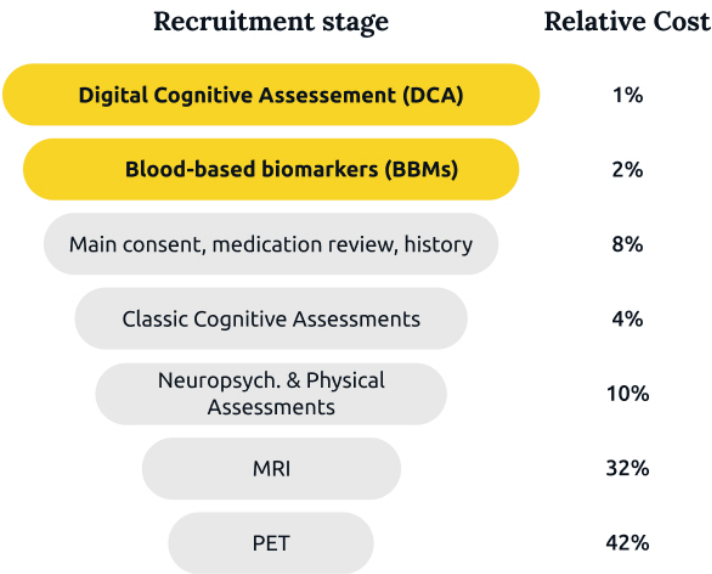
Integrate plasma biomarkers as a secondary enrichment step. Recent data demonstrate that sequential screening with DCAs followed by BBMs reduces overall recruitment costs by 35% and decreases on-site screening burden by 60% (Linz et al., 2024).



Predictive modeling

Utilize demographic, educational, and clinical data to calculate individualized pre-test probability scores with DCAs and BBMs, prioritizing high-probability candidates for confirmatory testing.

Figure 1. Staged funnel approach, with relative per-participant costs (%) at each recruitment stage.



This tiered approach functions analogously to clinical diagnostic algorithms, where low-cost, high-throughput tools identify candidates most likely to benefit from definitive but expensive testing. The result is improved positive predictive value at the PET/CSF stage, conserving both financial resources and limited site capacity.



Implementing a tiered screening approach including digital cognitive assessments could help reduce per-patient screening costs, while simultaneously improving amyloid-positive conversion rate. The operational efficiency gained might allow reallocation of resources toward sites struggling with enrollment.

- Lennert Steukers, Senior Clinical Sciences Leader, Johnson & Johnson Innovative Medicine

3. Neglecting Community-Based Recruitment Strategies



The Challenge

Traditional recruitment paradigms rely disproportionately on academic medical centers and tertiary care facilities. While these institutions offer robust infrastructure and experienced personnel, this approach constrains both the diversity and volume of the eligible participant pool. Geographic clustering around major metropolitan centers creates accessibility barriers for rural populations and underrepresented communities, ultimately limiting generalizability of trial findings.

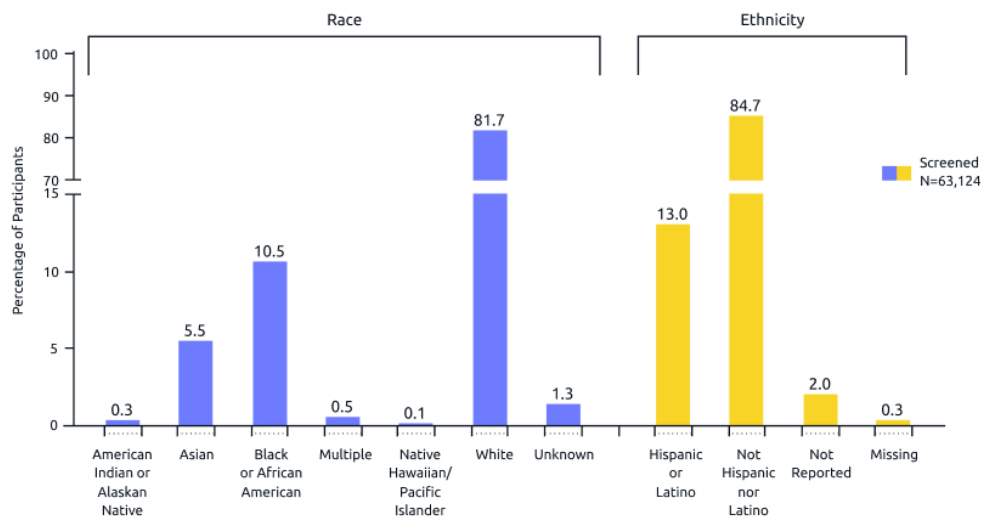


Mitigation Strategy

Research presented at CTAD 2025 by Eli Lilly on the TRAILBLAZER-ALZ 3 study shows that community engagement substantially enhances both recruitment numbers and participant diversity

