Alzheimer's Disease International

The global voice on dementia

World Alzheimer Report 2026

A new era in dementia clinical trials

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Cover photo caption: Twin brothers Peter (left) and Bill Yeates look at Bill's brain scans in July 2026. Bill was diagnosed with young-onset Alzheimer's disease in 2019 and has since participated in a clinical trial in Australia. (Photo by Belinda Cooper)

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Foreword

Chris Lynch,
Acting Chief Executive Officer, Alzheimer's Disease International, September 2026

We are at a pivotal moment for Alzheimer's disease and dementia. After decades of investment in research, we stand on the cusp of a giant leap forward at the intersection of innovation in diagnostics, treatments, and risk reduction. This momentum is challenging our very understanding of what constitutes a diagnosis and at what point we should start to make interventions. What is now evident is that a life-course approach is required, one that embraces prevention strategies, identification in the pre-symptomatic or 'at risk' stages, and robust post-diagnosis pathways.

All three of these elements are underpinned by the critical importance of clinical trials, the theme of this year's World Alzheimer Report. The pages that follow shine a light on the latest developments in clinical trials and make recommendations to ensure that we harness the momentum and take the research into policy and practice.

However, a major finding of the report is that many people are unaware of clinical trials and that the referral pathway for trials is flawed. This can be interpreted as people being denied the opportunity to participate in trials and to contribute towards progress, for themselves and for wider society.

Herein lies the challenge. In his 2026 Alzheimer's disease drug development pipeline update, Professor Jeffrey Cummings identified 158 drugs in 192 Alzheimer's disease trials, requiring around 55,000 clinical trial participants. When you factor in trials for other forms of dementia and trials related to care and risk reduction, we need many more people to become aware of trials and to be supported to make informed decisions about participation, particularly given the high recruitment screening criteria associated with complex trials. Prof Cummings estimates that at least 350,000 people would need to apply to join clinical trials to get a sufficient number of participants given the high screening fail rates – a daunting number.

Nonetheless, we should not see this as a herculean task, but as an unprecedented expression of confidence in dementia research. Our commitment is now to make sure that we revolutionise trial recruitment for sustainable, trial-ready populations that can meet the demand.

You will see that we have adopted a journalistic style to this year's World Alzheimer Report, purposefully aimed at demystifying an incredibly complex topic. Seasoned health correspondent Paul Gallagher, our lead writer, has interviewed over 45 key leaders in the field from around the world to inform us, challenge us, and, most importantly, galvanise us to truly harness this moment in time.

At the heart of all clinical trials are human stories of trepidation, hope, fear, and altruism. This report shows how people living with, or at risk of dementia, are integral to clinical trial success and must be involved at every stage, from identification of need to trial design, from recruitment to outcomes, whether successful or not. Trial participation is always a choice and one that should be made after informed conversations and support, including the knowledge that people with lived experience have been at the heart of design, development, and delivery.

The appeal of clinical trial participation is grounded in hope. Hope for individual medical benefit, and an altruistic hope for future generations. The referral pathway needs to appreciate hope as a driver to recruitment and participation, starting with increased awareness.

In the recommendations section of this report, you will also see a call for clinical trials to be designed from the outset to evaluate outcomes that matter most to people living with, or at risk of, dementia, as well as their carers, families, and friends. Outcomes related to independence, daily functioning, and quality of life need to be better incorporated into trial design protocols, alongside more traditional cognitive and biomarker endpoints. The focus must be on personal meaningful benefit, and we must include a better appreciation of the value we put on time – the time commitment required to participate in a clinical trial, but also the potential months or years of better health and independent living gained thanks to treatments or interventions that slow the progression of the dementia. Clearly identifying meaningful benefit measures at the outset should translate to better articulation of benefit for payers and health systems.

This report also highlights the changing role of Alzheimer and dementia associations across the world. Historically, Alzheimer and dementia federations and associations, including ADI's over 100 member associations, have supported people living with dementia, most often after diagnosis and in the mid- to late-stages of the condition. What is evident now is that associations' audiences are changing and their role in clinical trial information provision is growing, alongside their ability to advocate for trials, facilitate recruitment, and support choice. This comes at a time of broader change for associations. The innovation and science around trials, diagnostics, treatment, and risk reduction is far too often outpacing policy and practice. Associations need to become knowledgeable and confident advocates around clinical trial access, regulation, reimbursement, equity, and diversity, embracing their role in articulating choice and value.

This report aligns with our current pivotal moment, one that can profoundly change the trajectory and response to Alzheimer's disease and dementia. Never before has there been so much focus, investment, and hope in dementia research. For other highly stigmatised conditions, including cancer and HIV/AIDS, clinical trials underpinned revolutions in diagnostics and treatments that subsequently introduced hope, helped reduce stigma, and led to better awareness, screening, prevention, diagnosis, treatment, and support. It is high time dementia has its own breakthrough.

An investment in clinical trials is an investment in hope. Hope takes investment, not just of money, but time and energy. It is my hope that we all play our part in raising awareness of clinical trials and supporting those who choose to participate. Research can offer the possibility of a better future, but only people can make that future possible.

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Executive summary

Dementia has undeniably become one of the defining health and social challenges of our time. The number of people living with dementia is projected to surpass 139 million by 2050, and it is fast becoming one of the leading causes of death globally. Dementia not only affects the person with the condition and those at risk, but also their families, carers, communities, and health and social care systems, which are facing increasing pressure to meet their needs.

After more than thirty years of frustration in the field of new treatment development, we now find ourselves in an era of innovation and confidence in research. New drugs that slow the progression of Alzheimer's disease have entered the market, sparking hope that upcoming disease-modifying drugs could make an even more pronounced difference in the lives of people living with dementia. The possibility of a cure, while still far away, feels like a more palpable prospect than ever before.

Every new dementia treatment that makes it to the headlines came after years of work behind the scenes, in academic and industry laboratories and research centres. Clinical trials are the core mechanism through which treatments – whether pharmacological or non-pharmacological – are evaluated for efficacy and safety before becoming accessible to the public. Far too often, however, that process remains unknown and poorly understood by the general public, including people who could benefit from participating in clinical trials.

Alzheimer's Disease International's (ADI) 2026 World Alzheimer Report seeks to demystify this complex and often intimidating topic, with the hopes of empowering people living with dementia, those at risk, and those with a family history of neurodegenerative conditions to inform themselves and understand whether participating in clinical trials is an appropriate option for them. This report also aims to highlight the challenges and opportunities that must be addressed in order for clinical trials to have a meaningful impact in the real world.

Chapter 1 of the report introduces the current dementia research landscape, and explains why clinical trials are a core part of turning Alzheimer's disease and related conditions from something once seen as untreatable to a health condition that can be better understood, diagnosed, managed, and – hopefully one day – cured.

Chapter 2 breaks down how clinical trials came to be, and how they work – from the aims of each trial phase to the rigorous balance between evaluating the efficacy of prospective treatments and protecting participants from potentially adverse effects.

This chapter also includes a case study looking at the 5 Ironmans Beat Alzheimer's initiative, a project bringing together two men seeking to blend extreme endurance sport, personal storytelling, and emerging science to challenge dementia stigma, explore prevention, and push for systemic change.

Chapter 3 narrows in on the specific challenges and opportunities that arise in clinical trials focusing on dementia, from the biological complexities of the neurological conditions that fall under that wide umbrella to the difficulties of defining what constitutes meaningful success for researchers, regulators, the pharmacological industry, and, most importantly, people living with dementia and their carers.

In this chapter, a case study tells the story of the FTD Brothers, or how one family turned their experience with frontotemporal dementia into an impactful patient advocacy initiative to raise awareness of potential life-changing research into this underexplored condition.

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Chapter 4 looks at how people living with dementia enrol into clinical trials, and the importance of recruiting, retaining, and supporting diverse groups of participants. Ensuring that clinical trials are representative, accessible, and equitable has become one of the greatest challenges facing dementia research today.

This chapter's case study follows Julie Stauffer Moore's experience during – and after – being recruited and participating in a clinical trial in the United States after being diagnosed with early-onset dementia, and what her and her family learned along the way.

Chapter 5 tackles the complex topic of safety, regulation, and ethics in clinical trials, from how major regulatory bodies across the world apply differing standards and safety requirements to ethical issues arising around building trust in trials and the impact of ageism on clinical research around dementia.

The related case study follows ADI board member Bill Yeates and his personal experience of being diagnosed with early-onset Alzheimer's disease, enrolling in a study, and navigating the aftermath of it coming to an end while maintaining his sense of purpose.

Chapter 6 delves deeper into the crucial importance of including low- and middle-income countries(LMICs) in dementia clinical trials so they are not treated as afterthoughts, but essential actors in developing research with meaningful, practical applications in the real world. This chapter notably explores how LMICs can pave the way for new diagnosis pathways and non-pharmacological trials.

The final case study of the report looks at the work of the Brain and Mind Institute in Nairobi, Kenya, and the challenges and opportunities in developing a strong foundation for dementia research and clinical trials in Africa.

And finally, **Chapter 7** lays out ADI's recommendations for how to ensure that the momentous progress made in dementia clinical trials continues on its upward trajectory, ensuring the proactive and meaningful inclusion of people living with dementia and those at risk of developing it, no matter their background or location, so that the science benefits all those who need it.

Recommendations summary

For governments and policymakers

1. Invest in national diagnostic capacity and early detection pathways
2. Create incentives for clinical trials in underserved regions
3. Invest in dementia research infrastructure, diagnostic pathways, and public trial readiness globally

For national Alzheimer's associations

4. Strengthen the role of national Alzheimer's associations in dementia research and innovation

For trial sponsors and regulators

5. Embed diversity and inclusion into trial design from the outset
6. Reduce participant burden and strengthen participant-centred trial models
7. Continue strengthening safety standards and communication

For researchers and clinicians

8. Prioritise clinically meaningful outcomes
9. Further embed people living with dementia and carers in trial design and strengthen clinician referral pathways
10. Expand investment beyond Alzheimer's disease

Chapter 1:

A turning point in dementia research

A couple shares a morning coffee in their trailer during a day spent gold prospecting in the Mojave Desert in California in 2008. (Photo by Domenico Pugliese)

'The first brick has been laid – but there's an awful lot to build on'

Dementia is one of the defining health and social challenges of the 21st century. As of 2019, more than 55 million people worldwide were living with the condition, a figure projected to surpass 139 million by 2050 as populations age.[1] Behind these numbers are millions of individuals and families whose lives are profoundly affected by dementia, of which Alzheimer's disease is the most common form, as well as health and social care systems facing increasing pressure to meet their needs. While no country will be untouched by this demographic shift, the greatest increases are expected in many low- and middle-income countries (LMICs)[2] where healthcare systems are often the least equipped to respond.

Despite these challenges, we are witnessing a period of remarkable scientific momentum. After decades during which dementia was widely regarded as an inevitable consequence of old age and neurodegeneration with few therapeutic options beyond symptom management, research has entered an era of unprecedented activity. Across the world, hundreds of clinical trials are investigating medicines, diagnostics, lifestyle interventions, digital technologies, rehabilitation programmes, and new models of care. Together, they reflect a growing recognition that improving the lives of people living with dementia will require progress on many fronts – not a single breakthrough, but sustained advances across prevention, diagnosis, treatment, and care.

That momentum was evident at the 2026 Alzheimer's Association International Conference (AAIC) in London, where announcements centred on making Alzheimer's diagnosis earlier and more accessible, alongside new therapeutic and prevention strategies.[3] Researchers also reported that elevated levels of p-tau217 – a measure of the concentration of that specific protein in blood or cerebrospinal fluid – in cognitively healthy older adults predicted a substantially increased risk of developing cognitive impairment over the following decade, suggesting blood tests could identify individuals suitable for prevention trials long before symptoms emerge.[4]

Consequently, the mood across the research community is infectious. Alzheimer's disease is no longer universally described as untreatable; instead, it is increasingly viewed as a condition for which earlier diagnosis, better understanding of disease biology, and a wider range of interventions may collectively improve outcomes.

At the heart of this progress are clinical trials. Every medicine, therapy, and intervention that reaches clinical practice begins as a carefully designed research study. Clinical trials allow researchers to determine whether an intervention is safe, whether it works, who is most likely to benefit, and whether it makes a meaningful difference to people's lives. Even trials that fail to meet their primary objectives contribute valuable knowledge, refining scientific understanding and helping shape the next generation of research.

Despite their importance, however, clinical trials remain poorly understood. Many people living with dementia and their families are unfamiliar with what clinical trials currently exist, how they work, what participation involves, or why so many promising ideas never translate into approved treatments. Misunderstandings about research, combined with limited awareness of opportunities to participate, continue to present barriers around the world. This report therefore aims to demystify clinical trials – explaining how they are conducted, why they matter, and how today's research is shaping tomorrow's dementia care.

The 2026 World Alzheimer Report captures a field in transition. Recent years have brought renewed optimism to Alzheimer's disease research. Recent regulatory approvals of disease-modifying therapies (DMTs) lecanemab and donanemab in several countries[5] marked an important scientific milestone, providing the first evidence that therapies targeting amyloid pathology can slow clinical decline by about 30 percent. Despite parts of the scientific community labelling their efficacy "unimpressive,"[6] there is little doubt that the difficult and protracted approvals of the treatments are consequential.

"Their arrival marked a huge moment, but it was also a bittersweet moment," Professor Cath Mummery, director of the UK's Dementia Trials Network, tells ADI. "What you really hoped for was a bigger effect [on patients], but it was a huge moment because it showed you could change the course of the disease

1 https://www.alzint.org/about/dementia-facts-figures/
2 https://www.alzheimersresearchuk.org/news/worldwide-dementia-cases-to-triple-by-2050-to-over-150-million/
3 https://aaic.alz.org/releases-2026/overview.asp?
4 https://aaic.alz.org/releases-2026/blood-test-p-tau217-predicts-alzheimers-risk.asp?
5 https://www.alzint.org/news-events/news/donanemab-receives-marketing-authorisation-in-australia-brazil-and-mexico/
6 https://www.science.org/content/blog-post/does-it-work-does-it-do-harm-and-more-basic-questions

for the first time. To those dissenting voices that say they don't show significant change, they do. And they show consistent, significant change. So, for me, the breakthrough is that the amyloid hypothesis, which we've been chasing for decades, was confirmed at least in part, and that we've shown you can change things. That's the foundation. It's the first brick, and there's an awful lot to build on."

The development of lecanemab and donanemab has fundamentally changed expectations for what dementia research may achieve, even though questions remain about their clinical impact, safety, affordability, and implementation. Just as importantly, these medicines represent only one part of a much broader research landscape that extends far beyond anti-amyloid therapies.

In his latest annual review of Alzheimer's disease drug development, Professor Jeff Cummings of the University of Nevada reports that the number of candidate medicines under investigation has increased by around 40 percent over the past decade. Today, 158 potential therapies are being evaluated across 192 clinical trials worldwide, with eight Phase III trials expected to report during 2026.[7]

Around three-quarters of medicines currently in development aim to modify underlying disease processes. A further 18 percent aim to improve memory and thinking or support day-to-day functioning, while around 10 percent focus on neuropsychiatric symptoms such as agitation and anxiety.[8]

Those trials investigate symptomatic treatments that seek to improve memory, cognition, daily functioning, and neuropsychiatric symptoms, while an expanding range of non-pharmacological interventions – including cognitive rehabilitation, psychosocial support, exercise programmes, digital technologies, and models of care – are being evaluated using rigorous clinical trial designs. Together, these diverse approaches recognise that improving the lives of people living with dementia involves much more than slowing disease progression alone.

Parallel to therapeutic advances is the rapid advancement of precision diagnostics. Biomarker-driven approaches, once confined to research settings, are steadily entering clinical practice. Blood-based assays, advanced neuroimaging, and genetic profiling are also making it possible to identify Alzheimer's pathology years before cognitive symptoms fully manifest, creating opportunities to intervene earlier than ever before. The TRAILBLAZER-ALZ 3 study,[9] for example, is investigating whether treatment at the earliest biological stages of Alzheimer's disease can alter its course before symptoms develop.

Results from several late-stage clinical trials expected over the coming year are being watched closely and could represent another important step forward. New therapies are being tested across the full spectrum of the condition, from people who have no symptoms but are known to be at risk, to those living with more advanced dementia.

Researchers are also increasingly exploring the potential of repurposed medicines. More than a third of dementia drugs currently in the pipeline were originally developed for other conditions. One example is atomoxetine, a treatment for attention deficit hyperactivity disorder (ADHD), which was investigated in a Phase 2 trial to determine whether it could slow cognitive decline in people with mild cognitive impairment or early Alzheimer's disease, with mixed results.[10]

Another encouraging development is the growing number of studies testing combinations of therapies that target different biological pathways. These include a Phase 2 trial combining a tau vaccine with an anti-amyloid treatment.[11] As with diseases such as cancer, it is increasingly thought that the most effective approach to Alzheimer's may involve multiple therapies working together against different aspects of the disease. The fact that these combination strategies are now entering clinical trials offers another reason for cautious optimism.

As Prof Cummings reflected at the launch of his latest drugs pipeline report: "Anti-amyloid medicines such as lecanemab and donanemab have been a crucial breakthrough. They've shown that directly targeting the disease's process can slow decline. But they are only the beginning of what people with Alzheimer's will ultimately need."[12]

Dementia is being recast not as a gradual decline towards an inevitable loss of cognition, but as a continuum that might be interrupted or slowed, enabling many more years with a good quality of life.

Why the world cannot afford to wait

Yet perhaps the most consequential force reshaping the dementia clinical trial landscape lies not in laboratories or regulatory chambers, but in demography itself.

7 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251
8 Ibid
9 https://clinicaltrials.gov/study/NCT05026866
10 https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Atomoxetine.pdf
11 https://medconnection.ucsfhealth.org/news/new-alzheimer-s-trial-to-combine-anti-amyloid-and-anti-tau-therapies-to-arrest-disease-progression
12 https://www.theguardian.com/society/2026/may/05/slow-alzheimers-diagnoses-means-uk-patients-missing-out-on-experimental-treatments-says-charity

By the middle of this century, the world will be markedly older in ways that directly amplify the urgency of the questions this report seeks to address. According to the United Nations Department of Economic and Social Affairs, the number of people aged 65 and over is projected to more than double, reaching around 1.5 billion by 2050, with one in six people globally falling into this age group.[13] More striking still is the growth among the oldest cohorts. The number of those aged 80 and above – the group at highest risk of dementia – is expected to triple over the same period.

While global datasets often aggregate older populations into broad categories, it is within the over-75s that dementia risk accelerates most sharply. Epidemiological evidence suggests prevalence rises steeply with age, doubling approximately every five years after 70 and reaching well over 20 percent among those aged 85 and above. The implication is unavoidable: even if age-specific rates of dementia remain stable, the sheer expansion of older age groups will drive a dramatic increase in total cases.

What is often overlooked, however, is where this ageing will be most pronounced. While countries such as Italy and Japan and several more across Europe and Asia, are already "old" societies, with established healthcare systems and research infrastructures, the fastest growth in older populations – including those over 75 – is expected in low- and middle-income regions. Parts of sub-Saharan Africa, North Africa, the Middle East, and South Asia are projected to see the largest percentage increases in dementia cases, in some instances exceeding 1,000 percent in the United Arab Emirates and Bahrain and as high as 1,926 percent in Qatar.[14] These are regions where demographic transition is occurring at speed: falling fertility rates combined with rising life expectancy are rapidly reshaping population structures.

This shift has profound implications for clinical research. The countries experiencing the fastest growth in older populations – and therefore future dementia impact – are often those least represented in research. Indeed, countries like the Philippines – the 12th most populous nation in the world with 117 million people – cannot afford to carry out costly drug trials, sources tell ADI.[15] The result is a widening gap between where dementia is most prevalent now, or forecast to be soon, and where solutions are being developed. If the clinical trials landscape does not adapt to reflect these demographic realities, the risk is that future treatments will be designed, tested, and optimised for populations that represent a shrinking proportion of global need. Ensuring that clinical trials become more geographically representative is therefore not simply a matter of fairness; it is essential if future therapies are to be relevant, effective and accessible for the populations who will need them most.

Because dementia is so closely associated with older age, these demographic changes will inevitably reshape the global burden of disease. And it is longer life expectancy – one of humanity's greatest public health successes – that is driving this increase. The challenge for governments and health systems is to ensure that longer lives go hand in hand with healthier ones.

> **The challenge for governments and health systems is to ensure that longer lives go hand in hand with healthier ones.**

The implications extend far beyond healthcare. Dementia already places enormous emotional, social, and economic demands on individuals, families, and societies.[16] As populations age, the need for more effective prevention strategies, earlier diagnosis, improved treatments, and better models of care will only intensify. Clinical trials therefore represent an essential investment in the future health and wellbeing of ageing populations.

A world divided by progress

While high-income countries such as the United States, the United Kingdom, and parts of Europe have become hubs of clinical innovation, large swathes of the world remain on the periphery of this progress. The disparity is stark – and it was laid bare at ADI's 37th global conference in Lyon in April 2026.

"That hope of research, science, and clinical trials, feels a very long way from most of the world," Dr Fiona Carragher, then-chief policy and research officer of Alzheimer's Society, tells ADI shortly after her return from France. "So whilst there is hope, certainly for the very developed nations, the G7, the G20, we are also really grappling with the system element of it: how do you make the system work whilst the science is flying? That is profoundly not the reality in the majority of countries that I have the privilege of being alongside on ADI's member associations council. They are still very much probably seven to 10 years behind where we need to be, just because of where the health systems are and also the perception of dementia in many countries."

13 https://www.un.org/en/global-issues/ageing
14 https://www.thelancet.com/action/showPdf?pii=S2468-2667(21)00249-8
15 https://pubmed.ncbi.nlm.nih.gov/38306035/
16 https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf

The majority of clinical trials for Alzheimer's and related dementias are conducted in wealthier nations, where infrastructure, funding, and regulatory frameworks are conducive to complex research. In contrast, LMICs are significantly underrepresented. As of January 1, 2026, almost half (3,156) of the world's clinical trial sites for Alzheimer's disease are in North America, with 3,607 sites in non–North American regions, including 1,363 in Western Europe/Israel, 661 in Eastern Europe/Russia, 571 in Asia (not including Japan), 516 in Japan, 321 in Latin America, and 175 in South Africa, Australia, or New Zealand.[17]

This stark imbalance has consequences. Clinical trials shape not only the development of treatments, but also the populations for whom those treatments are validated. When trials lack geographic and ethnic diversity, the resulting therapies may be less effective, less accessible, or less relevant to those outside the narrow demographic bands in which they were tested. The risk is a two-tiered future of dementia care: one in which advances benefit a privileged minority while the global majority remains underserved.

> **The risk is a two-tiered future of dementia care: one in which advances benefit a privileged minority while the global majority remains underserved.**

The barriers to broader participation are complex and deeply rooted. Limited healthcare infrastructure, shortages of trained personnel, regulatory hurdles, and insufficient funding all play a role. Cultural factors and public awareness also influence participation in research, as does the absence of diagnostic capacity needed to identify eligible trial participants. Across the world, dementia itself remains underdiagnosed, misunderstood, or stigmatised, further complicating efforts to expand clinical research.

Efforts are underway to address these disparities, but progress is uneven. International collaborations, capacity-building initiatives, and policy reforms are beginning to extend the reach of clinical trials into previously excluded regions. However, the pace of change remains insufficient relative to the scale of the challenge. Bridging this gap will require sustained investment, not only in research but in healthcare systems more broadly. It will demand a rethinking of how trials are designed and conducted, with greater emphasis on inclusivity, accessibility, and local relevance.

Asked what she thinks future generations will see as the biggest missed opportunity in dementia research and what the world should be doing now to avoid experiencing it, Dr Emer MacSweeney, consultant interventional neuroradiologist and co-founder of Re:Cognition Health, tells ADI: "The biggest mistake that's happening at the minute is people who are clearly, obviously, most likely in the early stages of Alzheimer's, being ignored and completely missed… because that window of opportunity is really small for treatment."

"Today, there are clinical trials. All you have to do is be clinically eligible to join one, but there's a staggering level of ignorance among the medical profession about Alzheimer's disease and dementia. If you said to me: 'What's the most common thing patients say to you?' it is that they are so angry that nobody, i.e. their doctor, has told them about the opportunities available to them through clinical trials or to get access to these medications on the market. It's really sad and beggars belief."

"This is a pandemic," Dr MacSweeney emphasises. "The vast majority of patients with cognitive impairment who are over 55 will have Alzheimer's disease, but we need a change in mindset in the medical profession to ensure more people are told about clinical trials and supported to join them. We need action, not rhetoric."

Why clinical trials matter now more than ever

Dr MacSweeney's call to action contains a simple but critical truth: clinical trials are the engine of progress. They are the mechanism through which scientific hypotheses are tested, therapies are validated, and standards of care are established. Without them, the promise of disease-modifying treatments and precision medicine would remain theoretical, and the people at the heart of the matter – those with dementia and their loved ones – would be left without hope.

Today, fortunately, that is far from the case. We have moved from "the dark ages" of just a decade ago in the words of Jim Taylor, one of the world's leading patient advocates whose wife Geri was diagnosed with mild cognitive impairment (MCI) in 2012, "when the diagnostics did not even allow us to clarify whether it was Alzheimer's disease or another dementia" as PET scans and lumbar punctures – the "gold standard" methods of dementia diagnosis – were rarely used even in the United States.

Jim, whose wife died on August 4, 2024 at the age of 81 due to complications from Alzheimer's disease, describes the extraordinary progress he has witnessed firsthand, telling ADI: "Today we have much more hope, and I believe passionately that Geri benefitted tremendously [from treatments] and it gave us a couple of extra years with Alzheimer's disease at an early

17 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251

stage – that's a tremendous gift. There are people on treatments today who can validate that, so I think there's a greater incentive for people now more than ever to consider joining a clinical trial because we have had success in our lifetime."

> **'There's a greater incentive for people now more than ever to consider joining a clinical trial because we have had success in our lifetime.'**
>
> *Jim Taylor*

For researchers, the expanding clinical trials ecosystem offers unprecedented opportunities to explore new therapeutic avenues. For policymakers, it presents both a challenge and an imperative: to create environments that support innovation while ensuring equitable access. As Professor Steffen Thirstrup, the European Medicines Agency's chief medical officer, tells ADI in this report, regulatory frameworks must adapt to the accelerating pace of discovery, balancing the need for rigorous evaluation with the urgency of unmet medical need.

For the public, understanding the clinical trials landscape is equally vital. Participation in trials not only contributes to scientific advancement but can also provide access to cutting-edge therapies. Yet public engagement remains limited, often constrained by a lack of awareness, mistrust, or logistical barriers. Increasing participation will require transparent communication, community engagement, and a commitment to addressing potential participants' concerns.

The demographic tide now gathering force ensures that the stakes will only rise. Population ageing is not a distant prospect but an accelerating reality, one that will reshape societies as surely as any scientific breakthrough. The question posed implicitly by this report is whether the global research enterprise can keep pace – not only with the biology of dementia, but with the scale and distribution of the populations it will affect. If the past was defined by resignation, the present is characterised by possibility. The future, however, will depend on whether that possibility can be extended across borders, income levels, and healthcare systems – to meet a world that is, quite simply, growing older.

> **If the past was defined by resignation, the present is characterised by possibility.**

Chapter 2:

Understanding clinical trials: How new dementia treatments are developed

A gas delivery worker takes a break to read a newspaper on a street in Kolkata, India, in March 2026. (Photo by Domenico Pugliese)

Summary

Clinical trials are the foundation of modern medicine, providing the evidence needed to determine whether new treatments are safe, effective, and suitable for widespread use. Every medicine currently prescribed for Alzheimer's disease and other forms of dementia has reached people affected by the condition only after progressing through a rigorous process of scientific testing. Yet clinical trials remain widely misunderstood, with terms such as "Phase 3", "placebo-controlled" or "double-blind" often appearing in news reports without explanation.

This chapter provides an accessible introduction to how clinical trials work and why they are essential to developing new dementia treatments. It follows the journey of a potential medicine from laboratory discovery through testing in cells and animals, into carefully designed studies involving people, and ultimately to regulatory approval and use in everyday clinical practice. Along the way, it explains why most experimental treatments fail, how the drug development pipeline operates, and why this process, although slow and expensive, is critical for protecting patients and generating reliable evidence.

The chapter also introduces the different phases of clinical trials, explains the purpose of common trial designs such as randomised, double-blind, and placebo-controlled studies, and explores the complementary roles of universities, academic clinical trial networks, clinical research organisations, governments, and the pharmaceutical industry in advancing dementia research. Finally, it places clinical trials within a global context, highlighting how international collaboration, regulation, and increasingly diverse participant populations are shaping the next generation of Alzheimer's research.

As disease-modifying therapies begin to transform Alzheimer's care, understanding how evidence is generated has never been more important. Clinical trials are not simply a regulatory hurdle: they are the mechanism through which scientific discoveries become treatments that can improve – and ultimately change – the lives of people affected by dementia.

The origins of clinical trials

The resourceful Biblical military king Nebuchadnezzar II not only gave his name to a large bottle of wine capable of holding 15 litres, but is also remembered as the man responsible, perhaps unwittingly, for conducting the world's first clinical trial. The Book of Daniel describes how, during his 43-year rule in Babylon, Nebuchadnezzar ordered his people to only eat meat and only drink wine, a diet he believed would keep them in sound physical condition. When a group of young men of royal blood, including Daniel, were captured by the king to be trained for royal service, they rejected the king's "special diet" as it did not comply with Jewish dietary laws.

Their guards fretted that the king would notice his captives becoming sickly if they refused to eat at all, so the rebels convinced their captors to allow them to follow a diet of legumes and water – but only for 10 days. When the experiment ended, Daniel and his fellow vegetarians appeared better nourished than the meat-eaters, so the king permitted them to continue their diet. Consequently, the "trial" is probably one of the first times an open, uncontrolled human experiment guided a decision about public health.

It took medics a little longer to cotton on, but on May 20, 1747 the world's first clinical trial finally began, thanks to a brilliant young Scottish physician. The 18th century was a particularly perilous time for sailors, faced with numerous hazards – among them scurvy. Bleeding gums, stiff joints, and lassitude (a state of physical or mental weariness) were symptoms of the condition, now known to be caused by a dietary deficiency of vitamin C. Left untreated, it could be fatal. Commodore George Anson's circumnavigation of the globe from 1740 to 1744 had seen a crew of more than 1,800 men reduced to fewer than 200 by the ravages of the disease.

While serving on board the British ship HMS Salisbury, the Edinburgh-born naval surgeon Dr James Lind became appalled by the high mortality of scurvy amongst sailors. Although he had no concept of vitamins – the world had to wait until the 1930s

for that – Lind knew the condition was related to the sailors' poor diet, especially the lack of fresh meat and vegetables. He therefore planned a comparative trial of the most promising cure for scurvy involving 12 patients, thus transforming the vessel into a tightly controlled experimental space.[1]

"Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the forehold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like," Lind wrote.

"Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day… Two others took two spoonfuls of vinegar three times a day … Two of the worst patients were put on a course of seawater … Two others had each two oranges and one lemon given them every day … The two remaining patients, took … an electary recommended by a hospital surgeon … The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty … The other was the best recovered of any in his condition; and … was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects … I shall only observe, that the result of all my experiments was, that oranges and lemons were the most effectual remedies."

His vivid description, recorded in his "Treatise on Scurvy" and published in Edinburgh in 1753, covers the essential elements of a controlled trial.[2] Although the results were clear, Lind hesitated to recommend the use of oranges and lemons because they were too expensive. It was nearly 50 years before the British Navy eventually made lemon juice a compulsory part of the seafarer's diet, and this was soon replaced by lime juice because it was cheaper – a practice that gave rise to the term "limey" for Britons.

