Increasing trial participation and population diversity in early-phase Alzheimer's disease drug development

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This article is part of a series about challenges and opportunities in developing treatments for dementia.

The science around Alzheimer's disease identification and treatment is advancing rapidly – a promising trend for those at risk for or suffering from dementia. As of January 2023, there are 187 trials underway assessing 141 unique treatments for Alzheimer's disease, addressing a variety of pathological processes.[1] However, the completion of these studies requires more than 57,000 clinical trial participants. It is not surprising that *the pace of trial recruitment is lagging behind the pace of scientific advancement*.[2] This is particularly true in early-phase clinical trials, where recruitment for very small cohorts of Alzheimer's patients, as little as 8-16 patients, commonly takes 1-2 years to complete.[3]

In conversations with patients and their families regarding early-phase research participation, we hear the same concerns repeatedly: invasive procedures, long inpatient stays, limited treatment benefit, elevated risk, and overall concern about their frail loved one tolerating the demands of a study. *We consider this feedback as an opportunity to listen to and engage with the concerns of our prospective trial participants – improving how we conduct outreach and reshaping how we conduct early-phase Alzheimer's clinical trials*. Conversations with our patients have been the impetus for the solutions we discuss here, including actively facilitating earlier diagnosis in diverse populations, and finding surrogates for Alzheimer's patients in high-burden early-phase clinical trials.

1 Alzheimer's disease drug development pipeline: 2023, Alzheimer's Association, May 25, 2023.
2 Ibid.
3 Ibid.

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The problem of getting diagnosed

Parexel regularly collaborates with sponsor teams regarding the development of Alzheimer's disease study protocols. A commonality across many studies (with notable exceptions) is that inclusion/exclusion criteria tend to select Alzheimer's participants who are younger, healthier, and earlier in the disease process. This is particularly true in early-phase clinical trials where safety risks to participants are higher. Healthier, less impaired patients and their families can also be easier to partner with for the duration of the trial and may be less burdened by the challenges of trial participation.

The problem is that clinical research needs do not always align with the patients' and their families' needs and experiences. And part of the patient and family experience is *that Alzheimer's disease is not typically diagnosed in the earliest stages of the disease process when participation in a clinical trial can be the most helpful*. Often, patients do not receive a diagnosis until the disease is quite advanced, at which point they are not likely to be eligible or able to benefit from a trial.

There are numerous reasons why diagnosis is delayed. Global disparities in access to high-quality healthcare shape whether someone with dementia will ever be assessed or receive a diagnosis. In locations where dementia assessment is widely available for patients who speak the local languages, it may not be available to cultures and communities who speak different languages or have different beliefs about accessing medical care. Alzheimer's disease assessment, in particular, requires an elevated level of cultural sensitivity by the diagnosing provider. This necessitates the ability to speak with and assess cognitive functioning with patients in their preferred language, and to understand the role of culture in impacting patient presentation of symptoms and making a diagnosis. All of this can be compounded by cultural norms that consider dementia a normal part of the aging process.[4] The result is that entire cultures and communities may have reduced access to dementia assessment, particularly early in the disease process. A 2021 study of Medicare beneficiaries in California found that Black, Hispanic, and Asian older adults were less likely to be diagnosed with mild cognitive impairment (MCI) and less likely to receive a full dementia evaluation compared to their white counterparts.[5]

4 The experiences of stigma in diverse communities, DementiaUK.
5 Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California, March 29, 2021.

Changes in behavior and memory loss are often dismissed or mistaken for another condition, lack of sleep, or side effects of other medications, which also delays assessment and diagnosis. Loved ones who notice warning signs can hesitate to point them out, and some healthcare providers share this reluctance. There is often a lack of documented symptoms or patterns of decline, impeding the ability to pinpoint when the decline started.

Embarrassment, anxiety, and stigma associated with dementia also factor in. People delay assessments, fearing the diagnosis and its implications: being labeled and forced to make lifestyle changes, for example, and losing their autonomy and ability to care for others. And while low visibility of clinical trials is a perennial problem, how can people unaware of their own condition be expected to pay attention to research studies?