Community-based approach resulted in a more representative screening population

TRAILBLAZER-ALZ-3 race and ethnicity distribution in screened and randomized populations



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Adapted from research presented at CTAD 2025.

Trial sponsors should implement multi-channel recruitment strategies that extend beyond conventional clinical networks:



Community health partnerships

Establish collaborations with health fairs, community screening events, and retail pharmacy networks to engage potential participants in familiar, accessible environments.



Educational outreach

Develop culturally appropriate educational materials that encourage research participation. Community education represents not merely a recruitment tactic but an ethical imperative to ensure informed participation.



Decentralized site selection

Consider hybrid models incorporating both traditional sites and community-based research organizations that can provide local touchpoints without full site infra-structure requirements.

This approach addresses challenges of slow recruitment and limited participant diversity, both of which compromise trial validity and post-approval generalizability.

4. Not Adopting Remote and Hybrid Trial Designs



The Challenge

To fully realize community-based recruitment, clinical trial designs must incorporate tools for remote data collection. Traditional site-based assessments introduce systematic variability due to environmental differences and inconsistent ratings across personnel. More critically, the high participant burden associated with frequent site visits creates significant barriers to both enrollment and retention. This is particularly true for individuals residing in rural areas, those with mobility challenges, and pre-symptomatic participants juggling active personal and professional lives.

Currently, there is a prime opportunity to rethink clinical trial design. This is primarily due to the regulatory acceptance of decentralized trial components and the advancement of remote assessment technology.



Mitigation Strategy

Sponsors should evaluate opportunities for remote data collection across the trial lifecycle:



Objective digital endpoints

Use validated digital biomarkers that standardize data capture independent of site environment. Speech-based cognitive assessments, for example, can be administered remotely via smartphone or phone call, eliminating travel requirements.



Hybrid models

Reserve in-person visits for procedures requiring physical presence (imaging, biospecimen collection) while transitioning cognitive assessments to remote platforms.



Infrastructure investment

Select technology platforms with demonstrated reliability and participant usability. The initial investment in digital infrastructure is offset by reduced site burden, accelerated recruitment, and improved retention.

Remote-first designs not only reduce participant burden but also enable more frequent, ecologically valid assessments that capture cognitive function in naturalistic settings rather than artificial clinical environments.

5. Static Recruitment and Trial Management: The Absence of Real-Time Optimization



The Challenge

Recruitment is often approached by many research teams as a rigid, linear, and predetermined process lacking flexibility aka a “set-it-and-forget-it” approach. They set enrollment targets, launch recruitment channels, and then retrospectively monitor performance through scheduled reports. This static method prevents capitalizing on early warning signs of recruitment problems, making rapid adjustments difficult when certain sites, channels, or strategies fail to meet expectations.



Mitigation Strategy

Modern recruitment requires dynamic, data-driven management enabled by real-time analytics:



Dashboard oversight

Implement digital assessment platforms that provide live recruitment metrics, including conversion rates at each funnel stage, site-specific performance, and demographic distribution. Central study teams and site coordinators should have access to actionable data enabling immediate optimization.



Candidate prioritization

Leverage digital biomarker results to triage candidates, fast-tracking high-probability individuals to confirmatory testing while providing alternative options (observational studies, future trial notifications) for those unlikely to qualify.



Adaptive resource allocation

Use real-time data to redirect recruitment investment toward high-performing sites while rapidly addressing underperformance through additional training, materials, or strategic adjustments.

The transition from static to dynamic recruitment management represents a fundamental shift in operational philosophy, treating recruitment as an active process rather than a passive funnel.