The rise of placebo-controlled trials

For over 200 years, a drug without an active ingredient has been called a "placebo," literally "I will please" in Latin. However, even the physicians of antiquity knew about the placebo effect and used it in their attempts to heal the sick. The famous 2nd century physician Galen of Pergamon, for example, believed he had greater treatment success with patients who put their trust in medicines and in their physician – truly believing they would be cured – than the active substances administered per se.[3] The term "placebo" wasn't used, but physicians were very aware of the placebo effect.

Scottish physician William Cullen is thought to have been the first to use the word placebo in a medical context. In manuscript notes of his clinical lectures in the late 18th century, Cullen describes how he used "a pure placebo," as he called it, administering mustard powder externally in an attempt to comfort a dying patient.[4] Although he considered the ointment ineffective, he saw his medical duty as giving hope to a seriously ill patient through the use of a purportedly effective medicine. Therapeutic options were limited in any case, and no effective remedies were available for many diseases at that time.

Samuel Hahnemann (1755–1843), the founder of homoeopathy, was likely the first physician to administer placebos, but it was not until 1863 that the first recorded placebo-controlled trial was carried out by US physician Austin Flint for the treatment of rheumatism.[5] He compared the use of standard therapies such as opium liniment or dry flannel applied to joints with a placebo consisting of a highly diluted tincture of a plant called quassia. The active treatment showed no difference from the placebo group within Flint's trial, which indicated the symptoms of rheumatic fever subsided naturally over time. This conclusion marked a shift in medicine, and the importance of active drug treatments became central to clinical trials.

At the beginning of the 20th century, the importance of what we now understand as placebo treatment waned significantly, mainly because physicians were increasingly able to rely on effective pharmacological substances. However, placebos became increasingly relevant as controls in clinical trials testing drug efficacy. By the mid-20th century, placebo-controlled trials had become the standard in clinical research. The UK Medical Research Council's (MRC) 1943 trial of patulin for the common cold was the first double-blind, controlled trial. This paved the way for the first randomised controlled trial of streptomycin in pulmonary tuberculosis carried out in 1946 by the MRC.

The use of 'double blinding', when both the participants and the experimenters do not know which group receives the placebo or the active treatment, marked the next step and built the foundation of what we know as clinical trials today – a long way from Daniel's first foray.

1 Richard Hamblyn, *The Art of Science: A Natural History of Ideas*, p. 175
2 https://pmc.ncbi.nlm.nih.gov/articles/PMC3149409/
3 https://pmc.ncbi.nlm.nih.gov/articles/PMC8939383/
4 Cullen Clinical Lectures 1772-3 RCPE Manuscript Cullen 4/2 299-300
5 https://bepartofresearch.nihr.ac.uk/news-and-features/history-healthcare-research?language_id=4790801

From cells to humans: How new treatments are tested

Developing new treatments for dementia is a long and carefully managed process designed to protect people and improve the chances of real progress. Each step in the testing pathway builds on the last, moving from simple laboratory work to studies in people. This gradual approach exists because all forms of dementia are incredibly complex conditions and because any new treatment must be proven safe and effective before it can be widely used.

The process begins with testing in cells in a laboratory. Scientists expose human or animal cells to a potential treatment to see how they behave at a basic level. This helps them understand whether the drug affects the right biological targets and whether it might harm cells. At this early stage, researchers can quickly rule out many compounds that are either ineffective or unsafe. However, cells alone cannot show how a treatment will behave in the body. They cannot reflect the complexity of the brain, the immune system, or how different organs interact. This is especially important in dementia, where the disease affects the brain in ways that are still not fully understood.

If a treatment shows promise in cells, scientists move into testing in animals. This allows scientists to study how the drug works in a living organism. They can see how it is processed by the body, how it travels to the brain, and whether it causes harm at different doses. This step is essential for identifying risks before any human is exposed to the drug. In dementia research, animal studies have helped advance knowledge, but they also have clear limits. Many animals do not naturally develop dementia in the same way humans do, and even specially designed models cannot fully copy the condition.[6] As a result, some treatments that seem effective in animals do not work in people. Even so, this stage remains a critical safeguard and is tightly regulated.

Only after these steps can a treatment be tested in humans through clinical trials. This is where researchers find out whether a drug can genuinely help people living with dementia. They look at whether it can slow their cognitive decline, improve symptoms, or change the course of the disease, while closely monitoring side effects. Human trials are essential because they provide the only true evidence of how a treatment performs in real life.

This step-by-step system exists to protect participants and focus resources on the most promising ideas. Most potential treatments do not make it through all stages. Many fail early, while others fall short in later trials when they do not show enough benefit or reveal unexpected risks. A recent review found that approximately 58–59 percent of Alzheimer's compounds fail to advance out of Phase 2, while 40–41 percent fail in Phase 3 trials. In the last decade, over 200 investigational programs were abandoned or failed.[7]

Although this failure rate can appear discouraging, it is a necessary part of ensuring that only safe and effective treatments move forward. For dementia, this careful process is particularly important. The condition is complex, varies from person to person, and remains one of the greatest challenges in medicine today. By following a structured and closely monitored pathway, researchers can reduce risks, learn from each stage, and steadily work towards treatments that can make a meaningful difference in people's lives. And as disappointing as the number of failed programmes can feel from an outside perspective, the breakthrough disease-modifying therapies lecanemab and donanemab provide evidence that we have entered a new era for Alzheimer's disease.

Phases of a clinical trial

Clinical trials are the cornerstone of medical research, designed to determine whether new treatments, drugs, or medical devices are safe and effective. They are carried out in a series of structured phases, each with a specific purpose and often increasing levels of complexity. Together, these phases help ensure that promising therapies are carefully evaluated before they are approved for widespread use.

Phase 0

An early stage, known as Phase 0, is becoming increasingly common, particularly in cancer research. These exploratory studies involve only a small number of participants – typically between 10 and 20 people – who receive very low doses of an investigational treatment. The aim is not to assess whether the treatment works, but to determine whether it behaves in the human body as researchers predicted from laboratory and animal studies, including how it is absorbed, distributed, and eliminated. Information gained from Phase 0 studies can help researchers decide whether a treatment should progress into larger clinical trials.

Phase 1

The primary purpose of Phase 1 trials is to determine the safety and tolerability of a new investigational treatment. These studies also examine how the body processes the drug (its pharmacokinetics), how the drug affects the body (its pharmacodynamics), and establish an appropriate dosing schedule.

Phase 1 trials are often conducted as dose-escalation studies. Participants receive gradually increasing doses until researchers identify the maximum tolerated dose (MTD) – the highest dose

6 https://pmc.ncbi.nlm.nih.gov/articles/PMC11743453/
7 https://pmc.ncbi.nlm.nih.gov/articles/PMC9198803/

that can be given while maintaining an acceptable level of side effects. This information helps determine which doses should be studied further.

Phase 1 trials usually involve between 20 and 80 healthy volunteers or, in some cases, closely monitored patients, depending on the nature of the treatment. Recruitment is often gradual because of strict eligibility criteria and intensive safety monitoring. Although relatively small, these studies are essential because they establish the safety profile of a new treatment before larger numbers of patients are exposed to it.

Phase 2

If a treatment demonstrates an acceptable safety profile in Phase 1, it may progress to a Phase 2 trial. These studies typically involve between 100 and 300 participants with the condition the treatment is intended to address.

Phase 2 trials are randomised, allowing researchers to compare the investigational treatment with either the current standard treatment or a placebo while reducing bias. Their primary purpose is to identify the most promising dose by evaluating safety alongside early signals of efficacy – whether the treatment appears to produce the desired biological or clinical effect. Researchers also continue to refine the dosing schedule, monitor side effects, and identify questions that should be addressed in larger studies.

Many promising treatments do not progress beyond this stage. Phase 2 trials play a crucial role in determining whether the potential benefits of a treatment justify the considerable investment required for large-scale Phase 3 studies.

Phase 3

Phase 3 trials are the largest and most complex stage of clinical research, often involving hundreds or thousands of participants recruited from multiple clinical sites across many countries. These multinational studies allow researchers to evaluate whether a treatment performs consistently across diverse populations, while also helping sponsors engage with regulatory agencies in different regions before submitting applications for approval.

Participants are randomly assigned to receive either the investigational treatment, the current standard treatment or, where appropriate, a placebo. These trials are conducted using rigorous methods such as double-blinding to minimise bias and ensure reliable results.

The primary objective of Phase 3 trials is to provide robust evidence that a treatment is efficacious – that it produces meaningful clinical benefit under carefully controlled conditions – while continuing to evaluate its safety in much larger populations. The findings from these pivotal studies form the basis of applications for regulatory approval by agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the UK's Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

Without Phase 3 trials, there would be no reliable way to determine whether a treatment's benefits outweigh its risks or to establish the evidence required for regulatory approval. Without Phase 3 trials, there would be no way to confirm a treatment's long-term safety, making them perhaps the most critical phase of the drug development process.[8] Last year, out of more than 12,000 drugs that reached a pre-clinical stage, just over 1,200 made it to Phase 3 clinical trials.[9]

Efficacy versus effectiveness

Although the terms are often used interchangeably, efficacy and effectiveness have distinct meanings in clinical research. Clinical trials, particularly Phase 3 studies, are designed to measure efficacy – whether a treatment produces the intended benefit under carefully controlled conditions, with strict eligibility criteria and standardised monitoring. Effectiveness, by contrast, refers to how well a treatment performs in routine clinical practice, where patients are more diverse, healthcare settings vary, and people may not always take medicines exactly as prescribed. Evidence of effectiveness is often gathered after approval through Phase 4 studies and other forms of real-world research.

Phase 4

Once a treatment has been approved and is available for clinical use, Phase 4 studies – also known as post-marketing surveillance – continue to monitor its performance in routine healthcare. These studies often involve thousands of patients and provide valuable information on long-term safety, rare side effects, and how the treatment performs across broader, more diverse populations than those typically included in earlier trials.

8 https://pharma.nridigital.com/pharma_dec20/phase_iii_trials_improvements
9 https://www.statista.com/statistics/791263/total-r-and-d-pipeline-size-timeline-worldwide/

Phase 4 studies may also examine how a medicine works in specific patient groups, compare it with other treatments, or evaluate combinations of therapies. In some cases, findings from post-marketing surveillance have led to changes in prescribing information, restrictions on use or, rarely, withdrawal of a medicine from the market when previously unrecognised safety concerns emerge. For example, rare side effects or issues in certain populations may only come to light after a drug is used by a larger and more diverse group of patients.[10]

Each phase of clinical research serves a distinct purpose. Phase 0 provides early information on how a treatment behaves in the body. Phase 1 establishes safety, tolerability, pharmacokinetics and the maximum tolerated dose. Phase 2 identifies the most promising dose while evaluating safety and looking for early signals of efficacy. Phase 3 provides the large-scale evidence needed to demonstrate efficacy and further characterise safety before regulatory review. Phase 4 continues to monitor benefits and risks after approval in routine clinical practice.

The rigorous progression through these phases is fundamental to protecting participants and ensuring that only treatments with an acceptable balance of benefits and risks become available to patients. Although many investigational therapies fail along the way, every study contributes valuable knowledge that advances scientific understanding and helps guide the development of future treatments. Without these well-defined stages, the introduction of new drugs could lead to harmful consequences, both for individuals and for society at large.

From discovery to approval: The drug development pipeline

One would be forgiven for comparing the hunt for Alzheimer's drugs to the Marathon des Sables, often called the "toughest foot race on Earth," a 250-kilometre (155 mile) jaunt over six days through the Sahara Desert: hundreds of competitors lining up at the start, many showing early promise before dropping out, a few veering the wrong way, and only the best making it through to the finish line. Yet after decades of this marathon, the finish line appears closer than it ever has.

Researchers tracking the global Alzheimer's pipeline identified 158 drugs in 192 active clinical trials at the beginning of 2026, spanning anti-amyloid antibodies, inflammation therapies, metabolic interventions, and repurposed cancer drugs.[11] The sheer scale of the effort reflects both the scientific complexity of dementia and the commercial stakes involved. Worldwide, dementia care already costs more than $1 trillion annually, while ageing populations are pushing healthcare systems towards crisis.

The phrase "drug pipeline" is often used loosely in pharmaceutical circles, but in practice it describes a highly structured – and brutally attritional – process. A promising molecule may begin life in a university laboratory or biotech startup, where researchers test whether it can influence biological targets associated with disease. In Alzheimer's, those targets have historically centred on amyloid plaques and tau tangles, the proteins long believed to drive neurodegeneration. From there, preclinical testing in cells and animals precedes regulators allowing trials in humans. Phase 1 trials ask a basic question: Is the drug safe? Phase 2 examines whether it appears biologically active and worth pursuing. Only in vast, expensive Phase 3 trials does a company attempt to prove clinical benefit convincingly enough for regulators to approve the medicine.

The economics are daunting. Developing a neurological drug can take more than a decade and cost billions. Most fail. Alzheimer's has been especially punishing because the condition progresses slowly and because measuring success is notoriously difficult. A patient may deteriorate over years rather than months, forcing trials to run for prolonged periods of time with thousands of volunteers.

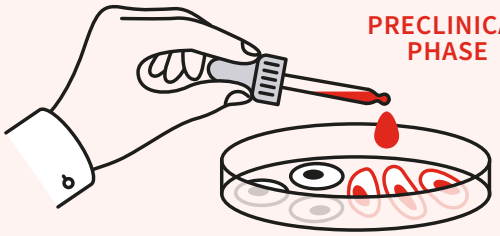
Trials of the anti-amyloid drugs lecanemab and donanemab have shown modest slowing of cognitive decline, but critics question whether the benefit is large enough to justify the cost and potential side effects. A 2025 Bayesian meta-analysis examining amyloid clearance as a surrogate marker concluded that the debate over whether removing plaques reliably predicts clinical improvement remains unresolved.[12]

Still, the field has changed dramatically from the despair of a decade ago, and the pipeline is no longer dominated by amyloid therapies. Today, roughly three-quarters of drugs in development are targeting other mechanisms, such as inflammation, vascular dysfunction, and cellular ageing.

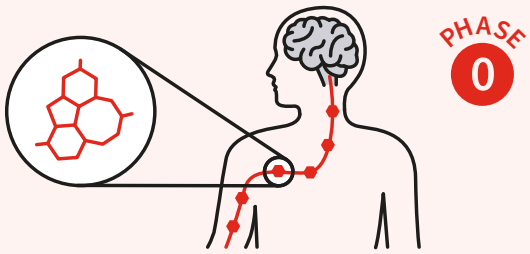
"For nearly 30 years, the Alzheimer's Drug Discovery Foundation (ADDF) has championed a biology-driven approach," said Howard Fillit, ADDF's cofounder and chief science officer. "Alzheimer's is a complex, multifactorial disease, and we have long believed that effectively treating it will require therapies that target multiple underlying mechanisms. Today, that shift is evident across the pipeline, including a significant increase in therapies targeting inflammation, which have grown from just 6 percent of trials to 18 percent over the past decade. This progress is laying the groundwork for a new generation of therapies, which will enable the same type of tailored precision medicine that transformed cancer care."[13]

10 https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/postmarketing-surveillance
11 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251
12 https://becarispublishing.com/doi/10.57264/cer-2025-0095
13 https://www.prnewswire.com/news-releases/goodes-prize-recipient-dr-jeff-cummings-2026-alzheimers-drug-pipeline-report-signals-new-era-of-biology-driven-approaches-302762691.html

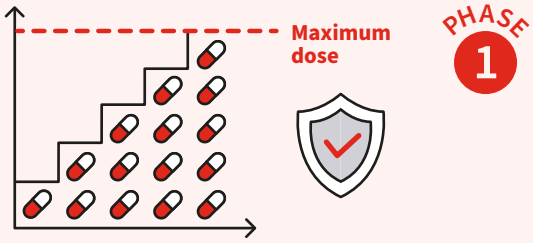
The phases of a clinical trial



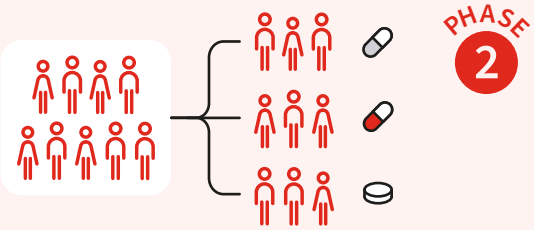
- **Preliminary phase**
- Scientists test **human or animal cells** to a potential treatment to see how they behave at a basic level.



- **10-20** healthy participants.
- Participants receive **very low doses of an investigational treatment** only to determine whether it behaves in the human body as researchers predicted from laboratory and animal studies.

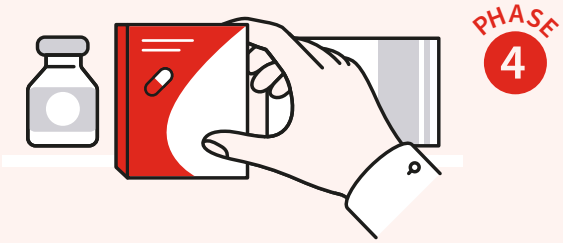


- **20-80** healthy participants or closely monitored patients.
- Gradual recruitment, strict eligibility criteria, and **intensive safety monitoring.**
- Participants receive gradually increasing doses until researchers identify the maximum tolerated dose – the highest dose that can be given while maintaining an acceptable level of side effects.



- **100-300** participants diagnosed with the condition the treatment seeks to address.
- **Randomised trial**: some participants are administered the treatment while others get a placebo or the current standard treatment
- Researchers seek to identify the most promising dose by evaluating **safety alongside early signals of efficacy** – whether the treatment appears to produce the desired biological or clinical effect.

- **Hundreds or thousands** of participants across sites in multiple countries.
- **Randomised, double-blind trial**: participants are assigned investigational treatment, current standard treatment, or a placebo. Neither researchers nor participants know who has received what to ensure reliable results.
- Researchers evaluate evidence that a treatment is efficacious – **that it produces meaningful clinical benefit** under carefully controlled conditions – while continuing to monitor its safety in much larger populations.



- **Thousands** of patients after the treatment reaches the market
- Treatment **performance is monitored in routine healthcare** to provide valuable information on long-term safety, rare side effects, and how the treatment performs across broader, more diverse populations than those typically included in earlier trials.
- Studies may also examine how a medicine works in specific patient groups, **compare it with other treatments**, or evaluate combinations of therapies.

That diversification matters because Alzheimer's increasingly looks less like a single disease and more like a cascade of interacting failures within the ageing brain. Tau-focused therapies, for instance, are now among the most closely watched areas of research. Reviews published in 2025 describe a rapidly expanding international effort to tackle tau aggregation directly with multiple monoclonal antibodies and gene-based approaches advancing through clinical trials.[14]

Types of clinical trials: Study design and who runs them

Between 2000 and 2020, more than 99 percent of experimental dementia drugs failed in clinical trials, leaving researchers, patients and investors frustrated. Yet the arrival of donanemab and lecanemab, alongside a surge in experimental drugs targeting inflammation, tau proteins, and metabolism, has transformed Alzheimer's disease clinical trials into one of the most closely watched arenas in modern medicine. At the heart of this transformation lies a deceptively simple question: How should Alzheimer's trials be designed?

Most modern dementia studies remain rooted in the gold standard of medical research – the randomised, double-blind, placebo-controlled trial. In these studies, neither participants nor clinicians know who is receiving the experimental drug or a placebo. The method is intended to eliminate bias, particularly important in Alzheimer's disease, where symptoms such as memory, mood, and cognition can fluctuate and are difficult to measure objectively.

Recent Alzheimer's trials have relied heavily on this structure. Eli Lilly's TRAILBLAZER-ALZ 2 study of donanemab, for example, was a placebo-controlled Phase 3 trial involving patients with early symptomatic Alzheimer's disease. Researchers reported that the drug slowed cognitive decline over 18 months compared with placebo, findings that later contributed to regulatory approval in several countries.[15] Similarly, the ABvac40 vaccine study, conducted across multiple centres in Europe, used a randomised double-blind placebo-controlled design to test an experimental active immunotherapy targeting amyloid-beta. Investigators said the design was crucial in distinguishing genuine biological effects from placebo responses or investigator expectations.[16]

Yet placebo-controlled dementia trials have become increasingly controversial as disease-modifying treatments enter clinical practice. Once an effective treatment is available, some researchers argue that it becomes more difficult to justify assigning participants to placebo when they could instead receive an established therapy. This raises questions about whether new treatments should increasingly be compared with existing disease-modifying therapies rather than a placebo.

A separate debate concerns how researchers can establish whether a treatment genuinely modifies the underlying course of dementia, rather than provide a temporary symptomatic benefit. Some researchers have proposed "delayed-start" designs for this purpose, in which one group begins treatment later than another. If the group treated earlier maintains an advantage after both groups have received the drug, this could provide evidence that the treatment has altered the course of disease. Adaptive trial designs, meanwhile, allow aspects of a trial to evolve as new data emerge.

The distinction matters because the ethical question of whether participants should receive placebo is not the same as the scientific question of how to demonstrate disease modification. The issue has become particularly relevant in long-term studies of Alzheimer's treatments. In the follow-up phase of TRAILBLAZER-ALZ 2, participants initially assigned to placebo were later switched to donanemab. Researchers found that earlier intervention was associated with greater long-term benefit, adding to the case for diagnosing and treating Alzheimer's as early as possible.[17]

The debate reflects a broader shift in dementia research. Increasingly, trials are moving away from testing drugs in patients with established dementia and toward individuals with mild cognitive impairment or even asymptomatic people who show amyloid buildup on brain scans or with a positive p-tau217 blood test. The ongoing TRAILBLAZER-ALZ 3 study, for example, is testing whether donanemab can delay symptoms before cognitive decline begins in people who are cognitively unimpaired with elevated blood p-tau217.[18]

Another major divide in global Alzheimer's research concerns who initiates and funds trials. Commercial pharmaceutical companies dominate late-stage Alzheimer's drug development because the costs are enormous, and those firms have the financial power to fund them. A single global Phase 3 dementia trial can involve thousands of participants across dozens of countries and cost hundreds of millions of dollars. Companies such as Eli Lilly and Company, Biogen, and Novo Nordisk have invested heavily in anti-amyloid therapies, venturing that even modestly effective drugs could transform a market affecting tens of millions of people.

14 https://link.springer.com/article/10.1186/s13195-025-01775-x
15 https://www.alzint.org/news-events/news/donanemab-receives-marketing-authorisation-in-australia-brazil-and-mexico/
16 https://pubmed.ncbi.nlm.nih.gov/41058018/
17 https://pubmed.ncbi.nlm.nih.gov/41330788/
18 https://pmc.ncbi.nlm.nih.gov/articles/PMC12439032/

Industry-led trials tend to be highly standardised, globally coordinated, and closely aligned with regulatory approval pathways. The emphasis is often on measurable clinical endpoints and biomarker changes that meet the requirements of agencies such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

Novo Nordisk's recent semaglutide Alzheimer's trials illustrate the risks involved. The company's large Phase 3 Evoke and Evoke+ studies tested whether oral semaglutide, an anti-diabetic medication better known under brand names such as Ozempic or Wegovy, could slow the progression of Alzheimer's disease. Despite strong biomarker effects, the studies failed to show that the dosage (up to 14 mg daily) slows the progression of early Alzheimer's disease. While the 3,808-participant studies demonstrated improvements in some Alzheimer's-related biomarkers, they did not confirm cognitive or functional benefits over a placebo.[19]

Some have criticised the trial design as having potentially been fundamentally flawed. Many researchers argued that GLP-1 medications like semaglutide might only work to prevent neurodegeneration but are unlikely to reverse or halt cognitive decline once dementia is already underway. However, Dr Peter Johannsen, Novo Nordisk's international medical vice president, said in an address at last year's Clinical Trials in Alzheimer's Disease meeting in San Diego, that "we still think it was the right decision... a scientific question that needed an answer." While Alzheimer's is defined by the presence of toxic amyloid plaques in the brain, "there are still things we don't know" about the pathology of the disease. "This is a very complex disease with a lot of things going on with different genetic signatures," Johannsen said.[20]

Robert Howard, professor of old-age psychiatry at University College London, said at the time the trial results were announced: "While failure of every potential treatment for Alzheimer's disease is disappointing, this was always something of a hopeful thinking longshot and I'm not completely surprised that the drug has failed to show activity against disease progression. But it was important to conduct such a large and carefully managed study so that we can confidently shut this line of enquiry and look elsewhere for progress. Clinical trial outcomes have a definite brutality to them, but this is important if we are to move on and find ultimate treatments that work."[21]

Professor Marwan Sabbagh, who co-authored an analysis of the trials,[22] points out there are about 15 different types of drugs targeting amyloid, tau, inflammation, and more in Jeff Cummings's annual report, and that noise is inevitable "every time a major event occurs, whether positive or negative."

He tells ADI: "Post-mortem, people always have an opinion. The truth is [Evoke/Evoke+] was well-designed and well-conducted. The fact is it was a negative study. You don't need to speculate otherwise… My point is that it's a very dynamic space, an accordion of expanding and contracting, and I suspect we'll see a little bit of contraction down for the next year or two. But the classes of drugs get bigger, and that's very exciting. We're seeing more and more drugs in more and more classes: for example, more behaviourally focused drugs, which is relatively positive because instead of trying to do a catch-all, they're looking at a targeted, specific symptom cluster."

Academic and government-backed trials, by contrast, often pursue questions that commercial firms may regard as too risky, too early-stage, or insufficiently profitable. Universities and publicly funded consortia have been particularly active in studying biomarkers, prevention strategies, and alternative disease mechanisms beyond amyloid.

Government-supported initiatives also play a critical role in data sharing and infrastructure. Programmes such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) have become foundational to global dementia research, providing imaging, biomarker, and longitudinal patient data used by both academic investigators and pharmaceutical companies. Increasingly, the boundary between commercial and academic research is blurring. Many of the largest Alzheimer's trials now operate through public-private partnerships involving universities, charities, biotechnology firms, and national health systems. This hybrid model reflects the view that Alzheimer's disease poses scientific and economic challenges that are difficult for any single sector to address alone.

Even so, major challenges remain. Recruiting diverse participants is difficult, diagnoses often occur too late, and LMICs remain largely excluded from cutting-edge research. Alzheimer's Research UK recently warned that delayed diagnosis is preventing many patients from accessing experimental therapies and enrolling in trials altogether.[23] Still, the overall sense is one of cautious optimism. The next generation of Alzheimer's trials is likely to become more personalised, biomarker-driven, and globally interconnected. Whether driven by pharmaceutical giants or academic laboratories, the central ambition remains the same: to turn Alzheimer's disease from an inevitable decline into a manageable condition – or eventually, to prevent it altogether.

19 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(26)00459-9/fulltext
20 https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisk-justifies-reasoning-behind-failed-glp-1-alzheimers-trials-2025-12-02/
21 https://www.sciencemediacentre.org/expert-reaction-to-news-from-novo-nordisk-that-semaglutide-does-not-reduce-alzheimers-disease-progression/
22 https://pubmed.ncbi.nlm.nih.gov/40337158/)
23 https://www.alzheimers.org.uk/news/2026-05-18/reports-expose-dementia-care-system-failing-patients-every-stage

Who conducts clinical trials?

The route from laboratory bench to patient bedside also depends on an often invisible industry: Clinical Research Organisations, or CROs. These companies have become the logistical backbone of modern drug development. Pharmaceutical giants increasingly outsource trial management to specialist firms capable of recruiting patients across dozens of countries, handling regulatory compliance, monitoring safety data, and coordinating biomarker analysis.

CROs provide the operational infrastructure needed to deliver increasingly complex multinational studies efficiently. Their ability to rapidly scale recruitment, employ local staff familiar with healthcare systems, languages, and regulatory requirements, and coordinate trial activities across multiple countries allows sponsors to conduct global studies without having to build large temporary workforces in every region. This makes large international trials considerably more practical and cost-effective while ensuring studies are conducted to consistent regulatory and scientific standards.

In dementia research, where recruitment is especially difficult, CROs have become indispensable. They actively seek out and establish partnerships, which may include pharmaceutical companies, biotechnology firms, academic institutions, and non-profit organisations. These collaborations are crucial in identifying and developing effective approaches for treating diseases, particularly those as complex and multifaceted as dementia.

Trials increasingly require highly specific candidates – often people in the earliest stages of cognitive decline with confirmed amyloid or tau pathology shown by PET scans or blood biomarkers. Coordinating that level of screening across multiple continents demands industrial-scale organisation. It is here that the geography of dementia research is changing. Once concentrated in the United States and Western Europe, Alzheimer's trials are now increasingly global, with sites in East Asia, Latin America, and Gulf states.

Conducting trials across multiple countries not only enables sponsors to recruit participants more quickly and include more diverse populations, but also gives investigators and regulatory authorities in different regions early experience with an investigational treatment before marketing applications are submitted. Global studies also generate evidence across a broader range of healthcare systems and populations, although critics warn that low-income countries can sometimes become testing grounds for treatments primarily intended for wealthier markets.[24]

Academic clinical trial networks are equally important to the global research ecosystem. Bringing together universities, hospitals, and specialist research centres, these networks provide scientific leadership, experienced investigators, and access to well-characterised patient populations. They have led many landmark Alzheimer's studies, pioneered innovative trial designs, validated biomarkers, and generated independent evidence that underpins future commercial development. Their long-term expertise and research infrastructure make them essential partners in advancing dementia science.

Their research spans the full spectrum of Alzheimer's science, from biomarkers and prevention strategies to novel therapeutic approaches that extend well beyond amyloid. Researchers at University College London (UCL) and collaborating institutions, for example, have explored how different anti-amyloid drugs bind to toxic amyloid-beta proteins, helping explain why some therapies appear more effective than others.[25] Meanwhile, academic-led investigations into neuroinflammation, neurotrophin receptors, and precision medicine are expanding rapidly. One example is the experimental drug LM11A-31, developed through academic collaboration, which targets nerve growth factor signalling rather than directly removing amyloid. A Phase 2 study published in 2024 found the treatment to be safe and well-tolerated after 26 weeks in people with mild to moderate Alzheimer's disease, supporting further investigation of this alternative therapeutic approach.[26]

Academic researchers are also often more willing to investigate novel or unconventional scientific questions that pharmaceutical companies may regard as too early stage, uncertain, or commercially risky. One striking example emerged from the University of California, San Francisco, where scientists used computational analysis of gene expression patterns to identify two existing cancer drugs – letrozole and irinotecan – as possible Alzheimer's therapies. In mouse studies published in 2025, the combination reportedly reversed memory deficits and reduced toxic tau accumulation.[27] Though still far from clinical application, the work illustrates the growing enthusiasm for drug repurposing, now representing roughly one-third of agents in the Alzheimer's pipeline.

Academic networks are also leading efforts to improve dementia diagnosis, an essential step in identifying people who may benefit from future treatments and participate in clinical trials. UCL researchers recently launched the Adapt study, part of the Blood Biomarker Challenge, a multi-million-pound programme supported by Alzheimer's Research UK, Alzheimer's Society, and players of the People's Postcode Lottery. This groundbreaking initiative aims to revolutionise dementia diagnosis by bringing blood tests into the UK's

24 https://pmc.ncbi.nlm.nih.gov/articles/PMC10081010/
25 https://www.ukdri.ac.uk/news-and-events/scientists-find-clues-why-new-drugs-are-effective-alzheimers
26 https://www.nature.com/articles/s41591-024-02977-w
27 https://nypost.com/2025/07/27/health/breakthrough-as-two-fda-approved-drugs-are-found-to-reverse-alzheimers-including-restoring-memory/

National Health Service by 2029. The hope is that cheaper blood tests could replace expensive PET scans and spinal taps, dramatically widening access to early diagnosis.