For early-phase trials, recruitment can be still more difficult, even when candidates are referred by their healthcare provider. The risks are greater, and the benefits are uncertain; there is no human data on the effectiveness of the drug, and researchers are just learning about possible side effects. Participation comes with a high burden and could require turning down other available treatment options. The lack of enthusiasm on the part of both patients and caregivers is completely understandable.

Early identification of Alzheimer's disease biomarkers in healthy older adults

Clearly, these obstacles to diagnosis need to be overcome if we are to accelerate drug development and get treatments into the hands of families who need them. *One of the ways we do this is to find ways to connect with patients earlier in the disease process, long before they ever receive a diagnosis*.

At the Los Angeles Early Phase Clinical Unit (EPCU), one of Parexel's four early-phase sites, we provide cognitive and biomarker testing as standard procedure for all healthy volunteers over age 60. We use cutting-edge blood testing to identify healthy older adult volunteers in the earliest stages of tau and beta-amyloid accumulation. These biomarkers of Alzheimer's disease, present in trace but detectable amounts in the blood, are known to accumulate in the brain long before the onset of Alzheimer's disease and its associated cognitive symptoms can be diagnosed. Blood biomarkers, while imperfect, allow us to screen large populations effectively and sensitively and thereby identify participants who may be at risk of developing Alzheimer's. A significant percentage of apparently normal older persons already show evidence of clinically significant brain pathology, ranging from 16-18% in the 60-69[6] age group and 23-33% for those over 70.[7]

6 Roberts RO, Aakre JA, Kremers WK, Vassilaki M, Knopman DS, Mielke MM, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. JAMA Neurol 2018; 75: 970–9.

7 Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015; 313: 1924–38.

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The objective is to build a database of experienced early-phase research participants who show sub-clinical or clinical levels of Alzheimer's blood biomarkers and who can participate in early-phase clinical trials in lieu of Alzheimer's patients and their families. Interest has been strong among those eligible for the project, as it allows these experienced early-phase volunteers to participate in more clinical trials.

Crucially, this project builds on longstanding relationships with healthy volunteers who already have knowledge and experience with clinical trials. Forming bonds and creating trust with these volunteers, their caregivers, and healthcare providers is fundamental to our ability to screen and monitor their progression. An important aspect of this practice is repeated engagement with frequent touchpoints and continual support over time. It is essential to make patients and their partners feel valued and part of the solution.

Making Alzhiemer's diagnosis and trials more accessible and inclusive

In parallel, we are implementing broader outreach strategies to promote early diagnosis and increased clinical trials visibility with emphasis on engaging diverse populations. Relationship building and education are key. For example:

- **Raising public awareness.** We are using relevant social media channels to push out positive, relatable messaging to raise awareness within the general public of the benefits of early detection and intervention. Many people can relate to an experience of a family member or friend who has suffered from dementia. As with the topic of mental health, the conversation has broadened across all generations, and the stigma is lessening. Clear educational messaging around clinical trials is a cornerstone of this initiative, serving to set expectations for families and patients and to help them understand the purpose and benefits.
- **Encouraging assessments through outreach.** We are using "bring a friend, share with a loved one" messaging to make it easier for family members and friends to invite those likely to benefit from an assessment who might be procrastinating.
- **Mitigating literacy and socioeconomic factors.** We are using regionally appropriate screening tests and instructions written in plain language and translated into local dialects, along with community face-to-face and virtual drop-in sessions to explain the benefits of screening.
- **Educating the healthcare community.** We are creating training videos and dialogue aids for site staff and healthcare providers to promote inclusivity and accessibility, considering gender identity, disabilities, and race and ethnicity.

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Blending innovative clinical solutions with a patient-first philosophy

Innovative clinical methods for gathering the data needed to get treatments to patients are the starting point, and Parexel is leading the way in that regard. Yet, for patients and their families, countless factors are involved in the decision to participate in a clinical trial. *Encouraging them to do so requires us to build trust within their ecosystem, to listen, to educate, and to show unwavering support for them over the short and long term.*

At our Los Angeles EPCU, we have decades of experience conducting Alzheimer's clinical trials and decades of experiences listening to and responding to feedback from patients and families about how to make this process more engaging and less burdensome. This collaboration has led to creative, comprehensive strategies for putting the patient first – which is central to everything we do at Parexel.

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