Adding highly validated remote cognitive screening has real potential to improve how we triage participants before they come in — helping ensure that the people making the trip are strong candidates. Reducing unnecessary screen-fails is a win for everyone: participants aren't burdened with a lengthy visit only to be turned away, and our team can focus energy on the participants most likely to qualify. We're actively exploring how to integrate this innovation into our process.

- Ralph Lee, CEO, Irvine Clinical Research

6. Reliance on Insensitive Cognitive Instruments



The Challenge

The Mini-Mental State Examination (MMSE) demonstrates fundamental limitations that make it suboptimal for modern AD trials. It has long been known to exhibit pronounced ceiling effects in cognitively intact and mildly impaired populations, precisely the target demographics for contemporary disease-modification studies. When most participants score 27-30 out of 30, the instrument lacks sensitivity to detect the subtle cognitive changes that characterize preclinical and prodromal AD. (Houx et al., 2002).

More recently, research examining electronic scale data from multinational Phase 3 trials has revealed that MMSE scores often fail to confirm inclusionary status at baseline when these measures were used as screening criteria, suggesting potential score inflation at screening that leads to inappropriate participant enrollment (Miller et al., 2023, Hackebeit et al., 2024).

Additional limitations include substantial inter-rater variability, susceptibility to practice effects, inadequate adjustment for educational and cultural background, and requirements for trained clinical raters. These factors combine to produce noisy data with limited discriminative ability in the populations most relevant to current therapeutic development.



Mitigation Strategy

The field requires transition to assessment tools commensurate with scientific objectives:



Objective digital endpoints

Implement objective, automated assessments capable of detecting micro-level cognitive change. Speech-based biomarkers, for example, can identify subtle alterations through natural language production tasks.



Elimination of raters and training requirements

Digital assessments administered via standardized protocols eliminate inter-rater variability and reduce operational costs associated with rater training, certification, and quality monitoring. This also has an advantage that there is no score inflation from raters to enhance recruitment numbers.



Comprehensive cognitive domain coverage

Select instruments assessing multiple cognitive domains (memory, executive function, language, processing speed) rather than global screeners that may miss domain-specific deficits.

The transition from traditional screening tools to digital biomarkers represents not merely technological advancement but fundamental improvement in measurement precision and clinical relevance.



The combination of real-time monitoring dashboards and standardized digital assessments has prevented recruitment fraud in our global programs.

- Alan Kott, Clinical VP, Data Analytics, Signant Health

Conclusion

Recruitment challenges in Alzheimer's disease clinical trials necessitate a systematic reassessment of how participants are identified and screened. The six mistakes outlined in this white paper represent substantial sources of inefficiency that continue to undermine trial timelines, costs, and data quality. The pharmaceutical industry is at a critical inflection point. Disease-modifying therapies have demonstrated clinical benefit, regulatory pathways are now clearer, and the scientific rationale for intervention earlier in the disease continuum is well established. Realizing the full potential of these advances requires operational capabilities that match scientific progress: scalable recruitment models, objective and sensitive assessment tools, data-driven screening decisions, and trial designs that balance participant burden with methodological rigor.

"Earlier signals, clearer decisions" captures the shift now underway in AD research. By adopting more robust and sophisticated recruitment approaches, sponsors can identify suitable participants earlier in the disease course, improve eligibility confidence, reduce costly downstream failures, and accelerate trial execution.

The recommendations presented here are practical, validated strategies grounded in real-world trial experience, which we have gathered from our work with global pharmaceutical companies over the years. Sponsors that treat pre-screening and screening as a strategic enabler rather than an operational cost will be better positioned to succeed in the increasingly complex and competitive landscape of Alzheimer's disease drug development.

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About *ki:elements*

ki:elements provides AI-driven digital speech biomarkers enabling highly scalable, objective, and remote screening for cognition. Our technology helps reduce unnecessary site burden, accelerate enrollment, and increase the proportion of biomarker-positive individuals sent to costly confirmatory testing. By capturing subtle cognitive changes through natural speech production, ki:elements supports pharmaceutical sponsors in building more efficient, participant-friendly trials while maintaining the scientific rigor required for regulatory success.

For more information on how we have enabled efficiencies in recruitment for global clinical trials with pharma sponsors, please visit:
[**www.ki-elements.de**](http://www.ki-elements.de)