"Currently only about 2 percent of people diagnosed with Alzheimer's have access to one of these gold-standard diagnostic tests," Prof Jonathan Schott, Chief Medical Officer at Alzheimer's Research UK and one of the study leads, said at the launch.[28] "While identifying Alzheimer's disease early and accurately is already important for enabling access to current therapies and planning care, it will become even more critical as a new generation of treatments emerges that can slow down the decline of memory and thinking."

Whereas the UCL study is looking at the p-tau217 biomarker, the second wing of the trial, called READ-OUT (REAl-world Dementia OUTcomes), led by Dementias Platform UK (DPUK) at the universities of Oxford and Cambridge, is looking at a combination of biomarkers. The researchers leading the trial believe it can "revolutionise" care, urging people across the UK to sign up.

Martin Short, a 79-year-old taking part in the trial, noticed his memory was deteriorating over the last few years. "If I can find out by a simple blood test that either there's nothing to worry about, or perhaps we should look at this more deeply. If that gives people the ability to do that, it's brilliant," he said.[29]

READ-OUT co-lead Professor Vanessa Raymont said: "Blood biomarker tests could be the answer to this problem, and the good news is that the technology already exists. What we're missing is the proof that they really do work in a real-world setting. Our team will be looking at a range of blood tests, and we'll be recruiting participants from a broad range of people, including those from minority ethnic groups, the very elderly, and people with other medical conditions. This will show us how the blood tests perform in different UK populations."

One of the biggest challenges in Alzheimer's disease is diagnosis. Millions of people living with the disease are never diagnosed, and for many who are, the diagnosis comes only after symptoms have significantly progressed. A 2025 global review of studies from Europe, the US, Australia, and China found that people wait an average of 3.5 years from the onset of symptoms before receiving a diagnosis. For those with young-onset dementia, the delay is even longer – 4.1 years on average.[30] Even then, diagnosis is not always accurate, with many people initially misdiagnosed or diagnosed only after multiple clinical assessments.

Prof Raymont, a consultant psychiatrist and associate professor at the University of Oxford, said the blood tests could be a "gamechanger," but stressed that the key is finding out which tests work for which people. "Both my parents died with dementia. I hope that the kind of experience they had will change quite drastically in the next few years. If we can show that these tests help us make a more accurate diagnosis, we should have a framework that we can roll out across the NHS [National Health Service]."[31]

Such diagnostic advances may prove just as important as the drugs themselves. Alzheimer's specialists increasingly argue that treatment must begin before extensive brain damage occurs. Yet even a country as wealthy as the UK risks falling behind. Alzheimer's Research UK warned in May that slow diagnosis rates mean many patients are missing opportunities to participate in experimental trials altogether.[32] That matters not only to individuals seeking treatment but also to the broader competitiveness of British biomedical research. Countries able to recruit patients rapidly are more likely to attract major commercial trials.

And in many LMICs, millions more people with dementia are never formally diagnosed at all. While wealthier nations debate access to expensive new anti-amyloid therapies, large parts of Latin America, Africa, and South Asia still struggle to identify dementia consistently in primary care. Researchers estimate that nearly two-thirds of the world's dementia patients will soon live in LMICs, yet diagnostic systems in many of those nations remain rudimentary. The reasons are structural as much as medical. Many healthcare systems remain oriented towards infectious diseases and acute illnesses rather than chronic neurodegeneration. Specialist neurologists are scarce. Brain imaging is expensive. Memory clinics are concentrated in major cities. Social stigma also remains powerful, with cognitive decline often dismissed as a normal part of ageing rather than recognised as a pathology.

Nature Reviews Neurology recently warned that dementia research and diagnosis in lower-income regions continue to be hampered by "lack of funding, scarce resources and equipment, and brain drain."[33] In parts of rural India, sub-Saharan Africa, and Latin America, families may never encounter a clinician trained to recognise early Alzheimer's symptoms. The consequences extend far beyond statistics. Patients diagnosed late lose opportunities for symptom management, clinical trial participation, and future disease-modifying therapies. Governments, meanwhile, underestimate the true scale of the problem and therefore underinvest in services.

28 https://www.alzheimersresearchuk.org/news/uk-trial-launches-to-transform-alzheimers-diagnosis-with-simple-blood-test/
29 https://www.bbc.co.uk/news/articles/cly4lej9gm4o
30 https://www.ucl.ac.uk/news/2025/jul/dementia-takes-35-years-diagnose-after-symptoms-begin
31 https://www.alzheimers.org.uk/cy/node/261591
32 https://www.theguardian.com/society/2026/may/05/slow-alzheimers-diagnoses-means-uk-patients-missing-out-on-experimental-treatments-says-charity
33 https://www.nature.com/collections/iaabadiiab

Yet emerging success stories suggest that progress is possible even in resource-constrained settings. Cuba has become one of the most closely watched examples. Researchers working with the Global Brain Health Institute recently completed a cluster-randomised trial involving primary care clinics across the country. Instead of relying on expensive specialist infrastructure, the programme trained ordinary family doctors to recognise dementia earlier and more confidently. Over 12 months, diagnosis rates rose significantly in the intervention clinics.[34]

The Cuban model matters because it shifts dementia care away from elite neurological centres and into community medicine. Researchers behind the project argued that "structured training can significantly enhance" early detection in lower-income healthcare systems. It is precisely the sort of scalable intervention global health experts believe could transform dementia care across much of the Global South.

Latin America has also become an increasingly important laboratory for innovation. Chile, Colombia, and Argentina have all expanded dementia awareness campaigns and strengthened academic partnerships with European and North American research centres. In Colombia, qualitative research published last year found growing recognition among policymakers and clinicians that dementia must be treated as a national public health priority rather than a private family burden.[35]

Argentina recently launched its national dementia plan on February 19, 2026.[36] The plan is structured around six key pillars, with an explicit focus on risk reduction and integrating dementia prevention into broader public health strategies for non-communicable diseases. Peru also recently approved its National Plan for the Prevention and Treatment of Alzheimer's Disease.[37] Brazil, Chile, Costa Rica, Cuba, and the Dominican Republic all have plans in place, but the question is whether governments follow through and actually implement them.

"For me, the big problem is the economic support for the plan, the money," Professor Ricardo Allegri, director of the Memory and Ageing Centre at the Neurological Research Institute Fleni in Buenos Aires, Argentina, tells ADI. "You can design an interesting plan, but if you don't have a lot of money to support it, it's not real, no? I believe that more clinical trials are possible in Latin America because there are centres where you can have PET scans, cyclotron [a particle accelerator used to produce medical isotopes needed for PET scans], and blood biomarkers."

Another issue is the cost of the new disease-modifying therapies themselves, which can vary widely between countries due to a mix of pricing strategy, health-system structure, regulatory decisions, and broader economic factors.

Prof Allegri adds: "We need to talk with the people from the pharmaceutical industry, because although we have collaborations with the USA, Europe, etc… the cost of lecanemab in Argentina is three times the cost in the USA, so firms are reluctant to choose Latin America for their trial sites. However, the ability to perform trials in Latin America will reduce costs. For example, one PET scan in Argentina costs less than in the USA, the same with one neurological assessment: $150 here but $800 in the USA. So we have advantages here. Buenos Aires, São Paolo, Mexico City, are huge populations, so we have the possibility to host trials not far from hospitals, making it easier to recruit."

Peru's IMPACT Salud programme, a four-year project focused on improving outcomes for people with dementia and their caregivers, and developed through international collaboration, is attempting something broader still: redesigning entire health systems around dementia preparedness.[38] Researchers involved in the initiative argue that LMICs should not simply replicate Western models but instead develop community-based systems tailored to local realities.

India, too, has begun investing more heavily in population-level screening and public education. Although diagnosis rates remain low overall, specialist memory clinics have expanded rapidly in major urban centres over the past decade, while Indian researchers are increasingly contributing to global dementia science rather than serving merely as recruitment partners for Western-led trials.

The nation's dementia research landscape is expanding from primarily observational studies to participation in large interventional and prevention-focused clinical trials, especially for Alzheimer's disease. One of the most important homegrown initiatives is the Strategic Multimodal Intervention in at-risk Elderly Indians for Prevention of Dementia, or SMRUTHI INDIA, programme, a landmark cohort study and randomised controlled trial aimed at preventing and delaying dementia among rural elderly populations in India. The study aims to create a "trial-ready" cohort of older adults at high risk of dementia, particularly in rural India, and evaluate whether multimodal interventions – including vascular risk control, cognitive stimulation, nutrition, and lifestyle modification – can delay or prevent dementia onset. Researchers chose this design

34 https://pmc.ncbi.nlm.nih.gov/articles/PMC12100495/
35 https://pmc.ncbi.nlm.nih.gov/articles/PMC11895336/
36 https://www.alzint.org/news-events/news/argentina-launches-national-dementia-plan/
37 https://www.alzint.org/news-events/news/peru-approves-its-national-dementia-plan-a-milestone-for-the-country-and-the-region/
38 https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(23)00239-9/fulltext)

because up to 45 percent of dementia risk may be linked to modifiable factors such as hypertension, diabetes, inactivity, and social isolation.[39]

Asia is increasingly being included in multinational pharmaceutical trials targeting the biological mechanisms of Alzheimer's disease. Several late-stage studies are evaluating anti-amyloid and anti-tau monoclonal antibodies in patients with mild cognitive impairment or early Alzheimer's dementia. Among the most prominent are Roche's trontinemab Phase 3 trials (TRONTIER-1 and TRONTIER-2), which investigate a next-generation antibody engineered to cross the blood–brain barrier more efficiently than earlier therapies. These studies reflect the broader global shift toward disease-modifying therapies rather than purely symptomatic treatment.[40]

There is also growing optimism around cheaper diagnostic technologies. Blood-based biomarker tests – now under rapid development in Europe, the United States, and Asia – could eventually prove transformative for poorer nations by reducing dependence on costly PET scanners and lumbar punctures. A reliable blood test that can be deployed in ordinary clinics would fundamentally alter the economics of dementia diagnosis worldwide.

The danger, however, is that scientific progress widens global inequality rather than reducing it. New Alzheimer's drugs already cost tens of thousands of dollars annually in some markets. Without substantial international investment, much of the developing world may remain excluded from the therapeutic revolution underway in richer countries. That prospect worries many researchers working in global brain health. "Most people with dementia live in low- and middle-income countries," a recent international review noted, yet scientific understanding of dementia still remains overwhelmingly shaped by "Global North perspectives."[41]

The challenge for the next decade will therefore be twofold: discovering better treatments while ensuring health systems are capable of diagnosing patients early enough to benefit from them. A breakthrough drug means little if the majority of people living with dementia are never identified in the first place. In that sense, the future of dementia care may depend as much on family doctors in Havana, Lima, or Bangalore as on billion-dollar laboratories in California.

Although the pipeline is flowing, it remains precarious. In May 2026, Biogen announced it would advance its experimental tau drug diranersen into late-stage trials despite mixed Phase 2 results that unsettled investors.[42] Although the study showed it slowed cognitive decline and reduced a key brain protein linked to the disease, the drug missed the trial's main goal of showing that higher doses worked better than lower doses on a standard scale used to track dementia severity at 76 weeks. The 18-month mid-stage study enrolled 416 participants with mild cognitive impairment, who had previously not received any anti-amyloid therapy.

The decision captures the peculiar uncertainty of Alzheimer's research: biological signals may look promising even when clinical outcomes remain ambiguous. That uncertainty has not deterred investment. If anything, the arrival of the first disease-modifying drugs has emboldened researchers who believe dementia treatment is entering a phase comparable to oncology in the 1990s – imperfect first-generation therapies opening the door to combinations, precision medicine, and earlier intervention. For families confronting dementia today, progress still feels painfully slow. But viewed historically, the field is changing with remarkable speed. Blood tests are emerging, computational drug discovery is accelerating, and the pipeline has become broader and more sophisticated than at any point in history.

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39 https://www.alzint.org/news-events/news/lancet-commission-identifies-two-new-risk-factors-for-dementia-and-suggests-45-of-cases-could-be-delayed-or-reduced/
40 https://www.alzforum.org/therapeutics/trontinemab
41 https://pmc.ncbi.nlm.nih.gov/articles/PMC13093691/
42 https://www.reuters.com/business/healthcare-pharmaceuticals/biogens-alzheimers-drug-fails-meet-mid-stage-trial-goal-2026-05-14/

CASE STUDY

Endurance, evidence, and empathy: The "5 Ironmans Beat Alzheimer's" initiative

When Hassan Fadli stood in a public market in Lausanne in 2022, handing out flyers about dementia, the reactions startled him. Some people recoiled at the mere mention of the word. A few even refused to take a leaflet, as if worried it might somehow "give" them the disease. Hassan, who had already been living the reality of Alzheimer's disease through his family, thought the disconnect between public perception and lived experience was striking – and troubling.

That moment captures the essence of the "5 Ironmans Beat Alzheimer's" (5IBA) initiative:[43] a project that blends extreme endurance sport, personal storytelling, and emerging science to challenge stigma, explore prevention, and push for systemic change in how societies understand and respond to dementia. At its core, this is not just an athletic feat. It is a deeply personal and scientific experiment – one that spans continents, disciplines, and emotional realities.

> **At its core, this is not just an athletic feat. It is a deeply personal and scientific experiment – one that spans continents, disciplines, and emotional realities.**

For Hassan, the project began not in a lab or on a racecourse, but at home in Normandy, France. His father and uncle were diagnosed with Alzheimer's disease, forcing him into the role of caregiver. "I had to take leave from my job to take care of my dad, which was very tough," he explains to ADI.

The experience exposed not only the emotional toll of dementia, but also systemic shortcomings in care infrastructure. His father's journey left a particularly lasting impression. "My dad was in denial over the disease, but on the day he finally acknowledged it for the first time, he became very emotional because he realised it was something that was real – and had been for six to eight years."

The final months of his father's life, spent in a nursing home, were especially difficult for the family. Across Europe, Hassan observed varying approaches to dementia care, shaped as much by culture as by policy. In Mediterranean countries, family-based care is more common, while northern European nations often rely more heavily on institutional care systems. Yet across all regions, gaps remain – particularly in community-based and preventative solutions.[44]

"Society has to change in the first place," he says. "There are many countries that take very few social initiatives, such as dementia-friendly cities or transport."

While Hassan's motivation was rooted in personal experience, his collaborator on the 5 Ironmans challenge, Thomas Roos, approached the challenge from a different angle: science and sports.

Thomas, an identical twin and a graduate of Stanford University's bioscience programme, had long been fascinated by how biology changes over time and how we can track it using advanced multi-omic technologies. These combine different biological data layers – such as genomics, transcriptomics, and proteomics – to provide a comprehensive view of how cells and systems function. Instead of studying one part of biology by itself, scientists use these tools to see how genes, RNA, and proteins work together. Thomas's involvement in research includes not only conducting studies with athletes but volunteering for many studies himself through the Stanford Twin Registry and the University of Lausanne.[45]

"My twin brother and I have been in quite a few cool studies as subjects in the intervention arm or as healthy controls," he explains. "We both have learned a lot about how our bodies change in response to our environment and behaviour."

With a background in biochemistry, genetics, epidemiology, and clinical trials, Thomas had already spent years studying longitudinal changes in human biology. Part of his academic work focused on protein homeostasis during ageing

43 https://www.5ironmansbeatalzheimer.com/en
44 https://www.alzheimer-europe.org/resources/publications/european-dementia-monitor-comparing-and-benchmarking-national-dementia?language_content_entity=en
45 https://lifeissues.net/writers/sym/sym_55geneticfuture.html

Thomas Roos (left) and Hassan Fadli of 5 Ironmans Beat Alzheimer's. Through five Ironman-distance races, a documentary and a programme of public talks, they've turned personal loss into public action. (Photo by Luca Zanetti)

– specifically the mechanisms of protein folding and/or misfolding behind tau and amyloid-beta plaques, key features of Alzheimer's disease.

"I have been on this journey since my 20s," he says. "Now I'm 40, and I'm trying to use all the preventative measures I can to delay the onset of cognitive impairment."

Like Hassan, Thomas has a strong personal connection to the condition, with a family history and genetic profile placing him at exceptionally high risk. "If you calculate my full risk profile, I'm at the 95th percentile, but we now have good evidence that lifestyle changes can reduce this risk substantially."

The concept: a human case study

The idea behind 5IBA emerged from the intersection of Hassan's advocacy, Thomas's scientific background, and their shared affinity for endurance sports. Together, they designed a multi-year experiment: train for and complete five Ironman-distance triathlons while collecting extensive biological data. An Ironman is an extreme multi-sport endurance event consisting of a 2.4-mile (3.86 km) swim, a 112-mile (180.25 km) bike ride, and a full 26.2-mile (42.2 km) marathon run.

"We thought, why not collect some data ourselves as we go through a three- to five-year period from 40 to 45," says Thomas, "a key period in life where things change inside our bodies."

The result is a unique hybrid: part endurance challenge, part scientific pilot study, and part awareness campaign. "This is not a clinical trial," Thomas emphasises. "It is a case study of just the two of us. We're collecting a lot of data – with no intention of making big claims – but we will make everything open access."

By combining endurance sport with rigorous data collection, Hassan and Thomas are exploring the boundaries of what lifestyle interventions can achieve. By sharing their stories, they are challenging stigma and raising awareness. And by advocating for systemic change, they are pushing for a more humane and effective approach to dementia care. Their work underscores a simple yet powerful idea: there are actions individuals and societies can take in the face of a complex and devastating condition.

> **'This is not a clinical trial. It is a case study of just the two of us. We're collecting a lot of data – with no intention of making big claims.'**
>
> *Thomas Roos*

Their methodology is comprehensive. Over nearly three years, they have collected blood samples, muscle tissue samples, saliva biomarkers, genetic and epigenetic sequencing, proteomic and metabolic data, microbiome samples, cognitive assessments, brain and body imaging, and lifestyle data, including sleep, diet, and physical activity. They have also biobanked samples for future analysis as technologies evolve.

"We're using all the best technologies that we have," Thomas explains, "and working with our amazing partners across various labs, companies, and academic research centres."

The athletic framework: health for performance

While the project involves completing five Ironman races – among the most physically demanding endurance events in the world – the athletic component is deliberately structured to balance training load with recovery, prioritising health while increasing performance. "The intention was to complete the race with a smile, no injuries, no taking any risks," Hassan says.

This philosophy is critical. The pair trains mostly at controlled intensities, with bouts of high intensity a few times a week to optimise physiological adaptation. This approach aligns with evidence suggesting that daily exercise meeting the World Health Organisation's guidelines may be the most beneficial thing for long-term health – particularly brain health.[46]

Hassan, who transitioned from a sedentary, high-stress lifestyle, believes the transformation has been profound. "Before, I was working 60–70 hours a week. My overall health condition had been getting worse. Now I'm eating well, sleeping well, and my health – including my brain health – is getting better," he says.

One of the most striking findings of their self-led study to date has been the divergence between chronological and biological/physiological age. "My physical age was increasing as I was training, but my biological age was decreasing and my fitness level increasing," Hassan says, laughing. "So I'm getting younger."

Thomas adds: "We can estimate how fast different organs are ageing. For Hassan, he started with a biological age of plus two and is now at minus two."

Thomas himself, coming from a professional athletic background, continues to train 15 hours a week and compete in endurance races while maintaining a biological age of minus 10. "That's good for me," he says. "I'm just trying not to have my fitness levels decline too much."

Although the study is still ongoing, several early observations have emerged. First, consistent lifestyle changes – exercise, nutrition, sleep – are associated with measurable improvements in physiological markers. This aligns with broader research suggesting that modifiable risk factors play a significant role in dementia prevention.[47] Second, the data highlights the complexity of human biology. "We have done genetic, epigenetic, proteomic, and metabolic sequencing," Thomas says. "That looks at different levels of what's happening inside your body."

One particularly intriguing area is the microbiome. "It's been interesting to see microbiome changes in conjunction with other biological changes," he notes. "We really think the microbiome has a direct connection to the brain."

This reflects growing scientific interest in the gut-brain axis – a system that links digestive health to neurological function. At the same time, both men are cautious about over-interpreting the data.[48] "Trying to understand it is way too complex at this time," Thomas admits. "We're just collecting the data and will analyse it in a couple of years when we have better models."

Although data collection is central to the project, its broader purpose is to bridge the gap between scientific knowledge and public awareness. "One of the main issues is a lack of awareness," Thomas says. "There's still this idea that dementia is inevitable and there's nothing you can do about it."

Hassan has witnessed this firsthand. "In 2022, people were shocked just to see the word dementia," he recalls. "Today, I see much more awareness – especially among younger people." The COVID-19 pandemic, he believes, has played a role in shifting attitudes toward mental and brain health. "Before, if you had a problem with your knee, you'd see a doctor," he says. "But if you had a problem with your brain, you wouldn't tell anyone."

That stigma is gradually changing, and the initiative aims to accelerate that process through education and storytelling. A key component of the project is a documentary film, set for release in Geneva and Paris next year, that chronicles Hassan's journey as a caregiver, athlete, and advocate. Unlike many narratives around dementia, which focus on decline and loss, this film emphasises agency and prevention.

The other core members of the group include Hassan's brother-in-law Adrien Rivollier, 5IBA cofounder with Hassan, co-author, and director of the documentary IRONMINDS. "He was part of the journey from day one, when our dad shared the vision with us," Hassan says. The quartet is completed by Dr Lavinia Alberi, neuroscientist and 5IBA head of strategy, who leads the scientific direction of the project.

"There have been lots of powerful documentaries about how dementia affects everyone," Thomas says. "But we wanted to have a message of hope. You can make changes in your lifestyle that will make you gain five to ten years of cognitive reserve."

46 https://pmc.ncbi.nlm.nih.gov/articles/PMC9651925/
47 https://www.sciencedirect.com/science/article/pii/S2274580724001055
48 https://med.stanford.edu/news/insights/2025/03/gut-brain-connection-long-covid-anxiety-parkinsons.html

Hassan Fadli (left) and Thomas Roos use endurance sport to raise awareness, mobilise support, and explore how lifestyle, resilience, and community can advance brain-health research. (Photo by Luca Zanetti)

Following the release, the pair plan to launch an educational roadshow, visiting 100 to 200 schools across France and Switzerland. The goal is to reach young people early, before risk factors accumulate. "Hassan will tell his story," Thomas says, "and I'll talk about preventative health and the science behind it."

Toward a larger study

The current project is limited to two participants, but it is designed as a proof-of-concept for a larger, more rigorous study that the pair hopes their work will evolve into. The proposed next phase would involve a cohort of around 10 participants, tracked over a longer period with more advanced testing, provided they secure the required financial support: the pair estimates they will need about $5 million for a five-year study.

The current project is limited to two participants, but it is designed as a proof-of-concept for a larger, more rigorous study that the pair hopes their work will evolve into.

They are also exploring collaboration with larger research initiatives, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the first trial in the world to demonstrate that multidomain lifestyle interventions – combining diet, exercise, cognitive training, social activity, and vascular risk monitoring – can improve our brain health and prevent cognitive decline.[49] "We're not officially part of that study," Thomas clarifies, "but we're effectively implementing the preventative measures ourselves."

One of the key challenges is access to advanced blood biomarker testing and PET scan brain imaging that can help in detecting early stages of disease progression. "The current scientific consensus is that these diagnostics should only be done in a clinical setting with symptomatic individuals, not population-based screening," he explains. "However, as the research and technologies advance, we hope to be able to accurately capture the fundamental biological and molecular level changes earlier."

Such data would provide valuable insights into preclinical stages of Alzheimer's disease, long before cognitive symptoms appear. Beyond prevention, Hassan is passionate about improving care systems. He advocates for a shift away from institutional models toward community-based solutions.

49 https://fbhi.se/the-finger-study/

The 5IBA team uses a variety of monitoring tools to track the impact of exercise on changes in their biology over time. (Photo by Luca Zanetti)

"Let's put money where families benefit most," he says. "Day care centres, home visits, dementia-friendly cities – these are the solutions we need. There is also the important cultural context in all this. Care is very much linked to traditions. In some countries, families take care of their parents. In others, that's less the case. Understanding these differences is essential for designing effective policies."

For both men, success is not measured solely in scientific outcomes or athletic achievements, but in changing perceptions and a better understanding of dementia among the general public. For Thomas, it is about creating a foundation for future research. "If scientists can get a few insights from our data, then we can conduct better trials, and that's a success," he says.

For both men, success is not measured solely in scientific outcomes or athletic achievements, but in changing perceptions and a better understanding of dementia among the general public.

Together, they are working toward a future in which dementia is not only better understood but also more effectively prevented and managed. "It's about the lifestyle," Hassan says. "It's about creating the conditions where your health – including your brain health – can get better."

Chapter 3:

Clinical trials in dementia: complexity and opportunities

A doctor inspects a patient in October 2016 on the Abaré, a Brazilian hospital ship that operates on the Amazon and tributaries to service remote communities. (Photo by Luca Zanetti)

Summary

Clinical trials are transforming the outlook for dementia research. After decades of disappointment, advances in biomarkers, genetics, and trial design have led to the first disease-modifying treatments for Alzheimer's disease and renewed optimism across the wider dementia field. Researchers are increasingly able to identify the condition earlier, recruit more appropriate participants, and test interventions with greater precision than ever before.

Yet dementia remains one of the most challenging areas of medicine in which to develop new therapies. The biological complexity of different dementia types, difficulties in diagnosis, lengthy trial timelines, high costs, and the need to recruit diverse populations mean that progress is often slow. Many studies do not achieve their primary endpoints, but each contributes valuable knowledge that informs future research, helping to refine biomarkers, improve trial design, and deepen understanding of disease mechanisms.

This chapter explores how clinical trials are evolving across both pharmacological and non-pharmacological interventions, from disease-modifying drugs and precision medicine to lifestyle programmes aimed at delaying cognitive decline. It also examines growing efforts to expand research beyond traditional centres in North America and Europe, recognising that globally representative clinical trials will be essential if future treatments are to benefit all populations (see Chapter 6 for more on this topic).

Finally, the chapter considers a question that has become increasingly important as new therapies emerge: what constitutes meaningful success? For researchers, regulators, and industry, trial outcomes are measured in biomarkers and statistical significance. For people living with dementia and their loved ones, success is measured differently – by preserving independence, maintaining quality of life, and extending the time people can continue doing the things that matter most.

Beyond Alzheimer's: expanding the clinical trial landscape

Dementia research is entering what many scientists describe as a paradoxical age: one of extraordinary promise, yet extraordinary difficulty. After decades of frustration, the field has finally begun to produce drugs capable of modestly slowing the progression of Alzheimer's disease. But each scientific advance has also highlighted an uncomfortable truth: dementia clinical trials are among the most complex, expensive, and ethically demanding in modern medicine.

The challenge begins with a deceptively simple fact: dementia is not one disease. It is an umbrella term covering a range of neurodegenerative conditions, including Alzheimer's disease, vascular dementia, frontotemporal dementia (FTD – itself an umbrella term) and Lewy body dementia (LBD), among more than 100 in all,[1] each with distinct biological mechanisms and clinical patterns. As Selina Wray, professor of molecular neuroscience at University College London, noted in a public discussion to coincide with last year's World Alzheimer's Day: "Dementia is a collection of different diseases rather than a single condition, which makes finding 'the' cure especially complex."[2]

Each of these diseases has its own biology, and even within Alzheimer's disease alone, there are different subtypes: early-onset genetic vs late-onset sporadic, atypical presentations, mixed Alzheimer's-vascular cases. That complexity runs through every stage of clinical trial design. By the time symptoms become visible, irreversible damage has often already occurred in the brain. This means researchers are increasingly trying to intervene earlier – sometimes years before symptoms emerge – when participants appear outwardly healthy but may already harbour amyloid or tau pathology. Identifying these individuals requires costly PET scans, lumbar punctures, or increasingly sophisticated blood biomarkers, all of which add logistical and financial burdens to recruitment. As Alzheimer's Research UK has noted, blood tests may transform diagnosis, but the field remains in transition between old and new methods.[3]

1 https://www.nhs.uk/conditions/dementia/about-dementia/what-is-dementia/
2 https://www.reddit.com/r/IAmA/comments/1nk4x34/hello_were_a_dementia_researcher_and_clinician/
3 https://www.alzheimersresearchuk.org/news/global-snapshot-of-alzheimers-research-offers-new-hope/

As we outline in this report, recruitment itself is another formidable obstacle. Dementia trials often demand strict eligibility criteria, repeated cognitive assessments, regular hospital visits, and the involvement of a study partner – usually a spouse or family carer.

These demands drastically narrow the pool of eligible participants. Then there is the problem of time. Dementia progresses slowly, often over years rather than months. Clinical trials must therefore run for long periods to detect meaningful changes in cognition or function. This creates high dropout rates and raises difficult ethical questions, particularly when participants in placebo arms may now have access to approved therapies. As Alifiya Tahir, who has managed a global Phase 2 trial in Alzheimer's with Bristol Myers Squibb, recently said, Alzheimer's studies are "among the most demanding in clinical research."[4]

This biological and clinical heterogeneity drives a need for far greater precision in trial design. A generic "dementia" drug trial is unlikely to succeed because different dementias – and even different forms of Alzheimer's disease – are driven by distinct biological processes. Increasingly, researchers enrol participants in narrowly defined groups based on the biology of their disease rather than on clinical symptoms alone. For example, many trials targeting amyloid now require participants to have confirmed amyloid pathology via PET imaging, cerebrospinal fluid analysis, or, increasingly, blood-based biomarkers before they are eligible to participate. Precision medicine is therefore reshaping dementia research from the point of recruitment onwards.

The growing emphasis on precision medicine reflects a broader shift in how researchers understand Alzheimer's disease itself. Rather than viewing it as a condition driven by a single biological pathway, scientists increasingly recognise that it involves multiple interacting processes, including amyloid accumulation, tau pathology, neuroinflammation, vascular dysfunction, and the loss of neurons and synapses. Geoff Kerchner, vice president and global head of neurodegeneration at Roche, argues that this biological complexity needs to be taken into account. "Like virtually every other age-related chronic illness," he says, "Alzheimer's disease will almost certainly require tailored and/or multiple treatment approaches."

That growing biological precision has been matched by increasing complexity in trial design. As Lynne Hughes of the Global Alzheimer's Platform Foundation – herself a veteran of central nervous system clinical trials at IQVIA – observed at a recent industry panel, trial protocols have become far more sophisticated over the past decade. "We've gone from quite simple scales, like ADAS-Cog, to more complex composite scales, CDR-SB," she says, referring to clinical rating batteries[5] – standardised tests used to measure the severity of cognitive symptoms, track disease progression, and evaluate treatment effectiveness in conditions like Alzheimer's disease. Researchers are also combining cognitive assessments with biomarkers, functional measures, and digital tools in an effort to build a more complete picture of whether a treatment is having a meaningful effect.

These composite cognitive/functional scales are needed to detect tiny changes in early disease, but they demand extensive training on sites and patients. Hughes notes that the workload for trial sites (and participants) has surged by 64 percent over the last 10 years; and in fact her group finds roughly a 25 percent share of all procedures in a typical Alzheimer's trial are now "non-core endpoints" – extras tacked on for exploratory or regulatory reasons. In other words, a quarter of what patients must do in these studies is not directly measuring cognition or daily function, but collecting ancillary data.

The result is that Alzheimer's clinical trials – and by extension many dementia trials – are slower, more expensive and carry a higher risk of not meeting their primary endpoints than trials in many other disease areas.[6] One widely cited analysis estimated that more than 98 percent of Alzheimer's drug development programmes have historically failed to reach regulatory approval, leading some companies to scale back or abandon dementia research.[7] However, many scientists caution against describing individual studies as "failures." They argue that the term implies the research produced no value, when in reality, well-conducted trials frequently generate important insights that improve future study design, refine biomarkers, and deepen understanding of disease biology. They also warn that describing trials as "failures" may discourage people from volunteering to take part in future research.

Researchers increasingly argue that the value of a clinical trial should not be judged solely by whether it meets its primary endpoint. Well-designed studies frequently refine future trial design, improve biomarkers, identify more appropriate participant groups and deepen understanding of disease biology. It is this cumulative process of learning, many scientists say, that has driven the recent acceleration in dementia research.

"We learn something from every study that we run, whether it's at the laboratory bench or whether it's a clinical trial," Dr Rebecca Edelmayer, Alzheimer's Association vice president of scientific engagement, tells ADI.

4 https://acrpnet.org/2025/09/02/alzheimers-trials-challenges-determination-and-the-people-behind-progress
5 https://videos.cdn.spotlightr.com/watch/gallery/NjYwMQ==
6 https://www.forbes.com/sites/greglicholai/2025/11/25/two-alzheimers-trial-failures-reveal-clinical-challenges/
7 https://pmc.ncbi.nlm.nih.gov/articles/PMC9198803/

"The successes that we are seeing today, in some of our more recent treatment studies and clinical trials, are often built on studies that did not meet their original endpoints, because they taught us how to design better studies, recruit the right participants, and improve adherence to clinical trial protocols. That's why I think one of our biggest missed opportunities is describing studies as 'failures' or 'negative.' That language can discourage people from participating in research. To a scientist, the question isn't whether a study failed. It's whether it answered the question it set out to ask. If it did, then we've learned something important, even if the answer wasn't the one we hoped for."

Dr Edelmayer believes a different emotional attachment applies to clinical trials involving people than to laboratory studies.

"Most laboratory experiments don't produce the result you're expecting – that's simply how science works," she says. "Clinical trials feel different because they involve people who have generously volunteered their time and placed their hopes in the research. That makes the language we use even more important. If a study is well designed, well conducted, and produces clear results, then it has been scientifically successful, regardless of whether the treatment met its endpoint. Those findings help shape the next generation of research. Framing studies in that way also sends a more positive message to people considering taking part in future clinical trials."

Finding the right participants

The USC Schaeffer Center reports that mild-Alzheimer's trials typically fail 44 percent of screened volunteers, while "preclinical" trials (before symptoms) see an 88 percent screen-failure rate.[8] Much of this is by design: trials often demand an amyloid PET scan or a strict cognitive score to qualify. As Dr Serge Gauthier, former director of the Alzheimer's Disease and Related Disorders Research Unit of the McGill Center for Studies in Aging, points out, such filters meant that "five years ago, finding patients took a long time in getting trials up and running" – you might screen thousands to find a few eligible people. By contrast, the new biomarker blood tests that have emerged allow pre-screening; "instead of screening 3,000 people to find the 150 you need…now you can do the blood work," dramatically raising efficiency, Dr Gauthier explains.

High screen-failure rates translate into delays. For one thing, imaging slots and specialist assessments add months to the recruitment process. More fundamentally, demonstrating a disease-modifying effect may require years, not months: researchers say slowing Alzheimer's progression by even a small amount necessitates long follow-up to accumulate enough difference. As a result, trials grind on, investigators scramble for funding, and patients often decline before a drug can show benefit.

> **'To a scientist, the question isn't whether a study failed. It's whether it answered the question it set out to ask. If it did, then we've learned something important, even if the answer wasn't the one we hoped for.'**
>
> *Dr Rebecca Edelmayer*

Another major barrier is simply finding patients in the first place. A Schaeffer report found that "approximately 99 percent of eligible patients are never referred to or consider participating in an Alzheimer's Disease clinical trial."[9] Across countries, lack of awareness, stigma, and shortages of diagnostic care mean that most people with memory loss are never connected to a research study. This referral gap is a critical bottleneck: it shrinks the pool of potential participants and biases samples toward more educated, urban populations. Advocates now urge broad public outreach and local clinic "dementia champions" to reverse the trend.

Researchers increasingly argue that improving diversity in dementia clinical trials is not simply a question of equity, but of scientific validity. Genetic ancestry, vascular health, educational attainment, language, socioeconomic circumstances, and access to healthcare can all influence dementia risk, diagnosis, and treatment response. Yet, historically, many Alzheimer's disease trials have enrolled predominantly white participants from high-income countries. Expanding recruitment across more diverse populations, researchers say, will strengthen confidence that new diagnostics, biomarkers, and therapies are effective across the broad range of communities expected to use them in routine clinical practice.

These obstacles – enormous heterogeneity of patients, impenetrable referral networks, and intricate protocols – help explain why Alzheimer's trials are so challenging. The USC Schaeffer Center report summarised the situation bluntly: "Alzheimer's disease trials tend to be slower to enrol, take longer to complete, and are more expensive than trials in most other therapeutic categories." That glum reality underlies the urgency for new approaches.

8 https://schaeffer.usc.edu/research/key-barriers-for-clinical-trials-for-alzheimers-disease/; https://schaeffer.usc.edu/wp-content/uploads/2024/10/Key-Barriers-to-Clinical-Trials-for-Alzheimers-Disease.pdf

9 https://schaeffer.usc.edu/research/key-barriers-for-clinical-trials-for-alzheimers-disease/

Taking clinical trials global

The challenges are not experienced equally around the world.[10] In many low- and middle-income countries (LMICs), the obstacles begin long before recruitment into a clinical trial. Limited access to specialist memory clinics, biomarker testing, and research infrastructure means many people are never diagnosed early enough to be eligible for studies. At the same time, researchers argue that these regions represent some of the greatest opportunities for future dementia research, both because the global burden of disease is rising fastest there and because more diverse participant populations are essential if new therapies are to benefit people worldwide. Increasingly, international trial networks are therefore exploring ways to expand research capacity beyond the traditional centres of North America and Europe through partnerships, training programmes and the wider use of blood-based biomarkers.

Yet despite these challenges, optimism in the field has shifted. The science is improving, biomarkers are becoming more accessible, and trial design is evolving. But dementia research remains defined by a hard reality: success depends not just on scientific discovery, but on navigating a disease that is biologically complex, clinically slow-moving, and profoundly human.

If these challenges define why dementia trials are complex, the science tells us what we're trying to do in them. Drug development in dementia involves multiple biological processes. Alzheimer's disease itself is now largely understood as a proteinopathy: a class of diseases where specific proteins, in this case amyloid and tau, fail to fold into their correct 3D shapes and drive neurodegeneration. Hence, most leading drug programs target those proteins: monoclonal antibodies like lecanemab, donanemab, or small molecules against tau, for example.

Indeed, the recent FDA approvals of aducanumab, lecanemab, and donanemab heralded the first disease-modifying therapies for Alzheimer's – but they come with caveats. In each case, these new drugs slow the progressive decline but do not cure it. As Dr Suzanne Schindler of Washington University points out, the key question for patients is not "how many percent did the rate of decline drop?" but "how long can I still drive? How long will I be able to take care of my own personal hygiene? How much time will this treatment give me?"[11]

Using that perspective, Prof Schindler's recent analysis translated the average benefit of these drugs into extra months of independent living: the typical very-mild Alzheimer's patient might gain 8–10 more months before losing independence, compared to no treatment.[12] Whether that degree of slowdown justifies expensive infusions is a personal decision for each patient – but from a research standpoint, it shows that disease-modifying agents are a very different prize than a cure.

Beyond Alzheimer's, other dementia types follow distinct pathways. Vascular dementia – the second most common form – is essentially brain injury from strokes or small-vessel disease. Trials here focus on managing blood pressure, cholesterol, and diabetes to slow progression. Dementia with Lewy bodies and Parkinson's dementia involve aggregates of alpha-synuclein protein; its trials may test drugs targeting that protein or symptomatic treatments for hallucinations and Parkinsonism. Frontotemporal dementias (FTDs) are linked to tau or TDP-43 protein and often occur in younger people. Unlike Alzheimer's, which mostly affects people aged 65 and over, FTD symptoms typically start between the ages of 45 and 65. Once they begin, life expectancy is seven to 13 years.

Consequently, although Alzheimer's disease dominates the current dementia drug pipeline, there is growing scientific interest in developing disease-modifying therapies for these other neurodegenerative dementias. Researchers emphasise that these conditions have distinct underlying biology and are likely to require different therapeutic approaches. Progress has been slower than in Alzheimer's disease, partly because diagnostic tools, biomarkers and trial infrastructure have developed more recently, but advances in each of these areas are beginning to accelerate research.

For people living with LBD, however, the scientific challenges are matched by practical ones. Jacqui Cannon, chief executive of The Lewy Body Society in the UK, says misdiagnosis and delayed diagnosis continue to limit both research and access to clinical trials. Many people are initially diagnosed with Alzheimer's disease, Parkinson's disease, or other neurological conditions, while others are recorded as having mixed or unspecified dementia. "The importance of a quality diagnosis cannot be overstated," she tells ADI. "Without it, people cannot be identified for research, and the data needed to build future clinical trials simply isn't there." She believes the true prevalence of Lewy body dementia may also be significantly underestimated, further reducing opportunities for people to participate in research.

Despite those challenges, Cannon says there is growing momentum within the field. She points to strong demand from people living with LBD and their families to participate in research, increasing engagement between UK charities and international pharmaceutical companies, and encouraging progress in early-stage clinical trials. She is also optimistic that advances in blood-based biomarkers and lessons from Alzheimer's disease

10 https://www.nature.com/articles/s41582-025-01125-3
11 https://medicine.washu.edu/news/next-gen-alzheimers-drugs-extend-independent-living-by-months/
12 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70033

research could help accelerate drug development for LBD. Looking ahead, she argues that people living with the condition should be involved from the earliest stages of trial design to ensure studies are practical and accessible, particularly for those living outside major research centres.

Several biotechnology companies and academic groups are now pursuing therapies aimed at these conditions. One example is US biotechnology company CervoMed, whose lead investigational therapy, neflamapimod, is being studied in dementia with Lewy bodies. The company's programme illustrates both the opportunities and the challenges facing clinical research outside Alzheimer's disease.

Speaking to ADI, CervoMed's chief commercial and business officer, Dr Matt Winton, says the firm chose to focus on LBD because of the substantial unmet clinical need and the limited number of therapies currently in development.

While Alzheimer's is primarily associated with memory loss, LBD presents a bewildering range of symptoms. Patients can experience cognitive decline, Parkinson's-like movement difficulties, visual hallucinations, sleep disturbances, and dramatic fluctuations in attention and awareness. Despite being the second most common progressive dementia after Alzheimer's, LBD receives far less research attention. For Dr Winton, that imbalance is one of the key reasons CervoMed has focused on the condition. "There's very little drug development compared to Alzheimer's disease."

Dr Winton argues that neflamapimod, which targets the p38 alpha kinase pathway, may help restore neuronal function by reducing neuroinflammation and α-synuclein-mediated neurotoxicity associated with disease progression. The approach is currently being evaluated in clinical trials and remains investigational.

The company's Phase 2 RewinD study enrolled 159 participants across 43 sites in three countries. Unlike many Alzheimer's disease trials, which often require well over 1,000 participants and lengthy follow-up, the more rapid progression of LBD may allow treatment effects to become apparent over a shorter period. CervoMed also used blood biomarkers to identify participants with what the company describes as relatively "pure" LBD, without significant coexisting Alzheimer's pathology, reflecting the wider trend towards increasingly precise, biomarker-guided recruitment across dementia trials.

Dr Winton believes that progress in Alzheimer's disease research is increasingly benefiting the wider dementia field by improving understanding of disease mechanisms, biomarkers, and trial methodology. He also highlighted the importance of collaboration between industry, academic researchers, and public funders. "Those partnerships, for small companies, really allow us to move faster," Dr Winton says. "I think they're great for advancing science. Hopefully, in the next few years, we will see more targeted drug development and a greater understanding and awareness, not only of LBD, but of other dementias."

While programmes such as CervoMed's illustrate growing momentum in non-Alzheimer dementia research, experts caution that the field remains at an earlier stage than Alzheimer's disease. Much remains to be learned about disease biology, optimal biomarkers, and clinically meaningful trial outcomes, and multiple therapeutic approaches are likely to be needed before effective treatments become widely available.

Interest in these less common dementias is also becoming increasingly international. Alongside programmes in North America, research groups across Europe, Japan, and Australia are expanding collaborative studies of LBD and frontotemporal dementia, while international consortia are working to harmonise biomarkers and outcome measures so that future clinical trials can recruit participants more efficiently across countries. Researchers say this growing collaboration will be essential if sufficiently large studies are to be completed in diseases that are individually much less common than Alzheimer's disease.

For patients and families facing diseases that currently offer few effective treatment options, the hope is that such collaborations will eventually deliver something that has long been missing: medicines capable of slowing, or even altering, the course of these conditions. Even within Alzheimer's itself, one size does not fit all. The experience of familial vs late-onset cases, or mild cognitive impairment vs overt dementia, demands different trial populations. Many of the new trials – such as the Alzheimer's Prevention Initiative or API trials – have stratified participants by age, genetics, or biomarker status. The fundamentals of the DIAN Obs (Dominantly Inherited Alzheimer Network Observational) Study underscores this: clinical trials are now enrolling young adults who carry early-onset Alzheimer's mutations alongside older adults with prodromal disease – an early sign or symptom that often indicates the onset of a disease before specific symptoms. Such precision medicine demands minute target selection, which slows down trial entry (many people are screened out) but, ideally, yields clearer results.

For patients and families facing diseases that currently offer few effective treatment options, the hope is that such collaborations will eventually deliver something that has long been missing: medicines capable of slowing, or even altering, the course of these conditions.

Another layer is the difference between disease-modifying drugs and symptomatic treatments. For years, most approved therapies for Alzheimer's and other dementias were symptomatic: cholinesterase inhibitors (for memory/cognitive symptoms in Alzheimer's or Lewy bodies), memantine, or dopaminergic drugs for Lewy body movement problems. These drugs ease symptoms but do not change the underlying disease course.

Today, the pharmaceutical quest is overwhelmingly for disease-modifying therapies (DMTs) – drugs that slow neuron loss. That goal raises the bar: a trial must measure not just short-term benefit on memory tests, but a durable change in decline trajectory. The downside is clear: DMT trials require longer timelines and larger sample sizes to demonstrate even a modest effect, compared to symptomatic drug trials, where improvement on a cognitive scale over six months might suffice. One estimate put the total development cost of a new Alzheimer's drug at over US$5–7 billion, though that number comes with wide uncertainty.[13] In any case, the result is that industry faces a choice: invest heavily in expensive DMT trials with low success odds, or pursue smaller ventures on symptom relief. Some are hedging: for example, trials of repurposed drugs (anti-diabetics, anti-inflammatories, even anti-amyloid vaccines) try to split the difference.

Beyond the pill: how lifestyle trials are reshaping the fight against Alzheimer's

In the long, faltering search for a cure to Alzheimer's disease, the spotlight has often fallen on drugs – on antibodies, plaques, and the promise of a pharmaceutical breakthrough. Yet, quietly and with growing conviction, another front has been advancing: the science of prevention without pills. Across Europe and the United States, a series of non-pharmacological clinical trials is challenging long-held assumptions about dementia. Their premise is disarmingly simple: that the trajectory of cognitive decline may be altered not only in laboratories, but in kitchens, gyms, and community centres. Their findings, increasingly difficult to ignore, are reshaping how researchers – and policymakers – think about Alzheimer's disease.

Originating in Finland in 2009 – and still going strong – is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability: better known as the FINGER trial, and arguably the most influential of these studies. Led by Dr Miia Kivipelto, it set out to test whether a combination of lifestyle interventions could protect the ageing brain. Its design was ambitious: participants aged 60 to 77, all at elevated risk of dementia, were enrolled in a two-year programme combining diet, exercise, cognitive training, social engagement, and vascular risk monitoring.

The results, first reported in *The Lancet*,[14] marked a turning point. For the first time, a large randomised controlled trial demonstrated that such a multidomain intervention could maintain or improve cognitive performance in at-risk older adults. The intervention group gained roughly 25 percent more global cognitive improvement than controls, with especially large gains in executive function and processing speed. Even more relevant, the risk of developing measurable cognitive impairment was 30 percent lower in the lifestyle arm, suggesting some true prevention of decline. Subsequent analyses have reinforced these findings. Participants in the intervention arm showed measurable gains in executive function, processing speed, and planning ability – core domains that often deteriorate early in dementia.

More striking still is the durability of the effect. The study reached an important milestone at the Alzheimer's Association International Conference (AAIC) in Toronto last year when Prof Kivipelto presented the long-term effects of the two-year FINGER intervention on lifestyle and cognitive change over 11 years.[15] The long-term follow-up suggested that the benefits of adhering to the programme extend beyond cognition, with reduced use of hospital services and emergency care observed years later.[16] Researchers believe this is not a marginal effect, suggesting that prevention is not only possible but scalable.

The model has been so successful that it has been exported globally as more countries adopt the trial. The worldwide FINGERS initiative spans more than 25 countries, adapting the Finnish approach to diverse populations. "We now have 95 teams working in 73 countries and we are improving the model all the time, so it has been an exciting journey," Prof Kivipelto tells ADI. "And we have spread to low- and middle-income countries that have not usually been as much a part of these types of trials, where the need is even higher given how the numbers are increasing and the prevalence of risk factors… I

13 https://pmc.ncbi.nlm.nih.gov/articles/PMC8940715/
14 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60461-5/abstract
15 https://fbhi.se/first-presentation-of-11-year-follow-up/
16 https://pmc.ncbi.nlm.nih.gov/articles/PMC12726459/

hope we are starting to see greater global collaboration. The work around FINGERS shows that. We share knowledge and results, and we want each country to be a part of that."

> **Non-pharmacological trials' premise is disarmingly simple: that the trajectory of cognitive decline may be altered not only in laboratories, but in kitchens, gyms, and community centres. Their findings, increasingly difficult to ignore, are reshaping how researchers – and policymakers – think about Alzheimer's disease.**

Naturally, getting multi-country clinical trials up and running can take longer than in a single setting. And even within one country or institute, processes vary depending on who you talk to, researchers told ADI. Prof Kivipelto adds: "Whether it's the ethics of the trial, or getting an agreement signed, and especially in multinational studies like ours, it took quite a long time to get all the institutes to agree. That's something we sometimes don't realise at the outset, so we need to work on that and be aware of it, prepare for it, so researchers don't get frustrated."

From observation to intervention

Not all prevention research, however, focuses on lifestyle. Some studies seek to prevent dementia by intervening in the biological processes that drive the disease years before symptoms develop. While the FINGER studies demonstrate the potential of multidomain lifestyle interventions to reduce dementia risk in the general population, the Dominantly Inherited Alzheimer's Network (DIAN) Observational Study addresses a very different question.

Rather than testing an intervention, it follows people who are genetically destined to develop Alzheimer's disease, providing researchers with an unparalleled window into the earliest biological changes that occur long before symptoms appear. The study enables researchers around the world to monitor individuals carrying one of the gene mutations (Presenilin 1, Presenilin 2, or APP) known to cause dominantly inherited Alzheimer's disease (DIAD). Its greatest value lies in revealing how the disease unfolds over time and informing the design of prevention trials that intervene before irreversible brain damage has occurred.

By following participants – often decades before symptoms appear – researchers have been able to map the sequence of biological changes that precede cognitive decline. Brain imaging, fluid biomarkers, and cognitive testing reveal that pathological changes begin many years before diagnosis, unfolding silently long before memory falters. This insight has profound implications. If Alzheimer's begins decades earlier than once thought, then interventions – pharmacological or otherwise – must also begin earlier. Prevention, rather than late-stage treatment, becomes the central challenge. The DIAN data has also helped validate biomarkers and clarify disease progression, providing a framework within which lifestyle trials can operate. In effect, the DIAN Observational study tells researchers when to intervene; trials like FINGER begin to show how.

Despite coming up to its 20th anniversary, the DIAN study remains "quite unique," its director, Eric McDade, professor of neurology at Washington University School of Medicine, tells ADI. Starting out in 2008 at a limited number of centres in the United States, UK and Australia, the study has more than 700 participants taking part today – some of whom have made up to 10 different visits to trial site centres over the years. "So we've used that study to really understand, in particular, the development of the disease, how it begins to unfold, up to 20 years before symptoms develop," Prof McDade says.

"We have been able to identify, really quite accurately, we think, when the disease begins to unfold. The first traces of amyloid pathology, these plaques, you can really start to identify these up to two decades before symptoms develop – almost every one of these mutations will lead to the development of plaques. From that, too, we continue to add on as technology develops, the ability to look at the different pathologies associated with Alzheimer's disease."

As Prof McDade says, many of these families have been excluded from participating in clinical trials for years, either because Dominantly Inherited Alzheimer's Dementia (DIAD) is an early-onset form of the condition, so they wouldn't qualify by age, even though they are already symptomatic, or because it was long thought that this was a unique form of Alzheimer's disease that would impact the potential success of a therapy, leading clinical trial leaders and companies sometimes to not want to involve people affected by the condition in trials.

"These trials have offered families an opportunity that simply did not exist before," Prof McDade says. "When we speak to participants, there is a genuine sense of hope. That is a remarkable change. At our first family meeting, people told the researchers, regulators, and pharmaceutical companies that they were willing to take part even though they did not expect the research to help them personally. They believed it might help future generations of their families. A decade later, at our family meeting in Toronto, the mood was very different. This younger generation is genuinely optimistic about the progress being made. They can see that we are beginning to understand the disease much better, and that creates hope that clinical trials may ultimately change its course."

Prof McDade believes one of the DIAN Observational study programme's greatest contributions has been advancing prevention research: "The DIAN Trials Unit launched its first prevention study in 2012, and the observational study has helped us design prevention trials that are far more precise. One of the key findings is that the way Alzheimer's disease develops in families with these inherited mutations closely mirrors what happens in people without the mutations. The difference is that, in the wider population, you have to screen thousands of people to identify those at exactly the right stage of disease for a prevention trial."

Last year, the DIAN research team published long-term results from its gantenerumab trial in *The Lancet Neurology*.[17] The findings suggested that people with inherited Alzheimer's disease mutations who began treatment before developing symptoms and received gantenerumab over an extended period may have reduced their likelihood of developing symptomatic disease by around 50 percent. Prof McDade is careful to emphasise that the findings remain preliminary. "There are plenty of caveats with the data," he says, "but we are beginning to see evidence that prolonged treatment before symptoms appear could reduce the likelihood of developing the disease in this population."

The past five years have seen an acceleration of similar studies, many inspired by the Finnish model. In the United States, the US POINTER trial – one of the largest lifestyle studies to date – reported in 2025 that structured multidomain interventions improved cognition in older adults at risk of decline, with more intensive programmes yielding greater benefits.[18] Elsewhere, smaller but rigorous trials have explored intensive lifestyle changes. A 2024 study found that participants undergoing a comprehensive intervention showed significant improvements in cognitive and functional measures, while control groups deteriorated.[19]

Taken together, these findings point to a consistent conclusion: targeting multiple risk factors simultaneously – diet, exercise, cardiovascular health, cognitive engagement – produces measurable cognitive benefits. This reflects a growing consensus about the nature of Alzheimer's itself. Far from being driven by a single pathological process, it is increasingly understood as a multifactorial disease, influenced by vascular, metabolic and lifestyle factors as much as by amyloid and tau. An earlier review led by Prof Kivipelto therefore concluded that "multidomain interventions… might be necessary for an optimal preventive effect."[20]

For all their promise, non-pharmacological trials are not without limitations and require trade-offs. Effects, while statistically significant, are often modest at the individual level. Adherence to lifestyle programmes can be variable and, unlike a pill, such interventions demand sustained behavioural change. Moreover, they are preventive rather than curative. They appear most effective in those at risk or in the earliest stages of decline, rather than in advanced disease. These trials also require careful design: often a placebo or "usual care" group, and validated outcome measures. Like drug studies, they need blinding (sometimes achieved via attention-matched activities) and long follow-up to show an effect. Recruitment can be challenging – it takes motivated volunteers to join a years-long exercise and diet programme. And while costs per patient are lower (no IV drugs or imaging needed), the sample sizes can still be large, since individual lifestyle factors have only modest effects on cognition.

Yet it is precisely this preventive focus that many researchers now see as essential. Drug trials targeting amyloid have produced mixed and often controversial results, while the global burden of dementia continues to rise. In this context, lifestyle interventions offer something different: a low-risk, scalable strategy that can be implemented at a population level. They also align with broader public health goals, such as addressing cardiovascular disease, diabetes, and social isolation alongside dementia risk.

In a similar vein, trials of purely exercise interventions – aerobic or strength training – have often reported modest but significant benefits in cognition and brain volume. A meta-review noted that patients in active exercise programmes "showed a significant improvement in memory, attention, executive function, and language skills" compared to sedentary controls.[21] Cognitive training programmes (computerised memory and thinking exercises) also yield small gains in test scores, though whether they translate into daily-life gains is debated.[22] Meanwhile, trials of nutritional supplements, such as omega-3

17 https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(25)00239-X/fulltext
18 https://jamanetwork.com/journals/jama/fullarticle/2837046
19 https://pmc.ncbi.nlm.nih.gov/articles/PMC11157928/
20 https://pubmed.ncbi.nlm.nih.gov/30291317/
21 https://pmc.ncbi.nlm.nih.gov/articles/PMC12229068/
22 https://pmc.ncbi.nlm.nih.gov/articles/PMC7045394/

fatty acids and vitamin E, have mostly been disappointing, apart from the Mediterranean/DASH diet results, which suggest some protective effect on cognitive ageing.[23]

Another big challenge for the research community concerns data sharing. Put several worldwide studies together, and you can start seeing patterns. Getting to that stage can be tricky, but it is the direction a lot of scientists want to travel in. "In an ideal world, there would be a centralised network of data that researchers can delve into. There are now luckily some countries that have started doing this, but it has taken quite some time to get there," Prof Kivipelto says.

Comparing non-drug vs drug trials highlights differences in practicality. A new drug like an antibody can cost tens of thousands per patient and requires regular doctor visits; a lifestyle intervention costs much less and has general health upsides, such as a healthier heart, along with improved mood and fitness levels. Drug trials, however, provide clearer evidence because they rely on measurable biological markers and follow tightly regulated testing processes. Non-pharmacological trials often end up in academic journals rather than FDA filings, and their success is judged primarily by public health impact rather than drug approval. Nonetheless, both approaches emphasise early intervention: delaying cognitive decline even by a few years can hugely reduce the number of people who progress to full dementia, and thus represents a meaningful success.

Perhaps the most significant impact of non-pharmacological trials is conceptual. For decades, Alzheimer's has been framed as an inexorable neurodegenerative process, largely beyond the reach of prevention. The emerging evidence challenges that fatalism. The FINGER trial demonstrated that cognitive decline is not inevitable. DIAN showed that the disease begins earlier – and is therefore potentially modifiable earlier – than previously believed. Together, they suggest a new paradigm: that Alzheimer's may be delayed, mitigated, or even partially prevented through sustained lifestyle change. The implications extend beyond the clinic. As populations age, even modest delays in the onset of dementia could translate into millions fewer cases worldwide.[24]

For now, there is no single breakthrough to rival the discovery of penicillin or the advent of statins. Instead, there is something quieter: a body of evidence accumulating across continents, pointing in the same direction. It is a shift from cure to prevention, from molecule to lifestyle, from inevitability to possibility. And in the slow, uncertain battle against Alzheimer's, that may prove to be the most important development of all.

It is a shift from cure to prevention, from molecule to lifestyle, from inevitability to possibility.

Clinical meaningfulness: redefining success in dementia trials

In the race to treat Alzheimer's disease, modern medicine has become extraordinarily good at measuring small changes in the brain. Researchers can now track amyloid plaques accumulating years before symptoms begin, chart the spread of tau proteins through neural pathways, and monitor subtle shifts in cognition through increasingly sophisticated digital assessments. Yet one deceptively simple question continues to haunt the field: what actually counts as meaningful?

It is a question that has become more urgent since the arrival of the first disease-modifying Alzheimer's drugs. Treatments such as lecanemab and donanemab have shown they can slow cognitive decline in carefully selected patients with early-stage disease. Regulators in several countries have approved them. Clinicians argue they represent the beginning of a new era. But the public response has often been more hesitant. Families confronted with percentages, biomarker curves, and abstract cognitive scales frequently ask the same thing: will this help my husband remember our grandchildren? Will my mother remain independent for longer? Will it delay the day she can no longer recognise home?

Behind those questions lies one of the deepest tensions in dementia research. Statistical significance and clinical meaningfulness are not necessarily the same thing, experts say. "From a patient perspective, what matters is, do you feel better?" Jeff Pohlig, co-owner and CEO of US-based Charter Research, tells ADI. "Has the disease gone away or has it slowed down or lessened in a way that makes your life appreciably better?"

For decades, Alzheimer's trials have relied on a constellation of measurements designed to quantify decline. Researchers use cognitive tests, biomarkers, and functional assessments to determine whether a therapy works. Regulators scrutinise changes on scales such as the Clinical Dementia Rating-Sum of Boxes (CDR-SB), the ADAS-Cog, and measures of activities of daily living. But patients do not live their lives on scales. "Somebody walking around and going about their daily life, they don't know how many molecules of amyloid they have in their brain," Pohlig says. "What they know is if they can remember what they're doing that day."

23 https://www.nejm.org/doi/full/10.1056/NEJMoa2302368
24 https://www.thelancet.com/commissions-do/dementia-prevention-intervention-and-care

The debate over clinical meaningfulness has intensified following the arrival of the first disease-modifying treatments for Alzheimer's disease. While these therapies have demonstrated statistically significant benefits in slowing cognitive and functional decline, researchers continue to debate how those effects translate into everyday life for people living with dementia and their families.

A recent Cochrane review – which gathers all past studies on a topic, tests them for fairness, and combines the results – concluded that currently available anti-amyloid medicines produce only small average improvements in cognition and function over 18 months,[25] but its methodology has been challenged by many dementia experts, who argue that pooling data from trials with differing designs and outcomes may underestimate the benefits observed in successful studies.[26] ADI has similarly emphasised that people living with dementia and their families need clear, balanced information to weigh the potential benefits and risks of treatment, rather than relying on a single interpretation of the evidence.[27] The discussion has therefore shifted beyond whether the drugs work to a broader question: how should meaningful benefit be defined and measured in clinical trials? Many dementia specialists argue that even relatively modest delays in disease progression may represent valuable additional time spent living independently or remaining engaged with family life.

Dr Sid O'Bryant, executive director of the Institute for Translational Research at the University of North Texas Health Science Center, argues that the public often misunderstands how tightly clinical trials are structured long before the first patient is enrolled. "All of the outcomes of a clinical trial are so carefully defined and presented to the regulatory bodies for approval," he tells ADI. "The primary outcomes are normally biology – does amyloid come out? – and then cognition and functional outcomes."

Drug companies must specify in advance precisely what level of change constitutes success. Once the trial begins, the protocol is fixed. "There are pretty specific rules stating that this much of a change means success, period," Dr O'Bryant says. The problem emerges afterwards. "The difficulty from a patient standpoint becomes once someone takes the drug, whether or not that change is meaningful. From a clinical trial perspective, it's: how does it affect 1,000 people? But from a one-to-one perspective, it becomes: how does it affect you?"

That gap between population averages and lived experience increasingly sits at the centre of Alzheimer's research. For many clinicians, the key question is no longer whether slowing decline matters, but how best to measure its real-world impact.

In practical terms, dementia researchers increasingly focus on functional independence rather than cognition alone. Families tend to remember the condition not as a collection of memory scores but as a sequence of losses: driving, cooking, paying bills, dressing independently, navigating public transport.

One of the most widely used tools in Alzheimer's trials remains the Alzheimer's Disease Cooperative Study Activities of Daily Living scale, known as the ADCS-ADL. It asks caregivers to evaluate how well patients perform everyday tasks. Professor Jeff Cummings, one of the world's leading Alzheimer's researchers, believes the field has outgrown many of its traditional instruments. He tells ADI that ADCS-ADL "was invented in San Diego in 1997. Think how much our lives have changed since then!"

Prof Cummings points to the growing mismatch between global clinical trials and culturally narrow assessments. He recalls work on functional instruments in Thailand, where researchers examined whether older people could use Bangkok's taxi boats independently. "Taxi boats are not commonly used globally, but if you are an older Thai person, the ability to use one is really a great measure of your functional capability."

Researchers working in low- and middle-income countries (LMICs) argue that the debate over clinical meaningfulness cannot be separated from inequality. Prof Ricardo Allegri, the Argentine neurologist and lead author of a recent *Nature Reviews Neurology* paper on dementia research in Latin America, warned that much of global Alzheimer's science still reflects a "neocolonial model" in which poorer countries provide patients and data, while wealthier nations define the standards of success. Dementia researchers in poorer regions, he wrote, face "lack of funding, scarce resources and equipment, and brain drain," even though prevalence is often higher than in high-income countries.[28]

Clinicians in low-income countries also point out that independence itself looks different across cultures, infrastructure, and family structures. A large international survey of dementia clinicians and researchers across 34 LMICs found major disparities in access to diagnostic tools, biomarkers, and formal cognitive assessments. Researchers reported that doctors in poorer countries saw more patients, had less time for evaluations, and far less access to specialist testing.[29]

Jorge Llibre Guerra, a Cuban behavioural neurologist involved in dementia preparedness programmes across Latin America, recently argued that the greatest meaningful gain in many low-resource settings may simply be earlier diagnosis itself. A 2025

25 https://www.cochrane.org/about-us/news/anti-amyloid-alzheimers-drugs-show-no-clinically-meaningful-effect
26 https://www.ukdri.ac.uk/news-and-events/uk-dementia-research-institute-responds-cochrane-review-suggesting-anti-amyloid
27 https://www.alzint.org/news-events/news/people-living-with-dementia-and-their-families-need-clear-guidance-when-weighing-choices-of-new-alzheimers-treatments/
28 https://www.nature.com/articles/s41582-025-01125-3
29 https://pubmed.ncbi.nlm.nih.gov/39302373/

study led by Dr Llibre Guerra found that training primary care doctors in Cuba significantly improved dementia detection rates in community clinics. The researchers concluded that scalable interventions in resource-constrained settings could reduce inequalities in dementia care long before expensive biomarker-driven therapies become widely available.[30]

These realities shape how meaningfulness is understood. In wealthier countries, preserving the ability to manage online banking or drive a car may be central markers of independence. In lower-income regions, maintaining social participation within multigenerational households or continuing informal work may matter more. Researchers are therefore increasingly recognising that meaningfulness is culturally dependent. The ability to navigate smartphone apps or use transport systems may matter far more to independence today than some older trial measures. In response, newer tools are emerging.

Among the most closely watched is the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q), a digital caregiver-completed assessment designed to detect subtle early declines in complex daily activities. It measures tasks ranging from household management to computer use and leisure activities. "This is cleverly designed and may give us better information," Prof Cummings says. "But it has not been used in enough clinical trials yet for us to know for sure."

That uncertainty reflects another uncomfortable reality in Alzheimer's research: the field still lacks consensus on what constitutes a clinically meaningful change. Recent academic work has attempted to quantify the issue more rigorously. A 2025 study from Washington University in St Louis examined how slowing progression on the CDR-SB scale translated into additional months of independence in daily living. Researchers concluded that disease-modifying therapies could potentially delay loss of independence in instrumental activities of daily living, reframing abstract numerical changes into something more tangible for families.[31]

Another study published last year asked a more provocative question in its title: "Meaningful to whom?" Researchers argued that minimal clinically important differences in dementia trials often fail to reflect the priorities of people living with the condition.[32] That challenge is becoming harder to ignore as the field evolves from experimental science into real-world treatment.

In clinic rooms across the UK, the United States, Japan, and elsewhere, neurologists now find themselves trying to explain nuanced statistical benefits to anxious families desperate for certainty. The new drugs do not stop Alzheimer's disease. They do not restore lost memory. They do not reverse established neurodegeneration. What they appear to do is slow decline. For some patients, that may mean an extra six months of independent living. For others, it could mean preserving the ability to recognise family members for longer, or delaying admission to residential care. "For most of us, the goal is that patients are safe," Dr O'Bryant says. "If we can get 24 months of complete stability, that is amazing. Are we there yet? No. But what we do see is 18 to 24 months of much slower decline."

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The question of meaningfulness becomes even more crucial in countries where anti-amyloid drugs remain effectively inaccessible. The newest Alzheimer's medicines require specialist scans, infusion infrastructure, and close monitoring for brain swelling – systems that barely exist in many less developed healthcare systems. Researchers increasingly warn that unless trial design, diagnostic tools, and outcome measures become more globally representative, the benefits of the dementia revolution may remain concentrated in wealthy nations.[33] That, scientists argue, would create a paradox at the heart of modern Alzheimer's medicine: treatments judged "clinically meaningful" in Boston or London may prove far less meaningful in Lagos, Lima, or rural India if patients cannot realistically access them.

To families already immersed in dementia care, even modest delays can carry enormous emotional weight. A few additional months in which a spouse can still prepare tea independently, remember birthdays, or hold coherent conversations may not sound dramatic in regulatory documents. In lived experience, it can feel profound. This tension between measurable improvement and perceived benefit has long existed across medicine. Cancer drugs

30 https://pubmed.ncbi.nlm.nih.gov/40407103/
31 https://pmc.ncbi.nlm.nih.gov/articles/PMC11822626/
32 https://pubmed.ncbi.nlm.nih.gov/39975468/
33 https://www.theguardian.com/global-development/2025/jan/08/health-medicine-new-era-drugs-dementia-alzheimers-disease-pharmaceuticals-lecanemab-donanemab

that extend life by several months are often embraced as breakthroughs. Cardiovascular therapies may reduce risk by relatively small percentages yet still transform public health. Dementia, however, occupies a uniquely emotional terrain. Because Alzheimer's progressively erodes identity, memory, and autonomy, families often evaluate treatments less by numerical gains than by moments preserved.

Researchers are increasingly trying to capture those experiences directly. Qualitative studies now incorporate interviews with caregivers and patients alongside formal scales. One recent study examining agitation in people with Alzheimer's disease asked physicians and professional caregivers what degree of behavioural improvement felt meaningful in practice.[34] The findings revealed considerable variation in perception, underscoring how difficult it remains to define universal thresholds of meaningful change.

Ultimately, clinical trials must ask: if a drug (or lifestyle programme) works, what does that mean for patients and carers? This is the question of clinical significance. In Alzheimer's research, statistical significance has often been easy to achieve as large trials can show tiny differences on cognitive scales, but translating that to real life impact is a constant struggle. Take the new amyloid antibodies: they statistically reduce the rate of cognitive decline by some percentage over a year or two. But does a couple of points on a memory test matter? To answer, researchers have turned to patient-centred outcomes.

In the WashU study mentioned above, scientists converted the cognitive gains into months of independence. They found that in very mild Alzheimer's disease, lecanemab might give an average person living with a diagnosis about 10 extra months of living independently before needing full care. In practical terms, an effective dementia trial might define success as "delaying the need for a nursing home" or "keeping someone engaged in daily activities" for longer.

Similarly, trials increasingly look at quality of life and caregiver burden as key endpoints. A drug that preserves basic daily function or stabilises mood may be hailed as a win, even if memory tests improve only modestly. Regulatory agencies are now asking sponsors to demonstrate meaningful change: for example, slowing decline on the Clinical Dementia Rating Scale (CDR-SB) is more convincing if it also correlates with delayed institutionalisation or improved daily care needs. Post-hoc analyses of unsuccessful trials sometimes reveal subgroups that did feel a benefit – younger patients, or those in the earlier stages of the condition – which helps researchers refine future trial designs.

Balancing benefit and risk

Another aspect is risk tolerance. Dementia treatments can have serious side effects, including swelling or small areas of bleeding in the brain that require careful monitoring during treatment. These safety considerations are among the main reasons why lecanemab and donanemab have undergone rigorous scrutiny by regulators and health technology assessment bodies around the world, alongside questions about clinical benefit, cost-effectiveness, and their impact on healthcare systems. While both drugs received regulatory approval in the United States, and lecanemab was subsequently licensed for a defined group of patients in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), other organisations reached different conclusions. The European Medicines Agency initially declined to recommend lecanemab, before later issuing a positive opinion for a restricted patient population. In 2025, it also declined to recommend donanemab, highlighting the continuing differences in how regulators assess the balance between benefit and risk.[35]

Momentum has continued to evolve, however. In July 2026, the US Food and Drug Administration (FDA) approved the option of administering lecanemab at home from the start of treatment, rather than requiring patients to receive their initial infusions in a healthcare facility. Dr Howard Fillit, cofounder and chief science officer emeritus of the Alzheimer's Drug Discovery Foundation, described the decision as marking "a new era" in Alzheimer's treatment. "For the first time," he said, "patients and their care partners have meaningful choice in how anti-amyloid treatment is delivered."[36]

Patients and families must weigh all this against a potentially limited upside. Success, then, is highly personal: one patient might say six more months of memory is priceless, another might decline any risk for such a gain. Clinical trials today increasingly incorporate patient and carer input in design. What outcome matters most to you? This typical question now being asked of trial developers reflects a broader shift: clinical meaningfulness is no longer just a numeric target, but a narrative of individual priorities.

Scientists emphasised these themes in many of the interviews conducted for this report. One noted that as the pipeline fills with barely positive trial results, defining success in patient terms is key. We also heard about the promise of prevention trials – a concept once nearly unthinkable. Dr Gauthier says: "If I were 60 and told I was at high risk of Alzheimer's disease, I would sign up immediately for a trial." This attitude – patients ready to try something – is a huge opportunity, but it also raises questions of ethics and clarity: what exactly are we promising in these trials, and how will we measure it?

34 https://pmc.ncbi.nlm.nih.gov/articles/PMC12549559/
35 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)00833-5/fulltext
36 https://www.bmj.com/content/394/bmj-2026-100318

Finally, the global dimension matters. So far, most large trials have been conducted in North America, Europe, and parts of Asia. But dementia is a worldwide problem – an estimated 57 million people lived with it in 2021, over 60 percent of them were in LMICs, and numbers are only growing. Recruiting diverse populations is vital, both to ensure findings apply broadly and to give benefits globally. Dr Gauthier believes the new blood biomarkers "should pave the way for more studies in LMICs," by making screening cheaper and easier. Likewise, simpler outcome measures (digital games, home-based cognitive tests) are being explored to allow remote trial participation. Tackling dementia effectively will require overcoming the complexity outlined above in every region of the world.

Many researchers believe the next phase of dementia clinical trials will depend as much on international collaboration as on scientific discovery. Adaptive platform trials, shared biomarker standards, and global data-sharing initiatives are beginning to reduce duplication between research groups and accelerate recruitment. Several international collaborations now routinely include sites across high-, middle- and low-income countries, reflecting growing recognition that treatments intended for global use should be evaluated in populations that better reflect the world's diversity.

Ashton Harper, global medical director of neurosciences at Roche Diagnostics, believes blood-based biomarkers could play a pivotal role in broadening access to clinical research. "Unlike PET scanning or lumbar puncture, blood biomarkers don't require specialist equipment, specialist staff, or centralised facilities," he tells ADI. "A blood draw can be performed in a primary care setting, processed in a standard laboratory, and returned rapidly to aid informed clinical decisions. Realising that potential, however, requires more than science. Reimbursement, supply chain, clinical training, and guideline development all need to keep pace."

As blood-based biomarkers become more widely available, investigators hope that participation in dementia research will become increasingly possible in healthcare systems where PET imaging and specialised cerebrospinal fluid testing remain inaccessible.

In summary, dementia clinical trials today sit at the intersection of scientific rigour and human aspiration. They are among the toughest studies in medicine: battling a myriad of underlying causes, recruiting appropriate participants, and pushing through long timelines. But each step forward – a successful recruitment strategy, a new biomarker, a modest drug effect translated into real-life benefit – is encouraging.

"It's a great time for clinical trials and dementia," says Dr Gauthier. "It's also exciting because more of an international effort is now underway. There are exchanges between Asia, North America, and Western Europe. The research does not just concern memory tests and how you feel about yourself. It's now very biological – a bit like diabetes and cancer research. There are things we can measure in the blood that allow research at the stage when you have no symptoms. That's really new. Hopefully, within the next five years, it means we can have studies that are only for specific people, with a very specific biological profile, like with some types of cancer research right now: if your tumour has a specific profile, then you are given a specific drug. And we're heading that way – of precision medicine for dementia."

CASE STUDY

The brothers racing time: How one family's fight against inherited dementia could transform global clinical trials

Jordan Adams, a fit and healthy 31-year-old, completed the 2026 London marathon with a 25kg fridge strapped to his back to highlight the impact frontotemporal dementia (FTD) has had, and will have, on him and his family.

"This marathon with a fridge on my back isn't just a challenge," Jordan wrote in a Facebook post prior to the race. "It's a symbol. Because that's what it feels like sometimes – like you're carrying something heavy that no one else can see. I'm doing this to make dementia visible."[37]

His mother, Geraldine, was diagnosed with FTD – a group of brain disorders affecting the frontal and temporal lobes – at the age of 47 and died five years later. His father, Glenn, broke the news of Geraldine's diagnosis after school one day when Jordan was 15, alongside his 17-year-old sister, Kennedy, and 9-year-old brother, Cian. When Jordan was 23, he discovered he was carrying the gene mutation that causes it, too, giving him a 99.9 percent chance of developing FTD in his forties.

"As a 15-year-old, I had no idea what dementia was," Jordan told *The Times* in May. "I thought it was to do with memory loss and old people. I couldn't understand why she would die from it. I used to lie in bed at night crying, praying Mum would make it to my 21st birthday… By the time I was 19, my prayers had changed, and I just wanted her to be at peace." The family spent six years caring for Geraldine as she became bedbound, incontinent, and unable to recognise her children, before she died at their home in Redditch, England, at the age of 52.[38]

After his wife's diagnosis, Glenn began looking into her family history and discovered Geraldine's mother was one of six siblings, four of whom developed familial FTD. Those four siblings had 13 children, and of those 13 cousins, eight went on to develop and later pass away from FTD. "For decades, dementia quietly and relentlessly affected our family. Generation after generation lived through repeated loss without answers, explanations, or understanding of why this kept happening," the brothers wrote on their GoFundMe website.[39] It was through medical research in Ireland that the cause was finally identified."

Both Jordan and Cian, known as The FTD Brothers after establishing a patient advocacy platform,[40] carry a mutation in the MAPT gene that encodes tau, a protein increasingly recognised as central to some of the most serious neurodegenerative diseases, including Alzheimer's disease. When tau malfunctions, it misfolds and accumulates in the brain, driving neuronal damage that eventually affects cognition, behaviour and personality.

The mutation is inherited, meaning each child of a carrier has a 50 percent chance of inheriting it. Kennedy tested negative, but Jordan and Cian, now 31 and 25 respectively, live with a level of certainty most people spend their lives trying to avoid. Barring a significant scientific breakthrough, they know they are both likely to develop frontotemporal dementia in their early to mid-forties. Together, the family has raised more than £2 million for dementia research,[41] to raise awareness, and to support families through community, education, and practical help.

After hearing about a study following a conversation with their genetic counsellor, both brothers are participants in the Genetic Frontotemporal Dementia Initiative (GENFI), a global research consortium led by Professor Jonathan Rohrer.[42] The study follows people from families with inherited forms of frontotemporal

37 https://www.facebook.com/mindforbettermentalhealth/posts/im-29-and-running-the-london-marathon-with-a-fridge-on-my-back-because-we-are-al/1524594526376344/
38 https://www.thetimes.com/life-style/health-fitness/article/jordan-adams-fridge-marathon-99k9mcbqx
39 https://www.gofundme.com/f/theftdbrothers
40 https://theftdbrothers.com
41 £300,000 for Alzheimer's Research UK, then £1.95 million on the brothers' most recent challenge, split equally between Alzheimer's Society of Ireland and The FTD Brothers Foundation.
42 https://www.genfi.org

dementia over many years, often long before symptoms emerge. Its purpose is to understand exactly what happens in the brain before the condition becomes clinically visible.

Unlike many forms of dementia, genetic FTD offers researchers a rare opportunity to study disease progression with unusual precision. Scientists know who is at risk. They know, broadly, when symptoms are likely to emerge. What they are trying to determine is when the biological process truly begins, and how early intervention must happen if it is to be delayed or prevented altogether. GENFI is not merely an observational study. Rather, it is laying the foundations for future prevention trials.

That distinction matters enormously to families like the Adamses, because time is measured differently when a neurodegenerative disease runs through generations. Cian joined the study after being offered genetic testing through the UK's National Health Service (NHS). In Britain, families with clear inherited patterns of FTD can often access testing through specialist genetic services, creating a pathway into research that remains difficult to replicate elsewhere.

Cian tells ADI: "It can be a little bit of a postcode lottery in the UK, and the services look very different in different parts of the country, but our pathway was through genetic services in Birmingham via a GP referral. They then take you through the genetic counselling process and deliver your genetic test results. Out of the back of that, if you are a [genetic mutation] carrier and if you want, you can be referred to become a participant in GENFI at University College London."

Participation involves repeated assessments at UCL, where researchers collect the data needed to map disease progression with extraordinary detail. Cognitive testing, MRI scans, blood biomarkers, spinal fluid analysis, and digital assessments all contribute to a growing body of evidence aimed at identifying the earliest detectable signs of degeneration. The burden of participation is not insignificant. Yet for Cian, the decision to take part was never primarily about personal gain.

"I don't look at it in the sense that I hope they come up with a treatment for me in a certain number of years," he says. "I see it as the right thing to do. I did a Master's [degree] in research, so I understand the importance of data, especially longitudinal data in presymptomatic individuals who have a very rare condition, of which there are three different genes in which mutations most commonly cause FTD."

"Jordan and I are MAPT carriers, which is the second most common. I want to make myself available to as many people as possible to help on that front. Not in a way that I'm checking every week if they've cured it or not, just to be helpful and to be in tune with what's on the horizon and which direction we need to take our advocacy, because at some point that will involve talking to scientists and people who fund science as well."

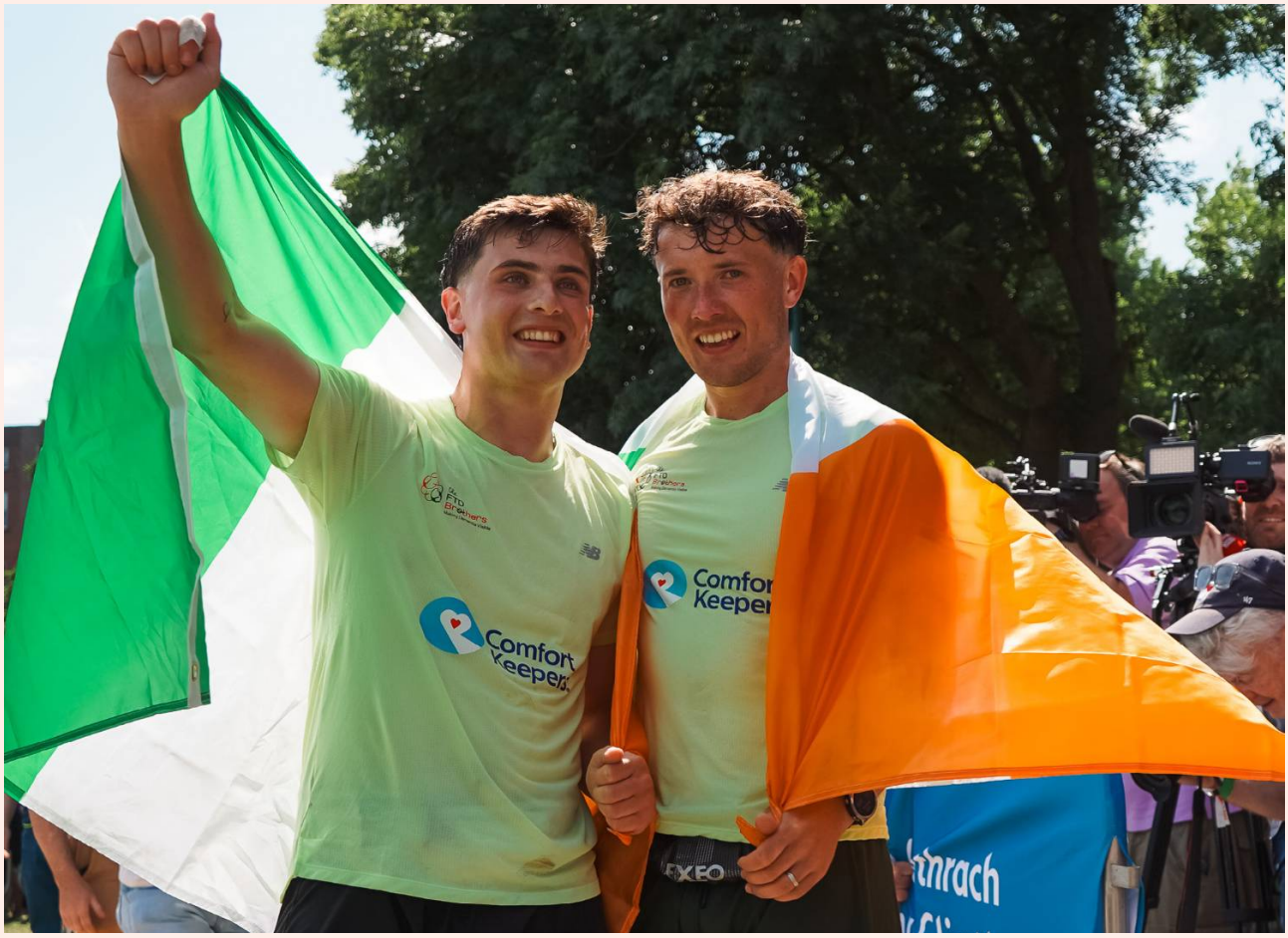
Jordan Adams runs marathons with a fridge on his back to symbolise the impact of frontotemporal dementia on his family (Photo courtesy of the FTD Brothers)

Cian's partner, Helen Jolly, brings both personal and scientific insight. Currently undertaking a PhD in neuroscience at the University of Oxford, she understands their family's experience through the wider dementia research landscape. She also sees why genetic FTD, despite being rare, offers a promising route to developing new treatments.

Helen explains: "GENFI is a global study because these mutations are so rare. Researchers have had to build an international network, with sites across Europe, North America, and beyond. The aim is to develop reliable biomarkers that can track when the disease begins and how it progresses. In FTD, the early behavioural changes are very different from those of Alzheimer's, so researchers use tests designed to detect those differences. The hope is that this research will eventually lead to platform trials where people with these mutations can receive treatment before symptoms develop, delaying or even preventing the disease. That's the ultimate goal of GENFI."

"Most therapeutic development has focused on Alzheimer's disease," she adds. "But for people with MAPT mutations, there are still no clinical trials testing tau-targeting therapies, even though they involve the same protein. That's what we'd like to see change. We'd like to be able to say to drug companies: 'You're already targeting tau. Why not test these treatments in people with rare genetic forms of FTD as well?'"

In recent years, tau has become one of the most important targets in dementia drug development, particularly in Alzheimer's disease. After decades in which amyloid dominated scientific attention, tau is increasingly regarded as more closely



Cian (left) and Jordan Adams are both carriers of the MAPT gene mutation that highly raises the risk of developing frontotemporal dementia (Photo courtesy of the FTD Brothers)

linked to neurodegeneration and cognitive decline. Once tau pathology spreads through the brain, decline often accelerates. That shift has triggered enormous investment in tau-targeting therapies. Drug developers are pursuing monoclonal antibodies, antisense oligonucleotides, and gene-silencing therapies designed to reduce toxic tau accumulation.

The irony is difficult to ignore. Although tau has become one of the most closely watched targets in Alzheimer's research, there are currently no dedicated therapeutic trials for people with MAPT mutations, despite the fact that tau dysfunction is the primary driver of their disease. The reason is straightforward. Alzheimer's disease is biologically complex, involving multiple overlapping pathways, including amyloid, tau, inflammation, and immune dysfunction. By contrast, MAPT-related FTD presents a far more direct disease mechanism. "You know what the starting point is," Helen says. "You know tau is going wrong."

In effect, MAPT mutation carriers represent one of the purest human models of tau-driven neurodegeneration available to researchers. If a therapy is designed to target tau, this population offers a uniquely powerful opportunity to test whether it is truly modifying disease biology. That opportunity is increasingly difficult to ignore as the global clinical trial landscape evolves.

Recent Alzheimer's therapies such as lecanemab and donanemab have shifted the mood in dementia research. While debate continues about the scale and clinical significance of their benefits, they have demonstrated something that had long seemed uncertain: that disease-modifying treatment is possible. That breakthrough has fundamentally changed expectations.

"When I started my PhD three years ago, there was a big shift in attitude in light of these drug approvals," Helen says. "Basic science that had been going on for decades was starting to translate clinically."

The field now feels as though it has reached an inflexion point. Advances in genetics, biomarker discovery, artificial intelligence, and molecular biology are feeding into better trial design and more sophisticated drug development. Years of painstaking laboratory work are beginning to generate tangible clinical momentum. Yet progress in rare diseases still depends on more than scientific readiness.

Funding remains a critical barrier. Infrastructure remains uneven. Recruitment remains challenging because patient populations are dispersed across countries and health systems. That is why GENFI was built as a global consortium. No single country has

enough patients to solve this problem alone. For Cian, the next challenge is clear. Awareness has helped build a public platform. The harder task now is translating awareness into clinical action.

"Our biggest task will be prevention trials," he says. "That has to be our goal. It's all well and good once that cascade of events has started in the brain to deliver a therapeutic treatment, but I know that I will develop symptoms of FTD due to our family history in my early to mid-forties. So our goal over the next 20 years would be to end up with prevention trials. That would represent our biggest achievement."

That objective lies at the heart of the next phase of inherited dementia research. By the time symptoms emerge, neurodegeneration is often already advanced. The future lies in treating people before symptoms begin. Even delaying onset by a few years could transform lives. For families affected by MAPT mutations, that could mean extra years of work, parenthood, independence, and memory. It could mean children growing up with a healthy parent for longer. It could mean changing the trajectory of a condition that currently feels inevitable.

Cian speaks about that reality without embellishment and offers a direct message to pharmaceutical companies. "I'm 25 now. Mum became symptomatic at 45 and formally diagnosed at 47, so we hope that a big difference can be made in the 20 years before I reach that age. That's 20 years' worth of research and funding that we can pump towards this. So if anything is working in that tau pipeline, bring it over to us, please!"

The science is moving, biomarkers are improving, the therapeutic pipeline is expanding, and both Cian and Helen hope the extra investment into Alzheimer's disease clinical trials around the world will have a trickle-down effect on people with rarer forms of dementia.

The question is no longer whether tau matters, but rather whether progress will reach families like Cian's in time, as Helen points out. "FTD is very aggressive. It's typically a much faster decline than Alzheimer's. It's very challenging for the time that it affects families, because often these are people in the prime of their lives, in their forties, fifties, they have young kids or younger families and the things that need to be in place aren't necessarily there," she says. "So it's absolutely devastating, and I think a lot of people with these mutations, if they were offered something that could delay the onset even by a few years, they would want it and would take the risk."

> **'It is a very difficult situation to be in – while time passes with the grief of losing someone to FTD, you move towards FTD for yourself and your family again. If there is anything that will stop that or break the cycle, it would be incredible.'**
>
> *Helen Jolly*

"Some people with these types of mutations would be willing to risk side effects or a failed clinical trial, considering the alternative is the future of this disease that they had to watch a parent or sibling go through. At the same time that people are moving away from that grief and trauma, they're moving towards their own. It is a very difficult situation to be in – while time passes with the grief of losing someone to FTD, you move towards FTD for yourself and your family again. If there is anything that will stop that or break the cycle, it would be incredible."

Asked what message he would like to give regulators, funders, and pharmaceutical companies, Cian says: "To consider putting us in some trials and give us some medications because, as a genetic mutation carrier, it's an extremely bleak future, and it's one that I've come to terms with over many years. I live my life in keeping with the fact that I will live a shorter life, and I've adjusted everything in my power to make my life better in the short term. But we have had to, Helen and I, come to terms with the fact that I'll live a shorter life, and I'll lose my life to a very cruel, neurodegenerative disease."

Chapter 4:

Recruitment, adherence, and global participation

Vegetable vendors trade their fresh produce at the historic floating market on Dal Lake in Srinagar, Kashmir, in May 2026. (Photo by Domenico Pugliese)

Summary

The success of dementia clinical trials depends not only on scientific innovation, but also on the ability to recruit, retain, and support diverse groups of participants. As disease-modifying therapies emerge and the global research landscape expands, ensuring that clinical trials are representative, accessible, and equitable has become one of the greatest challenges facing dementia research.

This chapter examines where dementia clinical trials are taking place, which countries are leading recruitment efforts, and the factors that influence participation across different healthcare systems and populations. While North America, Europe, and increasingly China continue to dominate the clinical trial landscape, many low- and middle-income countries (LMICs) remain underrepresented despite carrying a growing share of the global burden of dementia. This geographical imbalance limits both access to research opportunities and the global applicability of trial findings.

Recruitment remains a significant bottleneck throughout the clinical trial pathway. Delays in diagnosis, limited awareness of dementia, insufficient referral pathways, logistical barriers, transportation challenges, language and cultural differences, and concerns about potential risks all contribute to slow enrolment and participant dropout rates. Sustaining adherence throughout increasingly complex and lengthy trials presents an additional challenge for participants, families, and research teams alike.

The chapter also explores inequities in trial participation. Although women and men are equally represented in dementia trials, women's representation is lower than in the underlying dementia population.[1] Ethnic minority populations in many wealthier countries, socioeconomically disadvantaged communities, and people living in low-resource settings also continue to be underrepresented in many studies, raising important scientific and ethical concerns regarding the generalisability of results. Recent policy and funding changes, particularly those affecting diversity, equity, and inclusion initiatives in the United States, may further widen these disparities unless alternative approaches are developed.

Drawing on international case studies and expert perspectives, this chapter highlights innovative recruitment strategies, community partnerships, and policy initiatives that are improving participation across diverse settings. Achieving truly global, representative clinical trials will be essential if future dementia treatments are to benefit everyone who stands to gain from them, regardless of geography, ethnicity, or socioeconomic status.

Global recruitment efforts and Asia-Pacific's growing role

The race to develop effective treatments for Alzheimer's disease and other dementias has become one of the largest and most geographically diverse scientific endeavours in modern medicine. What was once a field dominated by North American and Western European research centres is increasingly global, with major clinical trial activity spanning Asia, Latin America, Australia, and low- and middle-income countries (LMICs).

That expansion reflects both scientific necessity and demographic reality. More than 57 million people worldwide are living with dementia, a figure projected to rise sharply as populations age, reaching 78 million in 2030 and 139 million in 2050.[2] Finding treatments for a condition that has long resisted medical intervention requires not only better science but also larger and more diverse groups of volunteers willing to participate in clinical trials.

1 https://pmc.ncbi.nlm.nih.gov/articles/PMC9445798/
2 https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/

The United States remains the undisputed leader in dementia research. It hosts the largest concentration of trial sites, academic research centres, and pharmaceutical investment. Recent analyses of the Alzheimer's drug development pipeline show that North America remains involved in every major global Alzheimer's trial currently underway, while around half of all sites participating in international studies are located in the US.[3] The country's dominance reflects decades of federal investment through the National Institutes of Health, the presence of leading pharmaceutical companies, and a highly developed network of specialist memory clinics.

Europe forms the second major pillar of global dementia research. The United Kingdom, Germany, France, Spain, Italy, and the Nordic countries collectively host a substantial share of international Alzheimer's studies, particularly in the later stages of drug development. Western Europe is involved in more than 70 percent of current global Alzheimer's trials, underlining the region's continuing importance to multinational recruitment efforts.

Yet the geography of dementia research is becoming steadily more diverse. China has emerged as perhaps the most significant growth story. Faced with a rapidly ageing population and an estimated 16 million people living with dementia, forecast to increase to over 45 million by 2050,[4] the country has dramatically expanded its research infrastructure in recent years. As of January 2026, 32 research centres in China had joined a new consortium, which aims to link Alzheimer's disease research centres across China and foster international collaborations in clinical trials, while more than 30 others are in the process of joining.[5]

The centres have amassed cohorts of tens of thousands of participants and hundreds of neurologists, geriatric psychiatrists, and geriatricians to screen, diagnose, and treat Alzheimer's disease, as well as run clinical studies. The body of Alzheimer's clinical trial centres in China is bigger than represented in the consortium, which is limited to excellence centres. Consequently, the number of clinical trials has increased rapidly: from just nine in 2021 to 107 in 2024, making China "a massive hub for global dementia research."[6]

Chinese regulators have also accelerated approvals for innovative therapies, while international pharmaceutical companies increasingly view the country as a critical market for both recruitment and future treatment uptake. To get a drug approved for use in China without running a separate trial in the country, China requires that at least 10 percent of participants in a global Phase 3 trial come from China. Hence, large pivotal trials have long included Chinese participants. Consortium leader Jiong Shi, of the University of Science and Technology of China, said ongoing examples include Roche's TRONTIER-1 trial, which includes 14 centres in China, and Eli Lilly's TRAILRUNNER-ALZ3, which is evaluating remternetug at 29 Chinese centres.[7]

Japan and South Korea have also become increasingly important players. Both countries possess sophisticated healthcare systems, ageing populations, and strong biotechnology sectors, making them attractive locations for multinational studies. Increasingly, researchers point to national dementia strategies as a key factor behind their growing importance. According to Saumya Nayak, director and head of clinical planning and analytics for Asia-Pacific at the clinical research organisation (CRO) IQVIA, government-backed dementia programmes are helping create the infrastructure needed to identify suitable participants much earlier in the disease process.

"Korea and Japan have national dementia plans that include memory clinics, and they can help with the screening programmes," she tells ADI. "The intention of these plans is to identify patients early and also create registries of potential Alzheimer's patients. China has also launched an awareness programme and campaign where they are introducing cognitive assessments as a routine care for elderly people."

Such initiatives are becoming increasingly valuable as researchers seek to recruit patients before significant brain damage has occurred. Earlier diagnosis not only improves access to treatment but also expands the pool of people eligible for prevention and early-intervention studies, which now make up a growing share of the Alzheimer's pipeline.

Nayak says practical support for patients and families can be just as important as national policy. "Having a clinical trial educator has helped a lot in getting the patients quickly referred to the study, because they liaise with the site staff and the patients and try to make them understand the trials. So that's something we have observed helps with recruitment, especially for Alzheimer's."

Australia punches above its weight in dementia research, benefiting from world-class neuroscience institutes, strong participation in prevention studies, and a regulatory environment that allows international trials to begin recruiting quickly. Together, these developments highlight how successful recruitment increasingly depends not only on scientific expertise, but on national infrastructure, public awareness, streamlined regulation, and sustained investment.

3 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251
4 https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(24)00152-4/fulltext
5 https://www.alzforum.org/news/conference-coverage/clinical-network-china-connects-trial-ready-cohorts-they-are-huge
6 https://www.chosun.com/english/industry-en/2026/02/26/SWPJC7HXYFDYXK2D2V35OIAIZQ/
7 Ibid.

"Alzheimer's disease is going gangbusters at the moment," Professor Colin Masters, the Australian neuroscientist whose work helped establish the amyloid hypothesis of Alzheimer's disease, tells ADI. "The feeling of optimism has never been so strong. We've moved from a great nihilistic, pessimistic era five years ago towards an era of extreme optimism."

> **'We've moved from a great nihilistic, pessimistic era five years ago towards an era of extreme optimism.'**
>
> *Professor Colin Masters*

Prof Masters, who confesses to being "an optimist by nature," adds: "What is keeping everyone on their toes right now is that at the end of this year and early next year, we will get the results of lecanemab and donanemab being used in preclinical [Alzheimer's] disease. So that's people like you and me who are cognitively intact, no signs of cognitive impairment, but who we know from taking a brain scan or blood test are on the pathway towards disease – so we can define preclinical disease right now. And that has been worked on over the last six years or so. Everyone in the field is expecting a positive result, simply because we know that using this method of intervention in MCI [mild cognitive impairment] is giving us the best results, and we expect even better results in preclinical disease. That's where the whole field is."

Prof Masters says "many, many new targets" are being explored around the world right now in biotech and in big pharma, with the next generation of antibodies "looking so much better than the current generation." He adds: "Overall the field is extremely optimistic, but we are beholden to the results of clinical trials, which will come through over the next 12–24 months."

Barriers to recruitment: why so many potential participants never make it into dementia clinical trials

Successful recruitment, meanwhile, also depends on how research centres organise their clinical trial programmes. Dr Sharon Cohen, medical director of the Toronto Memory Program in Canada, believes offering a broad portfolio of studies enables centres to match more people to appropriate trials while maintaining consistently high recruitment. "Most Alzheimer's trial sites would have maybe two to four clinical trials running concurrently. We typically have 15 to 20," she says. "We feel that having a broad range of trials is the way to go."

Dr Cohen's clinic recruits participants across prevention, mild cognitive impairment, and early Alzheimer's disease studies, allowing more volunteers to find a trial suited to their stage of disease. "We haven't had a shortage of interested participants," she adds. "Part of that is because we turn to the community and educate the community."

The sheer scale of the modern Alzheimer's research enterprise helps explain why recruitment has become such a strategic priority. According to Professor Jeff Cummings's 2026 annual review of the Alzheimer's drug development pipeline, there are currently 192 active clinical trials assessing 158 therapies worldwide, up from 182 trials and 138 therapies just a year earlier. Since the inaugural pipeline report was published in 2016, the number of active trials has increased by 35 percent, while the number of therapies under investigation has risen by 40 percent.[8]

Researchers estimate that the current pipeline requires 54,728 participants globally, including 38,417 participants in Phase 3 trials alone. Recruiting those numbers increasingly depends on international collaboration and the ability to identify eligible participants across multiple continents. The globalisation of dementia research has accelerated considerably over the past decade. Recent analyses have found that 46 countries now participate in active Alzheimer's trials.[9] Around one third of ongoing studies involve sites both inside and outside North America, illustrating how recruitment has evolved from a largely Western enterprise into a genuinely international effort.

Yet the expansion of dementia research raises an important question: can LMICs be fully integrated into the next generation of clinical trials? Professor Miia Kivipelto, one of the architects of the pioneering FINGER prevention study, believes concerns about recruitment in LMICs are often overstated. "Interest is great wherever you are if the messaging is right," she tells ADI. "FINGERS Latin America managed to put together 12 countries working with the same protocol and ready for their study for next summer. Recruitment has been working very well. If you have teams that can find the individuals, then it works."

Her experience suggests that successful recruitment is less about national wealth and more about local organisation, trust, and community engagement. The FINGERS programme, which aims to test lifestyle interventions that may reduce dementia risk, has become a model for international collaboration by adapting a common research framework across diverse healthcare systems. Prof Kivipelto also highlights how recruitment patterns can vary significantly between cultures. "In Latin America, we see 70 percent of women [among patients] engaging in FINGERS: Why? Maybe it is something in the culture. In China and South Korea, it was a bit more equal. In Nordic

8 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251
9 https://www.sciencedirect.com/science/article/pii/S1041610225003461

countries, it's very equal at 50/50. So one question is, how can we attract more men in, for example, Argentina, to be part of the trial? That's one for the future, I guess."

Her observations underline a growing recognition that diversity in trial participation is not simply a matter of geography. Researchers are increasingly focused on ensuring studies reflect differences in sex, ethnicity, socioeconomic status, and culture, particularly as evidence mounts that dementia risk factors and disease progression may vary across populations. Despite these encouraging developments, LMICs remain underrepresented in the global research ecosystem. Although many are now participating in international studies, the majority of trial sites remain concentrated in North America, Western Europe, and East Asia. Researchers argue that broadening participation will be essential if future therapies are to be tested in populations that reflect the global burden of disease.[10]

At the same time, the scientific pipeline is expanding rapidly. Dr Cummings's 2026 report found that 59 new clinical trials entered the Alzheimer's pipeline over the past year alone, signalling growing confidence among researchers and investors that effective therapies can be developed. Perhaps most striking is the increasing diversity of scientific approaches. A decade ago, the field was heavily concentrated on amyloid, the protein widely believed to play a central role in Alzheimer's disease. Today, amyloid-focused therapies account for only around one fifth of the pipeline. Researchers are increasingly pursuing treatments aimed at inflammation, immune dysfunction, tau pathology, metabolism, vascular health, and neuroprotection.[11]

Inflammation-targeting therapies, for example, have grown from just 6 percent of the pipeline in 2016 to almost one fifth today. Tau-directed treatments have expanded similarly. The shift reflects a growing consensus that Alzheimer's is a biologically complex disease that will likely require multiple therapeutic approaches rather than a single solution. The challenge, however, is not simply opening more trial sites. It is finding eligible participants quickly enough to keep pace with the rapidly expanding pipeline.

Blood biomarkers could transform recruitment

Recruitment has long been a bottleneck in Alzheimer's research, with many studies struggling to identify patients early enough in the disease process. Historically, screening often relied on expensive brain imaging or invasive lumbar punctures, limiting the pool of potential volunteers. Increasingly, researchers believe blood-based biomarkers could change that equation. Prof Masters believes these new diagnostic tools could transform recruitment. "The barriers to recruitment are beginning to be broken down because we have these blood tests, so we can do the screening and identify people who should be in clinical trials," he tells ADI.

Blood tests are increasingly being used both to identify suitable participants and to determine whether experimental therapies are affecting the underlying biology of the disease. Researchers hope that biomarkers will dramatically reduce screening costs and enable recruitment on a scale that was previously impossible. Prof Masters argues that dementia research should learn from oncology, where participation in clinical studies is often considered routine in patient care.

"The average clinician who sees people with mild cognitive impairment or early dementia needs to understand, just exactly as we have in oncology, that once you are diagnosed with cancer it's almost as if you automatically agree to go into a clinical trial in one form or another. That's the way the whole field of oncology works right now," he says. "But we're talking about Alzheimer's disease – a fatal illness within 10–15 years of onset. The average duration of disease is 10 years, and it is now the leading cause of death in Australia. It has surpassed cancer, so we have to learn from oncology colleagues and take a leaf out of their book that anybody who presents with Alzheimer's after a specific diagnosis, the practitioner has to be alert for the need for going into clinical trials, irrespective of the treatment that you get."

The comparison is becoming increasingly relevant as the Alzheimer's pipeline expands. Researchers are now testing therapies against a broader range of biological targets than at any point in the field's history, laying the groundwork for the kind of combination-treatment approaches that transformed cancer care over recent decades. Another notable trend is the rise of repurposed medicines. The 2026 pipeline includes 56 repurposed agents – drugs originally developed for other conditions – representing around 35 percent of all therapies currently under investigation. Because their safety profiles are already well understood, repurposed drugs can often progress through development more quickly than entirely new compounds. For Prof Cummings, the expansion of the pipeline marks a turning point in Alzheimer's research. "Alzheimer's is no longer an untreatable disease," he commented when his report was published earlier this year. "It is now a disease with treatments that successfully interfere in the disease process."

Several major trial results are expected over the coming year, raising hopes that the first generation of disease-modifying therapies may soon be joined by treatments targeting entirely different biological pathways. The next challenge will be ensuring that recruitment keeps pace with scientific ambition. As trial networks spread beyond their traditional

10 https://www.alz.org/stepupthepace/equity
11 https://www.brightfocus.org/resource/expanding-the-alzheimers-treatment-landscape-a-2026-forecast/

centres in North America and Europe, researchers hope that better diagnostics, broader international collaboration, and more diverse participation will help deliver the numbers needed to test the largest and most promising generation of Alzheimer's therapies yet. If those barriers can be overcome, the globalisation of dementia research may prove to be one of the most important developments in the search for effective treatments – a search that increasingly depends on one valuable resource: people. Not laboratory mice, sophisticated scanners, or breakthrough biomarkers, but ordinary individuals willing and able to volunteer for research. Yet while scientific progress has accelerated dramatically over the past decade, recruitment has struggled to keep pace and remains one of the greatest obstacles facing the field.[12] Across continents and healthcare systems, researchers encounter the same frustrating reality: finding eligible participants is often far harder than finding promising drugs to test.

The reasons are varied and interconnected. The vast majority of people never receive a diagnosis early enough to be considered for a trial. Others live too far from specialist research centres, lack access to transport, or cannot afford the time and expense required for participation. In many communities, dementia remains poorly understood, creating stigma and reluctance to seek medical help.[13] Language barriers, mistrust of medical research, and a shortage of trained clinicians can all further narrow the pool of potential participants. Even among those who enrol, concerns about side effects, repeated hospital visits, and the burden placed on family members can make long-term participation difficult. One analysis found recent multi-year Alzheimer's disease studies lost 10 to 54 percent of participants.[14]

The barriers begin long before an individual is offered a place on a trial and continue throughout their journey in research. Modern Alzheimer's trials increasingly target people in the earliest stages of disease, often before dementia has fully developed.[15] Researchers have become convinced that interventions are most likely to succeed when brain damage is still limited, shifting the focus towards individuals with mild cognitive impairment or even those who have no symptoms but show biological evidence of disease. The problem is that healthcare systems have struggled to keep pace with this scientific shift.[16] Across much of the world, people continue to receive diagnoses years after symptoms first emerge. By the time many patients reach a memory clinic, they may already have progressed beyond the stage at which they would qualify for a study.

Dr Fiona Carragher, former chief policy and research officer at Alzheimer's Society, now chief executive of Kidney Research UK, sees the consequences every day. "Five hundred and fifty-one people were recruited to late-stage dementia trials in England in the most recent five-year period, compared to 24,000 people for cancer," she tells ADI. "The difference is stark, and there's a whole set of reasons, not least that people are not being diagnosed."

Oncology has spent decades embedding clinical trials into routine care. Dementia, by contrast, remains some distance from that model. "Those who are being diagnosed are diagnosed late," Dr Carragher says. "They're often not told the form of dementia that they have, and they haven't necessarily had those specialist diagnostic tests that would say 'Yes, this person has got amyloid that we can see on the imaging, and they've been diagnosed at this stage of disease, which is early enough for them to go into a trial.' We're a long way from that."

The challenge is particularly acute as trials become more biologically targeted. Many studies now require confirmation that a participant has underlying Alzheimer's pathology through PET scans, cerebrospinal fluid analysis, or blood-based biomarkers.[17] A general dementia diagnosis is no longer sufficient. Recent analyses from the USC Schaeffer Center have identified delayed diagnosis and limited access to biomarker testing as two of the most significant barriers to trial participation in the United States, warning that many potentially eligible patients never enter the recruitment pipeline because they are simply never identified.[18] The arrival of blood-based biomarkers has generated considerable optimism because they promise to address this problem precisely. Cheaper, less invasive and potentially deployable in primary care settings, these tests could eventually transform recruitment by identifying suitable participants long before symptoms become severe. But for now, the gap between scientific ambition and clinical reality remains substantial.

Fear and stigma delay participation

Even where diagnostic services are available, another challenge emerges: persuading people to use them. For decades, dementia has occupied a unique and uncomfortable place in public consciousness. The condition continues to be associated with fear, loss of independence, and a perception that little can be done. The result is that many people delay seeking help even when they recognise symptoms.

12 https://www.sciencedirect.com/science/article/pii/S2274580725001736
13 https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00404-6/fulltext
14 https://pmc.ncbi.nlm.nih.gov/articles/PMC9673904/
15 https://doi.org/10.1002/trc2.70251
16 https://schaeffer.usc.edu/wp-content/uploads/2024/10/Key-Barriers-to-Clinical-Trials-for-Alzheimers-Disease.pdf
17 https://doi.org/10.1002/alz.13859
18 https://schaeffer.usc.edu/wp-content/uploads/2024/10/Key-Barriers-to-Clinical-Trials-for-Alzheimers-Disease.pdf

Yared Zewde, professor of neurology at Addis Ababa University and founder of Alzheimer's Ethiopia, says awareness remains one of the defining challenges facing recruitment efforts in parts of Africa. "Awareness is a problem, especially in rural communities," he tells ADI. "There is a hesitancy to come forward with cognitive problems, so we need to persuade people to seek medical care."

The reasons vary from country to country. In some communities, memory loss is viewed as a normal part of ageing. In others, symptoms may be interpreted through cultural or religious frameworks rather than medical ones. In many places, families fear the social consequences of a diagnosis. What is striking is how familiar these themes sound to researchers working in vastly different healthcare systems. Recent studies have found that fear of diagnosis remains a significant deterrent not only in LMICs but also across Europe and North America. Many people continue to believe that there is little value in obtaining a diagnosis because effective treatments do not exist, despite the arrival of the first disease-modifying therapies and the rapid expansion of clinical research opportunities.[19]

For recruitment specialists, this creates a paradox. The field increasingly depends on identifying people earlier than ever before, yet many individuals remain reluctant to engage with services until symptoms have become impossible to ignore. Recruitment challenges do not end once a patient enters the healthcare system. In many countries, the healthcare system itself becomes a bottleneck. Dementia services are often stretched, fragmented, and understaffed. Specialist memory clinics face long waiting lists. Research infrastructure often operates independently of clinical care. The result is that opportunities for participation can be missed even when suitable candidates are sitting in front of healthcare professionals.

"Anybody who has concerns about their memory, has risk factors or symptoms, should be referred to a clinical trial, which should be considered a natural continuation of clinical care," Dr Cohen says. "We're not there yet in Alzheimer's disease. There's still this stigma or lack of understanding that going early or paying attention to mild memory symptoms is somehow wrong." She argues that normalising research participation as part of routine care could substantially improve recruitment while ensuring more people gain access to specialist assessment and emerging therapies.

Maria C. Carrillo, chief science officer and medical affairs lead at the Alzheimer's Association in the US, believes the disconnect between clinical care and research remains one of the biggest missed opportunities in dementia. "Clinicians could offer so much more service and value to patients and the advancement of science if participation in clinical trials was offered in every doctor's office following diagnosis or a diagnostic work-up," she tells ADI. "Too many doctors are not aware of the Alzheimer's research studies in their area, and patients remain unaware that research participation is even an option. Unless a trusted clinician recommends participation, people can be very wary of research."

The problem becomes even more pronounced in countries where healthcare resources are already under pressure. "We need to educate our health professionals," says Prof Zewde. "And we are trying to push the government in Ethiopia to develop a national dementia plan. But we're competing with lots of other diseases and infections like malaria and HIV, for example, so it is very challenging."

Alongside infrastructure constraints comes a workforce challenge that extends across the global research landscape. "We also have a huge issue with manpower, with 'brain drain,' meaning we lose many good scientists who want to work abroad," Prof Zewde says. "Some of our colleagues leave to go work in the USA, so we have that to contend with too." Shortages of neurologists, psychiatrists, specialist nurses, and research coordinators are now being reported in many countries, creating concerns about whether healthcare systems can accommodate the growing demands of dementia research even as diagnostic technologies improve.[20]

Distance, transport, and the practical burden of participation

The practical realities of participating in a clinical trial can also be surprisingly daunting. Although researchers often focus on recruitment strategies and awareness campaigns, many participants face a more basic question: how do I physically get there? Dr Carragher points to geography as one of the most persistent barriers. "Big research centres are relatively few and far between. They're generally based in the big hospitals in the cities, in the big clinical academic centres." The challenge is compounded by the nature of dementia itself. Many participants require a family member or study partner to accompany them. Taking part may therefore involve coordinating the schedules of two people rather than one. "If you're going to see somebody on the rural part or on the coast in Kent [in southeast England], it's a long way to go up to a special centre in central London to do that," Dr Carragher says. "We know that people with dementia often need support. So have you got a really good study partner to go up and do that?"

For Dr Cohen, the solution is obvious. "We advocate pretty hard for sponsors of trials to cover transportation costs, and for the most part we're successful in covering that," she says. "Participants appreciate that and are willing to travel the

19 https://www.alzint.org/u/World-Alzheimer-Report-2024.pdf
20 https://iris.who.int/handle/10665/344701

distance, and we have many instances where the cost is covered by a manufacturer, allowing people to go through a long trial of 18 months or more involving frequent visits."

The benefits extend beyond convenience. Covering travel costs broadens participation and helps ensure studies recruit from a wider range of socioeconomic backgrounds. Without such support, exclusion can happen almost by accident. Carmel Geoghegan learned this firsthand when she volunteered as a participant in a dementia prevention study in Ireland. "A day or two before, they wanted me in Beaumont Hospital in Dublin at 8 am to do a lumbar puncture," the 64-year-old recalls. Living in Connemara, more than 170 miles away, she faced a logistical dilemma. "I asked them to put me up overnight, but they came back and said no as they didn't have the budget. But I said 'You can't have a clinical trial without a budget.' So they decided not to take me and only use people around Dublin who could use public transport to get there."

Geoghegan's advocacy work stems from becoming the primary carer for her late mum Angela in January 2011 after Angela received a "very late" diagnosis of vascular dementia. "Mum passed away in 2014, over-medicated, no support, and no rehabilitation. It was just seen as all part of the ageing process. There was no vision around the support needed for fit, able persons who receive a diagnosis, who can still contribute to their community but are not valued."

Geoghegan subsequently founded Dementia Ireland Empowering Communities[21], a social enterprise. Through this initiative, she facilitates workshops, bringing communities together to discuss how they can build a more inclusive society. But her own experience illustrates how recruitment barriers are often hidden in plain sight. A trial may appear open to all eligible participants, yet practical realities effectively restrict access to those who live nearby. Geoghegan says: "I survived cancer in 2019, and the difference in treatment from the point of diagnosis is chalk and cheese. We need to reach these standards around dementia."

For researchers seeking more representative study populations, language and culture pose additional challenges. Historically, ethnic minority communities have been underrepresented in dementia research despite evidence suggesting that some groups experience higher rates of dementia or face greater barriers to diagnosis and care.[22] The reasons are complex. Language differences can make recruitment materials inaccessible. Historical injustices can foster mistrust, as Jeff Pohlig, who operates three clinical research centres in the United States, points out. "There's still a level of mistrust in medicine and in a clinical trial, specifically because of famous atrocities like Tuskegee[23] where black people were not treated ethically, were treated horribly, where known cures were withheld. And even though many of those terrible actions were quite some time ago, that memory doesn't fade quickly. When you have parents or grandparents that lived through that, there's still a level of distrust and that takes longer to rebuild."

Cultural attitudes towards ageing, illness, and medical research may also influence willingness to participate. Dr Carragher acknowledges that trust remains an important issue. "I think for some communities there is still mistrust, not just in dementia, but more broadly."

Overcoming that mistrust requires more than translating a participant information sheet. Pohlig has built language accessibility into his recruitment model. "About a third of the population in Orlando speaks Spanish, so at our Orlando location, 100 percent of our patient-facing staff are bilingual in both English and Spanish," he says. The impact has been immediate. "Almost 40 percent of our screens are conducted in Spanish at the Orlando location. So we're doing a good job in terms of inclusivity and getting a good representation of the community that we work within in that regard."

Achieving that level of representation, however, comes with trade-offs. "It requires me to pass on every highly qualified applicant for our clinical roles who would be great, but they simply aren't fluent in Spanish," Pohlig says. "And so it slows down our hiring and makes it harder. It requires some intention and some commitment. And those many times when my business partner and I look at this, and we've said: 'Are we really going to pass on this person? How committed are we to being sure 100 percent of our staff can speak the language?' But we've stuck to it."

Are trials becoming too selective?

Pohlig's experience highlights an increasingly recognised reality within clinical research: diversity rarely emerges naturally. It requires deliberate investment, targeted recruitment strategies, and a willingness to redesign systems around the needs of communities rather than institutions. While researchers work to broaden participation, some argue that the design of trials themselves may be narrowing the pool of eligible volunteers. As Alzheimer's research has become more sophisticated, inclusion and exclusion criteria have become increasingly detailed.[24] Participants may be excluded because of cardiovascular disease, obesity, diabetes, high blood pressure, or other common health conditions.

21 https://dementiaireland.com
22 https://www.nia.nih.gov/2021-2022-alzheimers-disease-related-dementias-scientific-advances/improving-diversity-alzheimers
23 https://www.britannica.com/event/Tuskegee-syphilis-study
24 https://schaeffer.usc.edu/wp-content/uploads/2024/10/Key-Barriers-to-Clinical-Trials-for-Alzheimers-Disease.pdf

Jim Taylor, president and CEO of Voices of Alzheimer's, a patient advocacy organisation, worries that the pendulum may have swung too far. Asked if the design of clinical trials needs to change, he tells ADI: "Yes and no. The FDA [US regulator] is continuing to make it more and more specific who can and cannot be in the clinical trial."

Taylor's beliefs are rooted in personal experience. Following his wife Geri's diagnosis with Alzheimer's disease in 2012, he stepped up as both her primary care partner and a vocal champion for patient rights. Although he understands the need for scientific rigour, Taylor believes some studies are excluding people who would otherwise be appropriate candidates. "I'd like to see them loosen the criteria a little bit. It's critical we get the right candidates into the trial, but sometimes they are overly restrictive and rule out people who might be appropriate for the trial."

The irony, of course, is that many of the conditions that exclude people from studies are common among the very populations most affected by dementia. "So it becomes harder for those running the trial sites to get people who match the FDA criteria," Taylor adds.

Prof Jeff Cummings tells ADI that the current screening fail rates mean an astounding number of people would need to volunteer to get enough participants to support recruitment needs for existing clinical trials. "Given the usual screen fail rates (at least 70 percent), a reasonable figure is that will take 350,000 screens to produce 55,000 trial participants," he says. "This is a truly enormous number and is one area where improvements can be made. For example, if blood tests (p-tau 217) are obtained early, there would be many negative blood tests, but the rest of the screening process would be much higher yield."

Dr Cohen agrees that eligibility criteria have become increasingly complex as Alzheimer's trials have become more biologically targeted. However, she argues that the screening process still benefits participants, even when they ultimately prove ineligible. "People gain a lot of information," she says. "They may gain genetic information, biomarker information, and that is helpful. Knowledge is empowering, even if the trial doesn't end up being the right fit for them. What a great thing to find out you don't have amyloid brain changes. Alzheimer's is off the table. It doesn't mean your symptoms aren't there, but it means maybe we need to look for another cause."

Recruitment is, of course, only half the battle. Retention can be just as difficult. Alzheimer's trials often last 18 months or longer and may require repeated scans, blood tests, cognitive assessments, and clinical visits.[25] Participants must remain engaged while navigating a progressive condition that can itself undermine adherence. The emergence of anti-amyloid therapies has added another layer of complexity. Concerns about side effects, particularly amyloid-related imaging abnormalities (ARIA), can deter participation or lead to withdrawal. Researchers increasingly recognise that trial design must account for these realities. Home visits, remote assessments, telemedicine consultations, and decentralised trial models are all being explored to reduce participant burden. The challenge is particularly acute because every participant lost during a trial represents not only a personal decision but also a scientific setback.

Yet these challenges should not obscure the remarkable commitment shown by many participants and their families. Dr Cohen believes researchers sometimes underestimate both the willingness of people affected by Alzheimer's disease to accept the demands of clinical trials and the importance of the relationships that sustain their participation. "I'm impressed by the motivation of many of our participants," she says. "They will not only accept the burden of clinical trials, frequent visits, but also enrol in studies that maybe require extra PET scans, MRI scans, spinal taps, so we don't shy away from offering people what's available. Ultimately, it's up to the patient and the family to decide what makes sense for them."

While welcoming the growing use of decentralised trial models and telemedicine, Dr Cohen believes personal contact remains invaluable. "There is a shift towards decentralisation," she says, "so some of the visits can be administered via the phone or telemedicine. I think there's still a feeling that face-to-face visits add a lot of value because the relationship you build with the participants really stands you in good stead to get people through the burden of a long trial."

Dr Cohen's experience suggests that, given the opportunity, appropriate support and strong relationships with research teams, many people are willing to make considerable commitments in order to contribute to dementia research.

What becomes clear when speaking to researchers, clinicians, and participants is that recruitment is ultimately about far more than numbers. The challenge is not simply persuading people to join studies but creating systems that make participation genuinely possible. Earlier diagnosis, better public awareness, stronger referral pathways, more flexible trial designs, transportation support, culturally sensitive recruitment strategies, and investment in specialist workforces all form part of the solution. None alone will be sufficient.

The next decade is likely to bring an unprecedented expansion in dementia research, driven by new diagnostic technologies and a growing pipeline of therapies. Whether that scientific progress translates into meaningful advances for patients will depend, in large part, on the field's ability to overcome the

25 https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/alz.71250

barriers that continue to keep so many potential participants on the outside looking in. For all the excitement surrounding the latest treatments and biomarkers, the future of dementia research may ultimately hinge on a far simpler question: can the people who need these innovations the most actually gain access to the studies that will test them?

Equity and representation: who gets included in dementia research – and who gets left behind?

For much of the modern history of dementia research, a paradox has sat at the heart of the field. Alzheimer's disease is a global condition, affecting people of every ethnicity, income level, and geography, yet the evidence base used to understand it has often been built on a remarkably narrow slice of humanity. The consequences reach far beyond questions of fairness. Clinical trials do not simply determine whether a drug works. They shape who will benefit from future treatments, whose symptoms are recognised, whose biology is understood, and whose experiences become embedded within clinical practice. When certain populations are consistently absent from research, the result is not merely a lack of representation but a distortion of scientific knowledge itself.

That concern has become increasingly urgent as Alzheimer's disease research enters a new era. Disease-modifying therapies are beginning to reach patients. Blood-based biomarkers promise earlier diagnosis. Precision medicine approaches are becoming a realistic prospect rather than a distant aspiration. Yet these advances have also exposed a troubling reality: much of the science underpinning this progress has been derived from a population that looks very different from the global community now living with dementia. Women account for nearly two-thirds of people living with Alzheimer's disease worldwide.[26] Yet when it comes to clinical trials, they are underrepresented relative to their disease burden, and sex-disaggregated safety and efficacy outcomes are almost never reported.[27]

Many populations remain underrepresented in dementia clinical trials despite bearing a disproportionate burden of disease or facing significant barriers to diagnosis and care. This includes many racial and ethnic groups, as well as people living in LMICs, where almost 60 percent of people with dementia now reside, according to the World Health Organization.[28] Their limited representation raises concerns about whether trial findings can be applied confidently across the world's diverse populations.

For years, diversity was often framed as an equity issue. Increasingly, researchers argue it is a matter of scientific validity. Among those making that case most forcefully is Professor Sid O'Bryant of the University of North Texas Health Science Center, whose Health and Aging Brain Study among Latino Americans (HABS-HD) has become the largest Alzheimer's biomarker study ever conducted in underrepresented populations. The study emerged from a problem hidden within one of the field's greatest scientific achievements.

In 2018, researchers introduced the ATN framework, a biological model of Alzheimer's disease built around three core features: amyloid deposition, tau pathology, and neurodegeneration.[29] The framework transformed Alzheimer's research by moving diagnosis away from symptoms alone and towards measurable biological markers that could be detected through imaging, cerebrospinal fluid analysis, and, increasingly, blood tests.[30] For the first time, researchers could identify Alzheimer's pathology during life rather than waiting until autopsy. "The framework has revolutionised the field," Dr O'Bryant tells ADI. "It's really been responsible for helping advance new drugs to patients. The downside is that over approximately 90 percent of all people enrolled into research that led to the advancement of those biomarkers and the advancement of the framework were non-Hispanic white."

For decades, the overwhelming majority of participants in Alzheimer's biomarker research in the United States have been non-Hispanic white, highly educated, and medically screened to exclude many common coexisting conditions.[31] "What we know from cancer, heart disease, diabetes, and other spaces is that where you come from matters," Dr O'Bryant says.

Environmental exposures, educational experiences, socioeconomic circumstances, genetics, vascular health, and chronic disease all influence how illness develops and how biological markers behave.[32] Yet much of Alzheimer's science has historically treated its findings as universally applicable. The central question behind HABS-HD was therefore deceptively simple: do the biomarkers that define Alzheimer's disease behave in the same way across different populations? The answer appears to be no. Today, the study has enrolled more than 4,500 participants, including approximately 1,500 Hispanic Americans, 1,500 Black Americans, and 1,500 non-Hispanic white participants. Researchers are examining biomarkers alongside medical conditions, environmental exposures, and sociocultural influences. "I don't think you can study biology

26 https://www.alzint.org/u/Women-and-Dementia.pdf
27 https://neurologyopen.bmj.com/content/4/2/e000261
28 https://www.alzint.org/about/dementia-facts-figures/
29 https://pmc.ncbi.nlm.nih.gov/articles/PMC5958625/
30 https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf
31 https://www.nature.com/articles/s41582-024-00989-1
32 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781626

in the absence of environmental and sociocultural context," Dr O'Bryant says. "And you can't study environmental and sociocultural context in the absence of biology."

The team's findings have challenged some of the assumptions underpinning contemporary Alzheimer's research. Among non-Hispanic white participants, the ATN framework performs largely as expected. Amyloid accumulates, tau pathology follows, and cognitive decline accelerates. But among Hispanic and Black populations, the sequence appears less straightforward, Dr O'Bryant says.

One particularly striking finding concerns neurodegeneration. Whereas tau pathology is often considered the key driver of cognitive decline once amyloid is present, Dr O'Bryant's team has found evidence suggesting neurodegeneration may play a more important role among Hispanic populations. "We found that when amyloid is present and tau is not, the primary driver among Hispanics is neurodegeneration."

The implications extend beyond academic debate. If biomarkers behave differently across populations, then diagnostic tools, eligibility criteria, and even treatment decisions may need to be adapted accordingly. The same pattern emerges when researchers examine common coexisting conditions. Diabetes has long been recognised as a significant risk factor for dementia. Yet Dr O'Bryant's work suggests the relationship may be particularly important among Hispanic populations, who often develop diabetes at younger ages and live with the condition for longer periods. Those findings point towards a future in which precision medicine for Alzheimer's disease may require a far more nuanced understanding of population differences than currently exists. They also expose the risks of relying on evidence derived from narrowly representative populations.

Jennifer Manly, professor of neuropsychology at Columbia University in the United States, has spent much of her career highlighting similar concerns from a different perspective. Her research has demonstrated how educational experiences, structural inequalities, and cultural factors can profoundly influence cognitive testing and dementia diagnosis. In a landmark study published in *JAMA Network Open*, Prof Manly and colleagues argued that many observed differences in dementia outcomes between ethnicities reflect the cumulative effects of social determinants rather than innate biological differences.[33] More recently, she has emphasised that brain health research must account for the broader social environments in which people live, work, and age.

> **'I don't think you can study biology in the absence of environmental and sociocultural context. And you can't study environmental and sociocultural context in the absence of biology.'**
>
> *Professor Sid O'Bryant*

Together, the work of Prof Manly and Dr O'Bryant challenges a longstanding assumption within Alzheimer's research: that findings generated in one population can automatically be applied to all others. That challenge becomes particularly important as new therapies reach clinical practice. Dr O'Bryant worries that scientific progress may be outpacing efforts to ensure representative participation. "If progress stalls on representation, that really makes me nervous," he says. "We're going to put therapies out there, and right now, access is already a major barrier. If those barriers are overcome without overcoming representation in trials, we're going to have drugs hitting the market in complete and total unknown of how they're going to impact diverse populations."

The consequences could include differences in efficacy, unexpected side effects, or variations in risk. One area of concern involves APOE4, the strongest known genetic risk factor for Alzheimer's disease and an important predictor of amyloid-related imaging abnormalities (ARIA), the potentially serious side effect associated with anti-amyloid therapies.[34] "We know APOE4 has a strong impact on some of the ARIA risk," Dr O'Bryant says. "Well, APOE4 by itself varies drastically among populations." Without representative trial populations, researchers may struggle to predict how therapies will perform in the real world.

The problem is not that researchers are unaware of these challenges. On the contrary, diversity and inclusion have become major priorities across much of the field. "There has been a massive focus on diversity and inclusion in recent years," says Dr Fiona Carragher. "It was a core driving principle in the way the NHS blood biomarker challenge was set up.[35] [The trial] cannot just work in white middle-class people who are near the centres in Oxford and London. If we do that, we'd be creating even more injustice and variation."

Yet recognising the problem and solving it are not the same thing. Cath Mummery, professor of neurology at University College London (UCL), believes one reason progress has been

33 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781626
34 https://pmc.ncbi.nlm.nih.gov/articles/PMC13099593/
35 https://www.alzheimers.org.uk/what-we-do/researchers/news/blood-biomarker-tests

slow is that researchers often treat diversity as a recruitment problem rather than a relationship problem. "Patient diversity and inclusivity is a long game," she says. "People try to do it in a trial-specific way which just doesn't work." Instead, she argues, researchers must invest in long-term engagement. "As someone said to me recently: 'Listen rather than recruit.' You're not there to recruit. You're there to listen to people's concerns and gradually build familiarity."

The shift she describes mirrors lessons learned in cancer and cardiovascular research, fields that have become substantially more representative over recent decades. Dr O'Bryant believes Alzheimer's research has been too dependent on specialist clinics. "If we sit back and continue to recruit out of these dementia specialist clinics, those clinics don't see the vast majority of patients, and they almost never see underserved communities," he says.

His own studies abandoned that model years ago. "I don't even recruit from specialist clinics anymore and haven't in over a decade." Instead, his team works directly within communities, partnering with local organisations, faith groups, and primary care providers. "We have recruited over 20,000 people across different studies from underserved communities. It boils down to community engagement. We have to build relationships with the community."

While many Alzheimer's studies struggle to recruit diverse participants, Dr O'Bryant's programmes have achieved representation levels rarely seen elsewhere in the field. The lesson, he argues, is simple. "We try to never exclude. We try to get everyone involved because our research needs to be applicable to the whole community, not just one segment."

A different model for building representative datasets

One initiative offers a striking example of what can be achieved when improving representation is built into the design of the research itself. The Bio-Hermes studies, led by the Global Alzheimer's Platform (GAP) Foundation,[36] are not trials of new drugs. Instead, they are large observational studies designed to generate the biomarker data needed to make future dementia trials faster, more efficient, and more representative.

The model is deliberately collaborative. Pharmaceutical companies and other industry partners provide funding and contribute biomarker technologies. GAP coordinates the studies and the resulting data are hosted on the cloud-based Alzheimer's Disease Data Initiative platform. The partners commit to sharing the resulting dataset, giving participating companies 18 months after database lock to interrogate the data before the full database is made available to the wider industry and research community. The approach reflects a practical reality of modern drug development: pharmaceutical companies need these data, but their primary focus is on running therapeutic trials. By collectively funding the infrastructure required to generate them, they can share the cost without each having to conduct a separate study.

Bio-Hermes-001 produced more than 80,000 blood, digital, imaging, cognitive, and clinical measurements and deliberately recruited a diverse cohort. Around a quarter of participants came from traditionally understudied racial and ethnic groups. The dataset was subsequently opened to researchers through the Global Alzheimer's Platform's Scottish Challenge, which gave early-career researchers in the UK an opportunity to propose projects using the data during the initial access period. More than 40 research teams took part, with more than 20 resulting publications to date. The dataset was eventually made publicly available for free in 2025.

Bio-Hermes-002 builds on this model by combining amyloid and tau PET imaging with MRI, digital assessments, and a broad range of blood-based biomarkers, including CSF samples, and adding a longitudinal component. The MRI component will also allow researchers to examine vascular disease alongside Alzheimer's pathology. The study is being conducted across 28 sites in the US and UK and has again set a target of at least 25 percent participation from traditionally underrepresented communities – African Americans, Hispanics, Latinos – making the studies the richest biomarker data set globally. The study has completed enrolment with 27 percent of participants from underrepresented populations.

The significance extends beyond the individual studies. By deliberately recruiting populations that have historically been underrepresented in biomarker research, Bio-Hermes is helping to build the evidence base needed to determine whether emerging diagnostic technologies work equally well across different communities. It also demonstrates how industry, academia, and non-profit organisations can share the cost and infrastructure of generating research data that no single organisation might have an incentive or capacity to produce alone. In a field increasingly dependent on biomarkers to identify who is eligible for clinical trials, that may prove just as important as developing the therapies themselves.

Policy, regulation and the future of diversity

Despite growing recognition of these issues, structural tensions remain. Commercial trials operate under significant pressure to recruit participants rapidly[37] because delays in enrolment can

36 https://globalalzplatform.org/biohermesstudy/
37 https://pubmed.ncbi.nlm.nih.gov/38568347/

extend development timelines and substantially increase costs. Prof Mummery says: "There's a tension in this which we need to get past. You're trying to recruit as quickly as possible, and at the same time, you're trying to reach a diversity target." The challenge is compounded by the absence of strong regulatory requirements. Jeff Pohlig believes regulators should take a firmer stance. "There's no regulatory requirement on sponsors to ensure that a percentage of the sample is diverse," he says. "I think it would be great if the FDA said: here's the diversity of the United States, and your sample must match."

Recent developments suggest the opposite trend may be emerging. Earlier this year, the FDA removed guidance related to Diversity Action Plans following policy changes under the Trump administration.[38] The move prompted concern among researchers that efforts to improve representation could lose momentum just as the field was beginning to make meaningful progress. For Phyllis Ferrell, director of healthcare system readiness at the Davos Alzheimer's Collaborative, the issue has become increasingly frustrating. "There are a lot of papers [on improving representation]. I'm tired of papers. I want to see action. We can have more meetings, we can have more people sitting in our room, talking around a table. But at the end of the day, we've got to have a good evidence base on what works and doesn't work. Is it a simple scenario as a regulator saying, I'll allow this trial, provided you have X percent of African Americans, X percent Hispanics? Yeah, they did that. Diversity action plans were just pulled out by this [Trump] administration.[39] So that's a big setback."

The diversity debate often focuses on race and ethnicity within wealthy countries. Yet the largest disparities may be geographic. Most people living with dementia now reside in LMICs[40]. Yet most clinical trial infrastructure remains concentrated in North America, Europe, Australia, and parts of East Asia. Many countries lack access to PET scanners, specialist memory clinics, and advanced biomarker testing. Some cannot currently participate in disease-modifying therapy trials at all. Dr O'Bryant believes wealthier nations have a responsibility to help address these disparities. "The onus should be on us because we can build systems and structures that will facilitate those trials in other countries," he says, citing the Philippines, large parts of Africa, and regions of Latin America. "They all have wonderful scientists" Dr O'Bryant says. "They just lack the resources."

One solution may lie in blood-based biomarkers, which are substantially cheaper and easier to deploy than PET imaging. Yet even here, representation matters. Dr O'Bryant says: "Our data clearly show that if you apply the blood test broadly across populations, they're inaccurate. Plain and simple. They don't work." Before biomarkers can become global tools, researchers must ensure they perform accurately across different populations. That will require collaboration between governments, academia, industry, and communities themselves. For Dr O'Bryant, improving representation ultimately requires rethinking how the field approaches clinical research altogether. The first priority, he argues, is moving beyond specialist clinics. "Reaching 500 specialist clinics globally is very different from reaching 100,000 primary care clinics globally."

The second is changing the relationship between researchers and participants. Dr O'Bryant says: "I've recruited over 20,000 people [into clinical trials], and the number one reason people join and stay is because of the give-back." Too often, he argues, participants undergo extensive testing but receive little meaningful feedback. "When people come into my studies, they get MRIs back, PET scans back, clinical labs back. We give things back to the community." That philosophy aligns closely with recommendations from recent international calls for greater participant involvement in dementia research, which argue that communities should be treated as partners rather than passive subjects.[41]

Finally, Dr O'Bryant believes governments and health systems need to invest far more heavily in public education. "We need a true community approach across the globe that really educates people on an understandable level about what Alzheimer's disease is." The responsibility, he argues, should not rest solely with pharmaceutical companies. "Meaningful educational approaches will lead to meaningful trial-ready cohorts."

The future of Alzheimer's research will be shaped by extraordinary scientific advances. New biomarkers, diagnostics, and therapies are arriving at a pace that would have seemed unimaginable only a decade ago. Yet the success of those innovations may depend on a much older challenge: ensuring that the science reflects the diversity of the people it aims to serve. Because if representation remains an afterthought, the risk is not simply that some communities will be left behind. It is that the evidence base underpinning the entire field will remain incomplete. And in an era increasingly defined by precision medicine, incomplete evidence may prove one of the greatest inequities of all.

38 https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-drops-web-pages-improving-clinical-trial-diversity-2025-01-24/
39 https://kffhealthnews.org/morning-breakout/clinical-trial-diversity-caught-in-crossfire-of-trumps-ban-on-dei/
40 https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/
41 https://www.alz.org/news/2024/public-participant-involvement-dementia-research

CASE STUDY

'The best hope': Life during – and after – a clinical trial

Julie Stauffer Moore was diagnosed with early-onset Alzheimer's disease two years ago at the age of 53. Her grandmother "probably" had dementia, while both her parents died from Alzheimer's, she tells ADI. "My parents were medical professionals: dad was a doctor, mum was a nurse. So I have a heavy emphasis in belief in science and probably more faith in the medical community than most."

Julie has two copies of the APOE4 gene, one from each parent, which makes people like her 12 to 15 times more likely to develop Alzheimer's disease than those with the common APOE3 gene. The genes act by accelerating amyloid-beta plaque buildup, promoting tau tangles, causing lipid metabolism dysfunction in brain cells, and reducing the age of onset, often leading to symptoms in the mid-to-late sixties, but sometimes even younger.

Following her diagnosis, Julie wanted to take part in a clinical trial, primarily to advance the science and make things better for her daughter, who has one copy of the APOE4 gene. "The only way that's going to improve is through science in terms of the actual physiology that you're dealing with."

"We can deal with things for social stigma and social change, and that needs to happen too," Julie, now 55, says. "But a clinical trial is the best hope of finding something that's going to make this better. Whether it slows the progression of the disease, whether it makes it less painful and scary, or whether it makes it go away."

However, Julie and her husband Ron were surprised that neither their GP nor Julie's neurologist referred them towards a clinical trial following her diagnosis. "Our system is pretty darn broken on that," Julie adds. "I think it's because the doctors either don't know that much about any trials, or it's not part of their treatment model, so it's not a priority for them.[42]

"Ron, 59, was sent on a mission to find trials suitable for her. One problem that affected their choice was the fact that Julie has a secondary health condition that makes infusions a no-go for her. "I have responded poorly when donating blood in the past – it has caused me to have a seizure – so having a needle in my arm for an hour at a time is a bad idea," Julie says.

Luckily, a trial involving an oral treatment was open at UCI MIND, a research institute in nearby Irvine, California. The location made it "completely manageable" for her to attend in person and participate in the trial for an Alzheimer's drug called CT1812.

"Our running joke is me playing [Tchaikovsky's] *1812 Overture* to help me remember it," says Julie, who worked in finance and as a substitute teacher in special education over the course of her career.

The drug, also known as zervimesine, was being developed to address one of the underlying problems in Alzheimer's disease, which involves toxic protein clumps called amyloid-beta that attach to brain cells and interfere with communication between them.[43] Instead of trying to remove these clumps entirely, CT1812 works more like a dislodging agent, helping knock the harmful proteins off brain cells so normal signalling can resume – similar to clearing debris from a lock so it can function properly again.

CT1812 is taken as a once-daily pill, which makes it more convenient compared to some newer Alzheimer's treatments that require intravenous infusions. Importantly, it is able to cross into the brain – a key challenge for many drugs – by acting on the sigma-2 receptor, which plays a role in how these toxic proteins bind to neurons. By targeting this mechanism, the drug aims to prevent or reverse damage to brain cell connections.

Despite being within 10 miles of where the couple lives in Orange County, California, they still had to "do a lot of digging" to find the trial due to the difficulties of navigating the clinical trial landscape in the United States on their own.

"CT1812 was pretty much the only trial that worked for us; that combination of being local and an oral drug worked better for Julie. There wasn't much else out there to look at," according to Ron, whose background as an attorney helped the couple navigate the bureaucratic landscape of 40-odd page application forms containing complex legal and scientific information.

Julie adds: "I don't know what I would have done without Ron. My first thought was: 'Oh my God, the paperwork is overwhelming. I don't know the answers to half of these questions.'"

42 https://www.thecardiologyadvisor.com/features/clinical-trial-enrollment-patient-access-barriers/
43 https://clinicaltrials.gov/study/NCT03493282

The UCI Mind research team held a two-hour meeting with the couple to obtain informed consent. A nurse practitioner reviewed documents page by page to ensure both Julie and Ron understood exactly what they were getting involved in, given the potential risks.

Ron says: "Any time you're taking medication that involves the brain, there are potential risks of brain bleeds and other problems. We went through all of those, and you sign off on it. In addition, we had to give supplemental consent in case things occurred during the course of the study so that they were also covered for those eventualities."

Next came an initial screening process that involved baseline cognitive assessments along with imaging studies – MRI and a PET scan – to make sure Julie was at the stage of progression of the form of dementia the researchers were targeting the drug at.

"It was about six or eight weeks to get the imaging studies done, the cognitive assessment done, the implied consent done before Julie actually started on the drug," Ron says. "I was willing to do everything for her or with her in terms of getting her to all the appointments and making sure she took the drugs daily."

Asked if they felt they were given enough information to give informed consent, Ron says: "Oh yeah. We had a really good idea what was going to happen. It wasn't all that complicated a study: you take the drugs, you come in monthly for blood tests to make sure that this is not damaging your liver. And then quarterly, there was a half-day session where they would do all the different types of testing she was going to undertake. I would fill out a couple of questionnaires and read a book."

Julie says she felt "hopeful" as the trial began. "You are hoping that this is a drug that's going to do something positive, and it seemed to. We wanted to try something and be able to advance the science."

Like all randomised clinical trials, Julie did not know whether she was being given the experimental drug or a placebo, although she suspects the former. "I took two pills once a day. And I believe that I was on the meds, because the first week I got hit with some side effects that were positive instead of negative – I slept like the dead! – so I was thrilled," Julie says.

"I also had issues attributed to menopause that got better. So my sneaking suspicion was that I was on the medication during those 18 months. And both of those hit pretty hard within the first week, and then they both eased back. I still slept better, and my gut was still better, but not as good. And that's also normal."

Julie Stauffer Moore gets a check-up in Irvine, California in July 2026. (Photo by Jason Sullivan)

"Everybody was amazingly supportive and amazingly kind. Everything was professional. The institute ran things in a timely manner. The place was clean. They were courteous. They were respectful. I've had an amazingly positive experience."

Julie's experience was such that the only "downside" came when the trial ended, as she would have liked to have stayed on it for longer. "I tried to see if they would have open access afterwards, so trial participants could continue to access the drug, but at this point they haven't said they will do that."

Ron adds: "It starts to raise an ethical question if you give somebody an experimental drug that's really working for them and then take it away. That is what we signed up for. We were aware that it could happen, but we were hoping that if she was doing really well on it, there'd be a chance of staying on it."

"They're currently looking at legislation here in the US, where one of the conditions of participating in a clinical trial like this is that trial sites might be required to keep people on the drug if they want to stay on the drug after the study is over, if they're seeing a benefit."

Julie also believes dementia remains a taboo issue among medics. "A lot of physicians will suspect or know that you have dementia and not want to tell you because of the stigma associated with the disease… Through other dementia campaign groups, I often heard people being told, *'You have dementia, so you need to get your affairs in order.'* The message was that you had a much shorter time to live than is often the reality."

"I understand why professionals want to encourage people to plan ahead, because many are reluctant to do it. But presenting the worst-case scenario isn't empathetic, and it doesn't provide the support or resources people actually need," Julie adds. "After my diagnosis, I found the Dementia Action Alliance,[44] a

44 https://daanow.org

nonprofit run largely by people living with dementia. Meeting people living with Parkinson's disease, dementia, Lewy body dementia, and frontotemporal dementia gave me hope.

"My diagnosis was accurate, but the prognosis wasn't. I'm speaking to you more than two years after my diagnosis, and I know people who have been living with dementia for 20 years. That's a long way from being told you have six months of capacity."

"Telling people they have only a limited lifespan or capacity can be damaging in two ways," she adds. "It's emotionally devastating, but it also affects financial planning. If you believe you'll only be alive for six months or a year, you'll make very different decisions than if you may live for another 20 years. You could face decades without an income while also dealing with rising medical costs, and that's one of the main reasons people in the US end up bankrupt."

So far, early and mid-stage trials have shown that CT1812 appears generally safe and well tolerated, and there are early signs that it may slow the decline in memory and thinking capacities in some patients, with certain subgroups showing noticeably slower progression than expected. However, these findings are still preliminary, meaning they suggest potential benefit but do not yet prove that the drug works.[45]

At present, CT1812 remains an experimental treatment and has not been approved for general use, as it is still in Phase 2, where effectiveness and safety are being studied in larger groups of people. Further Phase 3 trials are planned to confirm whether the drug truly provides meaningful benefits.

As with many Alzheimer's treatments, there are limitations and uncertainties, including the possibility that early, promising results may not hold up in larger studies, or that the overall effects observed so far are modest or limited to certain patient groups. In simple terms, CT1812 is a promising but still unproven daily pill that aims to protect brain cells by removing harmful proteins, with the hope that it could slow the progression of Alzheimer's disease, although more research is needed before it can be considered a reliable treatment. Julie remains happy to have played her part in the trial.

For Julie, having her husband Ron (left) by her side made navigating the clinical trial experience much easier. (Photo by Jason Sullivan)

Ron adds: "I think the thing to keep in mind is that the people conducting the clinical trials really have your best interest at heart. They want to come up with something that's going to make a difference and so they're not really trying to exploit you other than they need human subjects to test the drugs on to make sure they actually do what we hope they do."

"But you can quit at any time. They tell you over and over again that it's entirely voluntary and if you feel like it's no longer for you, if you're not getting a benefit, or if it's uncomfortable and you don't like it, you can leave. That's important information. So it's not like you're signing your life away. You're volunteering to participate for as long as you feel able and benefit."

"There are some risks that go with that," Julie points out before her husband adds: "Yeah, but there are risks crossing the street, too."

45 https://pmc.ncbi.nlm.nih.gov/articles/PMC12715698/

Chapter 5:

Safety, regulation, and ethics in clinical trials

A porter carries a large woven basket on his head while working at the historic Mullick Ghat Flower Market in Kolkata, West Bengal, India, in March 2026. (Photo by Domenico Pugliese)

Summary

The emergence of disease-modifying therapies for Alzheimer's disease has transformed the global clinical trial landscape, bringing renewed hope but also unprecedented regulatory, safety, and ethical challenges. After decades of repeated failure, anti-amyloid therapies such as lecanemab and donanemab have demonstrated that it is possible to alter the biology of Alzheimer's disease and slow clinical decline. Yet these advances have exposed difficult questions about how regulators, clinicians, patients, and carers should balance benefit against risk.

This chapter examines how major regulatory authorities approach Alzheimer's clinical trials and drug approval, highlighting global differences in regulatory standards, trial speed, costs, and evidentiary requirements. While regulatory systems differ, all face the same central challenge: enabling innovation while protecting vulnerable patients.

Safety concerns now sit at the heart of Alzheimer's drug development. Amyloid-related imaging abnormalities (ARIA), serious adverse events, and treatment-related deaths have intensified scrutiny of anti-amyloid therapies, particularly among patients with high-risk APOE genotypes. These risks raise complex ethical questions about acceptable harm, patient choice and autonomy, and informed consent in a health condition marked by progressive cognitive decline.

The chapter also explores broader ethical issues, including ageism in trial design, the underrepresentation of older adults with multiple comorbidities, and the growing importance of trust in clinical research. As biomarkers, genetic testing, and preventive therapies reshape dementia care, regulators will increasingly be asked not only to assess drugs, but to navigate profound questions about risk, fairness, and access to hope – questions that have been asked when other conditions have experienced their pivotal moment of new treatments, including cancer and HIV/AIDS.

The regulatory landscape

Every medicine that reaches a patient has first passed through one of the most rigorous evaluation processes in healthcare. Behind every new treatment is a network of regulatory bodies responsible for answering a fundamental question: Does the potential benefit of this intervention outweigh the risks involved?

Regulators are independent authorities established to protect public health by overseeing the development, testing, and approval of medicines, vaccines, and medical technologies. Their role is not to prevent innovation, but to ensure that new treatments are supported by robust scientific evidence before they become widely available. In clinical trials, regulators assess whether a potential treatment is sufficiently safe and scientifically justified to be tested in humans, whether the trial has been designed appropriately, and whether participants are adequately protected.

Before a clinical trial begins, researchers must submit detailed evidence about the experimental treatment, including laboratory studies, previous research findings, manufacturing standards, and proposed trial protocols. Regulators review whether the potential benefits justify exposing volunteers to possible risks. They examine how participants will be recruited, how informed consent will be obtained, and how safety will be monitored throughout the study.

This process continues throughout the life of a clinical trial. Researchers must report adverse events, regulators can request changes to trial protocols, and studies may be paused or stopped if safety concerns emerge. If a treatment successfully completes clinical trials, regulators conduct a further assessment of the evidence before deciding whether to approve it for use in the wider population.

Around the world, different regulatory authorities oversee this process, reflecting the diverse healthcare systems and legal frameworks of individual countries and regions. Among the most influential are the US Food and Drug Administration (FDA); the European Medicines Agency (EMA), which coordinates medicines regulation across the European Union; the UK's Medicines and Healthcare products Regulatory Agency (MHRA); and China's National Medical Products Administration (NMPA).

While their approaches can differ, their shared goal is to ensure that medical advances are delivered safely, ethically, and based on reliable evidence.

Increasingly, however, these agencies do not work in isolation. Drug development has become a global enterprise, with many pivotal clinical trials recruiting participants across multiple continents and generating evidence that is submitted simultaneously to regulators worldwide. This has encouraged closer international collaboration between regulatory authorities. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has become an increasingly important contributor to international scientific dialogue, working closely with the FDA and EMA on issues such as biomarker qualification, clinical trial methodology, and evidentiary standards for neurodegenerative diseases.[1]

Australia's Therapeutic Goods Administration (TGA) and Health Canada are similarly engaged in international regulatory collaboration through initiatives such as the Access Consortium[2] alongside the MHRA, Singapore's Health Sciences Authority, and Swissmedic. Rather than replacing national decision-making, these partnerships enable regulators to share scientific expertise, coordinate aspects of medicine reviews where appropriate, and develop more consistent approaches to emerging technologies.

As the TGA explains in its 2025–2028 Access Strategic Plan, the consortium seeks to "enhance cooperation amongst member countries to streamline procedures and improve access to safe, effective medicines,"[3] reflecting the increasingly global nature of drug development and regulation. Although each regulator ultimately reaches its own decisions, these partnerships reflect a growing recognition that many of the scientific and ethical challenges surrounding dementia therapeutics are global rather than national.

This spirit of collaboration also extends to disease-specific initiatives. As chair of the National Institute for Health and Care Research (NIHR) Dementia Translational Research Collaboration Trials Network, Professor Cath Mummery has played a leading role in bringing together regulators working in dementia through an international network that enables agencies to exchange scientific experience and discuss emerging regulatory challenges, while preserving the independence of each authority's decision-making.

The forum, which aims to make the UK a global leader in testing new dementia treatments, is creating a coordinated national network of specialist dementia trial sites, allowing studies to be delivered consistently across the UK rather than at a handful of centres. Its core objectives include accelerating trial set-up and regulatory processes, reducing delays in launching clinical studies by working closely with industry, academia, the NHS, and patient organisations to attract more commercial and investigator-led dementia trials to the UK.

As the science of Alzheimer's disease continues to evolve rapidly, these forums have become increasingly valuable in promoting dialogue on complex issues such as biomarkers, surrogate endpoints, and the assessment of disease-modifying therapies. Yet the relationship between regulation and innovation has always been complex. This tension has been particularly visible in Alzheimer's disease, where decades of scientific setbacks have created enormous pressure to accelerate the search for effective treatments. For a long time, Alzheimer's drug development has been defined by frustration. Trial after trial came to an unsuccessful end in late-stage testing, if they made it that far; billions of dollars were spent chasing biological theories that never translated into meaningful clinical improvement; and patients and families were left with the same grim reality: no treatment could meaningfully slow the course of the disease.

Against that backdrop, regulators were often cast as obstacles – bureaucratic institutions standing between desperate people and potentially life-changing therapies. However, that framing has always been too simplistic and in Alzheimer's disease it is becoming increasingly unhelpful. The modern regulator is no longer simply an official at the end of the process deciding whether a drug can be approved. Increasingly, regulators shape the science itself, influencing trial design, evidence standards, biomarkers, safety monitoring, and even the very definition of Alzheimer's disease.

This evolution reflects a much broader shift in regulatory science. In recent years, regulators have increasingly moved away from a purely reactive role – assessing evidence once clinical trials have finished – towards becoming active partners in medicines development. Scientific advice, regulatory guidance, and early engagement with researchers now help shape study design, endpoint selection, and evidence generation long before a marketing application is submitted. As the EMA's Chief Medical Officer Steffen Thirstrup and colleagues have argued, the goal is to create "a fast path from innovation to safe and effective medicines," accelerating patient access while maintaining rigorous standards of quality, safety, and efficacy.[4]

The shift is perhaps most visible at the FDA, where Alzheimer's drug regulation has increasingly moved upstream into the design of clinical trials themselves. FDA scientists now work with sponsors throughout development, advising on trial populations,

1 https://www.iconplc.com/insights/blog/2026/06/05/japans-clinical-trial-transformation-building-global-future
2 https://www.tga.gov.au/about-us/international-engagements/australia-canada-singapore-switzerland-united-kingdom-access-consortium
3 https://www.tga.gov.au/news/news-articles/access-strategic-plan-updated-2025-2028
4 https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70107

endpoints, biomarkers, and statistical approaches. The agency's updated guidance for early Alzheimer's disease reflects this evolution, recognising that regulators must help ensure studies can demonstrate not only biological activity but also clinically meaningful benefits to patients. As Teresa Buracchio, director of the FDA's Office of Neuroscience, has explained, the guidance aims to help developers navigate "diagnostic criteria and clinical staging" together with appropriate outcome measures and the potential use of surrogate endpoints.[5]

Dr Maria C. Carrillo, chief science officer and medical affairs lead at the Alzheimer's Association, believes that scientific advances such as blood-based biomarkers are already changing what regulators and trial sponsors can realistically achieve. "Adoption of blood tests for diagnosis and to ensure inclusion into clinical trials is key, and that is happening now," she tells ADI.

However, Dr Carrillo cautions that an easier diagnosis does not remove the need for sophisticated clinical infrastructure. "Some dementia clinical trials are very high risk in terms of mode of administration and require very sensitive monitoring with technology that sometimes is not available, especially in rural areas and in low- and middle-income countries. There needs to be investment and training in low- and middle-income countries before the extensive monitoring that is required would be possible."

Writing from an FDA perspective in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in 2025, Buracchio and colleagues argued that regulators must consider whether trial outcomes reflect benefits that matter to patients, and that these benefits may differ depending on how advanced the condition is and the priorities of people living with Alzheimer's disease and their caregivers.[6] This represents a significant evolution in regulatory thinking. Regulators are increasingly helping define what "working" should mean before the first participant is even enrolled.

Prof Thirstrup is particularly clear on this point. He resists the idea that regulators exist primarily to block or slow innovation. "Regulators are sometimes called gatekeepers," Prof Thirstrup tells ADI. "I don't see us as gatekeepers in the sense that we are stifling innovation and making it difficult for products to reach the market. But we are gatekeepers of public health."

"I don't see us as gatekeepers in the sense that we are stifling innovation and making it difficult for products to reach the market. But we are gatekeepers of public health."

That distinction matters because it goes to the heart of the challenge in dementia drug development. Regulators are tasked with doing two things at once that often pull in opposite directions: moving fast enough to respond to extraordinary unmet need while remaining cautious enough to protect vulnerable patients from harm.

In no field is that balance more difficult than Alzheimer's disease. Unlike oncology, where survival endpoints can often be measured within months, Alzheimer's disease unfolds slowly, sometimes over decades. Clinical effects can be subtle, and trial endpoints are notoriously difficult to interpret. Biomarkers are improving rapidly, but the relationship between biomarker change and real-world clinical benefit remains fiercely debated. The result is that regulators are not merely assessing whether a therapy works. They are being asked to judge whether the evidence being generated is meaningful enough to justify exposing patients to uncertainty and risk.

This question of "meaningful benefit" has become central to FDA thinking. In a recent regulatory perspective, Buracchio and colleagues argued that the value of an Alzheimer's therapy cannot be judged solely by changes in biomarkers or cognitive scales, but must ultimately be interpreted in the context of outcomes that matter to patients and caregivers. As disease-modifying therapies move into earlier stages of disease, defining those outcomes has become one of the most important challenges facing regulators worldwide.[7]

This challenge plays out differently across the world because there is no single global regulatory system for dementia therapeutics. Instead, developers must navigate a patchwork of agencies, each with its own institutional culture, evidentiary standards, political pressures, and practical realities.

5 https://www.fda.gov/drugs/drug-alerts-and-statements/fda-issues-guidance-regarding-drug-development-early-alzheimers-disease
6 https://pubmed.ncbi.nlm.nih.gov/40469853/
7 Ibid

How lecanemab moved through global regulators

Lecanemab has become one of the clearest examples of how different regulatory frameworks can shape access to new dementia treatments. Although the underlying clinical evidence was largely the same, regulators around the world reached their decisions at different times and, in some cases, reached different conclusions about the balance of benefits and risks.

The **US Food and Drug Administration (FDA)** granted accelerated approval in January 2023 based on lecanemab's ability to reduce amyloid plaques, a biomarker considered reasonably likely to predict clinical benefit. Following publication of the Phase 3 CLARITY AD trial, which demonstrated a statistically significant slowing of cognitive and functional decline in people with early Alzheimer's disease, the FDA converted this to traditional approval in July 2023.

The **European Medicines Agency (EMA)** adopted a more cautious approach. Its scientific committee initially recommended against approval, citing concerns that the modest clinical benefit should be weighed carefully against the risk of amyloid-related imaging abnormalities (ARIA), including brain swelling and bleeding. After the decision was re-examined using additional analyses and proposed risk-management measures, the EMA ultimately issued a positive recommendation for a more narrowly defined group of patients judged most likely to benefit with acceptable safety.

The **UK Medicines and Healthcare products Regulatory Agency (MHRA)** also approved lecanemab for adults with mild cognitive impairment or mild Alzheimer's associated with confirmed amyloid pathology, while restricting use to people at lower genetic risk of serious ARIA. However, approval did not automatically lead to routine NHS availability. In England, the National Institute for Health and Care Excellence (NICE) subsequently concluded that the treatment was not cost-effective for routine NHS use under current arrangements, illustrating that regulatory approval and reimbursement are separate decisions.

Other regulators have taken similarly varied approaches. Authorities in countries including **Japan, China, South Korea, Hong Kong, and Israel** have approved lecanemab, while reviews have continued in several other jurisdictions. Each decision has reflected local legal frameworks, healthcare priorities, population characteristics, and tolerance for uncertainty.

The global journey of lecanemab demonstrates that regulatory decisions are not determined solely by clinical trial results. They also depend on how individual agencies interpret evidence, weigh benefits against risks, and balance the urgent need for new dementia therapies with the responsibility to protect patients. As more disease-modifying treatments emerge, understanding these differences will become increasingly important for researchers, clinicians, policymakers, and people living with dementia.

In the United States, the FDA remains the most influential regulatory body in global drug development, largely because approval in the US market often determines whether a therapy becomes commercially viable. In the European Union, the EMA provides central scientific oversight but works through a complex network involving 27 member states.

China, meanwhile, illustrates how quickly a regulatory system can evolve in response to scientific innovation and growing investment in biomedical research. Over the past decade, the NMPA has introduced a series of reforms designed to modernise drug regulation, streamline regulatory review, and reduce approval timelines, and encourage the development of innovative medicines. Through its Centre for Drug Evaluation (CDE), China has expanded mechanisms such as priority review and approval pathways for medicines that address major unmet medical needs, while also increasing opportunities for early dialogue between regulators and developers.

Writing about these reforms, Yuan Lijia of the CDE said their purpose is to improve the efficiency of regulatory review while maintaining rigorous scientific standards for innovative medicines. Rather than lowering evidentiary thresholds, the reforms seek to streamline administrative processes, strengthen technical review capacity, and reduce unnecessary delays, making China a more attractive environment for innovative drug development and clinical research.[8] As a result, China has become an increasingly important contributor to global Alzheimer's disease research, both as a destination for multinational clinical trials and as a market for the introduction of disease-modifying therapies such as lecanemab. The international perception of these reforms, however, has not always matched how they are presented by Chinese regulators.

Dr Marwan Sabbagh, one of the leading clinical researchers in Alzheimer's disease, is strikingly blunt about these differences. "Every regulatory process seems to be unique to itself," he

8 https://english.nmpa.gov.cn/2025-03/21/c_1080286.htm

says. "China tends to strongly favour Chinese enterprise and innovation." His view may sound stark, but it reflects a wider truth: regulation, wherever it takes place, is never purely scientific. Scientific evidence sits at the centre of regulatory decisions, but those decisions are also shaped by economics, politics, public trust, industrial strategy, and national healthcare priorities.

Sponsors seeking FDA approval generally need substantial US participation in pivotal trials, suggesting that, in practice, regulators expect a large proportion of participants to come from US sites. Although there is no formal FDA requirement specifying a minimum percentage of US participants, many sponsors deliberately recruit sizeable US cohorts to demonstrate the relevance of their findings to American clinical practice.

The EMA did not approve aducanumab, and only approved lecanemab and donanemab following an appeal, having initially concluded that the benefits did not outweigh the risks of ARIA. By contrast, the FDA approved all three treatments the first time around. That means an Alzheimer's drug developer cannot assume that evidence acceptable in one jurisdiction will automatically satisfy another. Global development increasingly requires a global regulatory strategy.

Prof Thirstrup emphasises that regulators are engaging much earlier in the process than many outsiders realise. In Europe, this early dialogue has become increasingly important as dementia research grows more complex.

"We may even start discussions before kicking off with a clinical trial," Prof Thirstrup says. "Some academic institutions do a lot of very nice science, but they may not have a mindset that is regulatory. They sometimes need a little bit of handholding to support what they are doing to enable that to be translated into something that hopefully can be commercial and be commercialised, but properly developed to meet regulatory standards."

His point is revealing. Many promising Alzheimer's therapies begin in academia rather than in large pharmaceutical companies. Academic researchers may produce exciting science – novel targets, compelling biomarker findings, innovative mechanisms – but translating that science into a trial capable of supporting regulatory approval is an entirely different challenge. Academic science rewards discovery and exploration. Regulatory science demands something else: standardisation, reproducibility, defined endpoints, and evidence robust enough to justify treatment at scale.

That distinction is becoming even more important as Alzheimer's research moves beyond traditional symptom-based frameworks. The science is changing rapidly as blood biomarkers transform diagnosis. Tau and amyloid imaging are becoming more sophisticated.[9] Trials are moving earlier into disease, sometimes targeting individuals before symptoms even appear.[10] Regulators therefore face a moving target: not only are the therapies changing, but the disease definitions themselves are evolving.

This has become a major issue in global Alzheimer's research. Competing frameworks for defining Alzheimer's disease – particularly the biological definitions increasingly favoured in research settings – are creating new regulatory complexity.[11] The EMA has explicitly acknowledged this challenge in its revised guidance on Alzheimer's clinical investigation,[12] which places far greater emphasis on biomarkers and earlier-stage disease.

Prof Thirstrup has repeatedly highlighted the importance of aligning diagnostic definitions across research, regulation, and clinical care.[13] Without agreement on what counts as Alzheimer's disease, trial design becomes fragmented. Companies may be forced to run different studies or generate different evidence packages for different regulators. This increases cost, slows innovation, and complicates global approval pathways. Yet even if scientific definitions become more aligned, another major challenge remains: speed.

The pressure to accelerate clinical trial approval has intensified dramatically over the past five years. This is partly because the economics of drug development are brutal. Clinical trials are expensive. As we have seen in Chapter 2, Alzheimer's trials are among the most expensive of all.[14] PET imaging, MRI monitoring, biomarker assays, specialist clinics, and long follow-up periods create enormous costs. Delays in trial activation or regulatory review can therefore have major consequences for investment.

Professor Jeff Cummings is unequivocal about the importance of speed. "I can't overemphasise the importance of having a strong regulator," he says. "The speed of review is really important because if you have all the investment to get a drug to the point where it could be approved and you have to wait a year or more because a regulatory body might be inappropriately staffed, that year is a year of patent life, and therefore a year of being off the market."

9 https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf
10 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12748
11 https://jnnp.bmj.com/content/97/7/660
12 https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-need-revision-guideline-clinical-investigation-medicines-treatment-alzheimers-disease_en.pdf
13 https://ascpt.onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.70107
14 https://pmc.ncbi.nlm.nih.gov/articles/PMC8940715/

"Investors will look at that and think that cancer drugs are approved more quickly, or they go to Europe or China to get their drug approved more quickly, so why would they do it where there's a disrupted, slow approval process?"

That lost year matters far beyond corporate profit. It shapes where investors choose to place capital. "Speed is important because it translates into money, and money translates into investment," Prof Cummings adds. "Investment drives the whole process forward. You can't do the science without the investment."

This is why regulatory efficiency has become such a strategic issue globally. Countries and regions are increasingly competing to attract clinical trials by reducing friction in startup processes and streamlining regulatory review. The UK offers a striking example. Prof Mummery believes significant progress has been made, though much remains to be done. "The UK government has put in place targets that are reasonable incentives in terms of getting clinical trials from submission to opening within 150 days," she says. "We need to be doing it much quicker, and in the [NIHR] Network we have got it down to 42 days."

The difference between 150 days and 42 days is transformational. In global clinical research, speed affects everything: investment, competitiveness, recruitment, and, ultimately, access to therapies. Prof Mummery says China's MHRA has improved substantially on these fronts.

"They increased their staffing and they're looking at more streamlined ways of enabling trials that are low risk," she adds. "They're tiering their risk assessment much better than they used to. In dementia, they are putting in a specific theme regulatory strain, which means there will be many more experts streamlined in that area, which I think is terrific."

But regulation is only part of the picture. Trial ecosystems also depend on hospitals, universities, research networks, and administrative systems. "One of the issues is still that big universities and big hospitals have slow, clunky processes when it comes to things like contracts," Prof Mummery says. "We really need to grease the wheels in that area and make it much simpler."

China has pursued similar objectives through national regulatory reform. Recent NMPA initiatives have focused on optimising review procedures for innovative medicines, strengthening technical review capacity, and further reducing the time required to initiate and evaluate eligible clinical trials.[15] These reforms reflect a broader recognition that regulatory efficiency has become an important component of international competitiveness. For Alzheimer's disease, where trials are lengthy and expensive, reducing avoidable delays may help accelerate both research and patient access without compromising regulatory oversight.

That observation is echoed across global dementia research. The bottleneck is often not regulatory review itself, but everything around it. This is one reason the Asia-Pacific (APAC) region has emerged as an increasingly important region in dementia trials. Greg van Wyk, senior medical director and APAC medical strategy lead at the clinical research organiser IQVIA, describes a highly varied but increasingly attractive landscape.

"There's this rich tapestry across APAC," he tells ADI. "In some countries, we're able to start studies very quickly. In those jurisdictions, we can get trials up and running much faster."

Australia and New Zealand, he says, have become particularly attractive locations for sponsors because of simplified administrative processes. "Contracting the sites is a lot easier because we have a national indemnity process, we have a national contract template that we use in all of our studies."

"The regulatory hurdles are lower to getting the study up and running so, depending on the country, we can do that well," van Wyk adds. "That doesn't mean we're going to get the bulk of the patients, but getting those first patients in, getting the study up and running is very important to make sure that a lot of these countries are able to access the best tranche of funding – and funding is critical because if they are not even going to fund these innovations, then they are not even going to come to market. We can play a critical role with that."

Importantly, lower hurdles do not necessarily mean weaker standards. Often, they simply mean less duplication and bureaucracy. Cost is equally significant. "The cost of doing clinical trials in APAC is much, much lower than especially the US," van Wyk says, with a recent estimate putting the figure at between 30 percent and 40 percent.[16] "Cost and speed are some of the things we can really bring and I don't think that comes at the expense of quality either."

That matters enormously in Alzheimer's disease, where trial costs are extraordinarily high. The ability to launch quickly and run efficiently without compromising quality creates a major competitive advantage. Yet speed alone cannot solve the central problem in dementia regulation. The hardest question remains the oldest one: how much evidence is enough? This question has become more urgent because regulators are now dealing with therapies that do appear to alter disease biology. The era of repeated trials that didn't lead to treatments has given way

15 https://english.nmpa.gov.cn/2025-10/14/c_1138493.htm
16 https://www.clinicalleader.com/doc/why-clinical-trials-in-the-apac-region-cost-less-0001

to something more complicated: therapies that work, but only modestly, and not without significant risk. That changes the regulatory conversation entirely.

The challenge is no longer simply whether disease modification is possible. The question is now whether regulators should approve treatments whose benefits may be incremental while risks remain substantial. This dilemma has become increasingly prominent within the FDA's own thinking. Buracchio and colleagues have argued that as Alzheimer's therapies move into earlier disease stages, regulators must balance the urgency of delivering treatments with the need to demonstrate meaningful benefits to patients while maintaining acceptable safety. Rather than lowering evidentiary standards, the challenge is to ensure that clinical trials are designed to capture benefits that genuinely matter to the people who may eventually receive these medicines.[17]

It is here, in the space between hope and caution, that Alzheimer's regulation becomes most difficult – and most consequential. And it is here that the conversation turns from regulation alone to safety.

Safety, risk, and the new dilemma in Alzheimer's treatment

The arrival of anti-amyloid therapies has changed the field fundamentally, not because they represent a cure, but because they have forced the scientific, regulatory and ethical debates around Alzheimer's into sharper focus. For years, the central question was whether disease modification was possible at all. That question has now, at least partly, been answered: amyloid plaques can be reduced, biomarkers can shift, and clinical decline can be slowed. But these advances have not simplified regulation; they have made it far more complex.[18]

The reason is straightforward. The new therapies do not offer dramatic improvements. They slow progression rather than reverse it, and the magnitude of benefit remains modest. At the same time, they introduce serious risks, some of them potentially fatal.[19] Regulators are therefore no longer deciding whether to approve a therapy that is clearly ineffective. They are deciding whether modest but measurable benefits justify exposing vulnerable patients to significant and sometimes poorly understood harms.[20] That is a far more difficult judgment.

Few issues capture this tension more starkly than ARIA, or amyloid-related imaging abnormalities. Before anti-amyloid therapies entered clinical practice, ARIA was largely a specialist research term. Today, it sits at the centre of nearly every serious conversation about Alzheimer's therapeutics.

ARIA typically appears in two forms: ARIA-E, where fluid leaks into brain tissue, causing swelling or inflammation, and ARIA-H, tiny areas of bleeding (micro-haemorrhages) in the brain, often only visible on an MRI scan. In many cases, ARIA is asymptomatic and detected only through routine MRI monitoring, but not always. In more serious cases, patients may develop headaches, confusion, dizziness, visual disturbance, seizures, neurological deterioration, or life-threatening complications.[21]

This has transformed the practical reality of Alzheimer's treatment. Anti-amyloid therapies are not simply drugs administered and monitored in routine outpatient settings. They require infrastructure: regular infusions, repeated MRI scans, specialist neurological assessment, and careful surveillance for complications. The promise of disease modification, therefore, comes tied to a substantial clinical burden.[22]

Prof Thirstrup returns repeatedly to this issue when discussing how regulators assess Alzheimer's therapies. "Every regulatory decision is a risk/benefit decision. And we only recommend a pool of products where we believe that the benefits outweigh the risks. In the case of these products [lecanemab and donanemab] we acknowledge the risk, but we have also put in place a lot of measures to detect and minimise those risks. So it's risks in the context of a risk minimisation programme we are talking about."

That phrasing – "detect and minimise" – is revealing. Regulators increasingly recognise that risks like ARIA cannot be eliminated entirely. The question is whether they can be managed well enough for treatment benefits to remain favourable. This is where benefit-risk assessment becomes extraordinarily difficult. In many areas of medicine, the calculus is relatively clear. For a mild condition such as a common migraine or seasonal allergy, the acceptable threshold for harm is very low. Even small risks may be unacceptable. In life-threatening diseases such as aggressive cancers, regulators are often willing to tolerate far higher levels of toxicity because the alternative may be near-certain death. Alzheimer's sits somewhere between these extremes. It is progressive, irreversible, and ultimately fatal, but unlike metastatic cancer, progression usually unfolds over years rather than months. Patients may still have substantial functional independence when treatment begins, changing how risk is perceived. The question regulators must answer is

17 https://pubmed.ncbi.nlm.nih.gov/40469853/
18 https://www.americanbrainfoundation.org/controversies-in-dementia-research/
19 https://www.alzforum.org/news/research-news/brain-woman-who-died-leqembi-shows-worst-case-scenario
20 https://www.itv.com/news/2025-06-18/alzheimers-drugs-rejected-for-nhs-because-benefits-too-small-to-justify-cost
21 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.71361
22 https://www.nature.com/articles/d41586-025-02927-7

where Alzheimer's should sit on that spectrum. How much risk is acceptable for a treatment that may preserve cognitive function slightly longer, delay functional decline by several months, or extend independence in meaningful but modest ways?

Anti-amyloid therapies have brought this dilemma into sharp focus. Clinical trials have shown statistically significant slowing of cognitive and functional decline, but the practical meaning of those gains remains contested. Some clinicians view these treatments as an important first step towards a new era of disease modification, while others question whether modest benefits justify the risks, costs, and complexity of treatment.[23] Regulators are forced to adjudicate between these competing interpretations.

Prof Thirstrup is candid about this. "These benefit-risk decisions are based on science," he says, "but in the end, there is always a degree of subjectivity." That admission matters because regulatory agencies are often imagined as purely objective institutions governed entirely by data. In reality, judgment is unavoidable. Data may indicate effect size, confidence intervals, and adverse event rates, but data alone cannot answer the deeper question of what constitutes meaningful benefit or acceptable risk.

This subjectivity becomes even more pronounced when genetic risk enters the equation. One of the most significant discoveries in anti-amyloid therapy has been the relationship between ARIA risk and APOE genotype. Carriers of the APOE4 allele – particularly individuals who carry two copies – face significantly elevated risks both of developing Alzheimer's disease and of experiencing treatment-related ARIA.[24] This transforms APOE testing from a research tool into a regulatory and ethical challenge.

Should genetic testing be required before treatment? If a patient is identified as APOE4 homozygous, should regulators restrict access, or should patients retain autonomy to make informed decisions despite elevated risk? These are deeply difficult questions because they sit at the intersection of precision medicine and patient autonomy. Restrict access too aggressively and regulators risk paternalism, effectively deciding that some patients are too high-risk to choose treatment for themselves. Allow unrestricted access, and regulators may expose highly vulnerable patients to serious harm.

Prof Thirstrup acknowledges that no simple answer exists. "We know patients generally are less risk-averse than regulators," he says. This observation is crucial. People living with early-stage Alzheimer's often evaluate risk very differently from regulators or clinicians. A person facing progressive cognitive decline may willingly accept substantial risk in exchange for even a modest chance of preserving independence, extending meaningful time with family, or delaying functional deterioration. Regulators, by contrast, must think at a population-level scale. Their responsibility is not to individual hope, but to collective safety. This creates unavoidable tension.

The tension between regulatory caution and patient willingness to accept risk became starkly visible following reports of deaths associated with anti-amyloid treatment complications.[25] Although rare, these cases transformed ARIA from a theoretical safety concern into a tangible public debate about whether the field had underestimated the seriousness of these risks. Critics argued regulators were moving too quickly.[26] Supporters countered that all meaningful advances in medicine carry risk, and that refusing progress because of safety concerns would effectively freeze innovation.

The intensity of the debate was such that the EMA's scientific committee decided to do something it had never done before: publish a paper in *The Lancet Regional Health – Europe* explaining its reasoning for approving the two disease-modifying therapies.[27] Prof Thirstrup described the paper as an unprecedented attempt to show the complexity of the regulatory discussion behind the decision.

As the paper states, the committee's first assessment was to reject both drugs for approval. The companies appealed, and a new set of evaluators looked at the drugs and decided to grant them a licence for Europe. "All the evaluators, both those who ended up being negative and those who ended up being positive in the end, contributed to that paper," Prof Thirstrup says. "We were really trying to reflect what the pros and the cons were, and what led to the final majority vote decision, not a unanimous decision of recommending approval. We had never done that before."

The decision reflected the complexity of regulating the first generation of disease-modifying Alzheimer's therapies: products that showed a measurable benefit but not the dramatic improvements traditionally associated with major therapeutic breakthroughs.

Progress can look different when tackling a complicated disease

Prof Thirstrup sees the debate as reflecting a deeper issue in how society understands progress in difficult diseases. "We need to accept incremental steps," he says. He points to oncology as a useful comparison. "For decades, we have accepted small incremental steps in treating malignant

23 https://www.nejm.org/doi/full/10.1056/NEJMoa2212948
24 https://pubmed.ncbi.nlm.nih.gov/40227662/
25 https://pubmed.ncbi.nlm.nih.gov/39121446/
26 https://pmc.ncbi.nlm.nih.gov/articles/PMC11624191/
27 https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(26)00056-6/fulltext

diseases." In dementia, however, expectations often remain unrealistically binary: either a therapy dramatically changes outcomes, or it is dismissed as insufficient.

This binary thinking may itself distort regulatory discussions. In Alzheimer's disease, even modest slowing of decline may represent meaningful clinical progress, particularly when viewed across millions of people living with the disease.

"If we deny industry the ability to bring products for incremental steps," Prof Thirstrup says, "I don't think we will get anywhere. I'm pretty sure if one of us gets Alzheimer's down the road, it will be another kind of therapy we will be offered than these [anti-amyloid therapies]. For me, this is the first stepping stone in understanding the disease. These monoclonal antibodies target beta amyloid, but there are a lot of other targets in the brain. We cannot sit waiting for the magic bullet that will cure the disease."

Ultimately, the challenge for regulators is not to eliminate risks when taking a treatment – an impossible goal – but to determine when risk is sufficiently understood and appropriately balanced by meaningful clinical benefit. As scientific understanding improves, these judgements will become increasingly personalised, with biomarkers, genetics, and better risk prediction helping identify those most likely to benefit from treatment. Yet greater scientific precision will not remove the ethical dilemmas surrounding who should receive treatment, what level of risk is acceptable, and who should make those decisions. Those questions lead directly to the next challenge: informed consent, autonomy, ageism, and the ethics of decision-making in a disease defined by progressive cognitive decline.

Ethics, autonomy, and the future of regulation

If the scientific challenge of Alzheimer's disease is formidable, the ethical challenge may be even greater. Regulation in dementia has never been simply about molecules, biomarkers, or statistical significance. At its core, it is about people: people living with progressive cognitive decline, families navigating fear and uncertainty, clinicians trying to balance hope with realism, and regulators tasked with making decisions that carry enormous consequences for millions of lives. As disease-modifying therapies begin to emerge, the ethical questions surrounding clinical trials are becoming more urgent.[28] The science may be improving, but so too is the complexity of the decisions people living with dementia, carers, and regulators are being asked to make.

This complexity begins with informed consent, a concept that appears straightforward in theory but becomes deeply complicated in dementia. Modern clinical research rests on a foundational ethical principle: patients should understand the risks and benefits of participation and should be free to decide whether those risks are acceptable. But Alzheimer's disease directly complicates that principle because the disease itself affects memory, reasoning, and decision-making capacity.[29]

A person with early-stage Alzheimer's may retain substantial autonomy and clear insight into their choices, while another at more advanced stages of the condition may struggle to fully comprehend complex risk-benefit information. At present, this distinction is important because disease-modifying therapies such as lecanemab and donanemab are indicated only for people with early Alzheimer's disease or mild cognitive impairment, meaning that most patients being considered for treatment should retain the capacity to make informed decisions, particularly when appropriate support and accommodations are provided.

However, as new therapies emerge – including treatments for later stages of Alzheimer's or for other forms of dementia – the challenges surrounding informed consent are likely to become more complex. In dementia, informed consent cannot be treated as a single event or a signed document filed away at the start of a trial. It must instead be understood as a continuous process.

That process becomes more difficult as treatment choices become more complex. In the era before anti-amyloid therapies, the decision to participate in a trial often involved balancing uncertainty against the possibility – however slim – of therapeutic benefit. Today, the decision involves something more complicated. Even for people in the early stages of Alzheimer's disease, patients may be considering therapies that offer measurable but modest benefit while carrying real risks of serious adverse events.

They must weigh the possibility of slowing decline against the burden of repeated infusions, MRI surveillance, potential complications, and significant uncertainty about long-term outcomes. This is not a simple calculation, even for highly informed individuals. Should future therapies become available for people at more advanced stages of dementia, these ethical and practical challenges will become still more complex, requiring even greater attention to supported decision-making and ongoing consent.

Steffen Thirstrup believes regulators must recognise this complexity without assuming people living with dementia are incapable of making difficult decisions. He says: "These benefit/risk decisions are, of course, based on science, but in the end, there is a degree of subjectivity to that decision: in terms of how

28 https://pennmemorycenter.org/ethical-considerations-of-dementia-research/
29 https://www.alzint.org/about/

do you, as a regulator, as a physician who is treating Alzheimer's patients, see it? How do you as a patient? How do you as a caregiver, a friend, see that balance between benefits and risks? And they may not be the same."

"We know patients generally are less risk-averse than regulators. We see examples where we actually have doubts about the safety of a product [but] patients come in and say, 'Well, the benefit is clear. We haven't seen anything else that can help our patient population. We acknowledge the risk. But if you regulators can put in place risk minimisation programmes, so the risk for patients is as minimal as it can be, we are willing to take the residual risk [of having the drug].'"

His observation highlights a tension that runs through modern Alzheimer's regulation. Regulators are structurally conservative. Their mandate is to protect public health, avoid preventable harm, and ensure that approved therapies meet acceptable standards of safety and efficacy. Patients, however, often see the equation differently. For someone living with early Alzheimer's disease, the prospect of progressive cognitive decline may fundamentally alter how risk is perceived. The possibility of preserving memory, independence, or recognition of loved ones – even for a relatively short period – may outweigh risks that regulators find deeply concerning.

This divergence raises difficult questions about paternalism. How much should regulators protect people living with dementia from risks that they may be willing to accept? Should regulatory caution override patient autonomy when uncertainty is high? Or should patients and families have greater freedom to determine what level of risk is acceptable in a disease where the alternative is inevitable decline?

There are no easy answers. But these questions become especially difficult in dementia because autonomy itself is unstable. Decision-making capacity can deteriorate over time.

Should regulatory caution override patient autonomy when uncertainty is high? Or should patients and families have greater freedom to determine what level of risk is acceptable in a disease where the alternative is inevitable decline?

This means decisions made at one point in disease progression may not align neatly with future circumstances. It also means carers become central to decision-making in ways that are emotionally and ethically complex. Unlike many other areas of medicine, participants rarely undertake a dementia clinical trial study alone.

"Caregivers are oftentimes asked to also participate in the clinical trial," Paul Wynn, a patient and caregiver advocate based in the US, tells ADI. "They're keeping the diaries. They're tracking what they're witnessing with their loved one. They become part of the clinical trial. They're the eyes and the ears for the investigators to see how their loved one is doing over time."

Yet while caregivers provide essential information for researchers, their own experiences and needs are not always fully recognised. Wynn, whose father-in-law is in the early stages of Alzheimer's, says: "Unless they have been in the field for a while, I think [researchers] probably overlook the burden that's on the caregivers, be it financial or emotional. Let's face it, these caregivers are actively grieving the loss of their family member."

Carers often occupy an impossible position. They are asked to support decisions involving therapies that may offer modest benefit but substantial risk, while also anticipating future decline and trying to interpret what their loved one would want. They may carry the emotional burden of choosing whether to continue treatment, withdraw from a trial, or pursue experimental options in the face of growing uncertainty. The emotional reality of these decisions is often far messier than the rational frameworks used in regulatory discussions.

However, for many families affected by dementia, the arrival of new therapies has created something that has been missing for decades: the possibility of taking action. "They feel like they're able to be proactive and take control," explains Wynn. "They want to be able to influence the rest of their life somehow. And I think being part of a clinical trial allows them to take that initiative… So I do think that, from the caregiver's perspective, there's a renewed sense of hope, and I also think it's related to the number of clinical trials that are available now too."

As Julie Stauffer Moore, who was diagnosed with early-onset Alzheimer's disease two years ago at the age of 53, explains on page 67: "A clinical trial is the best hope of finding something that's going to make this better. Whether it slows progression of the disease, whether it makes it less painful and scary, or whether it makes it go away."

Hope plays a powerful role here. Alzheimer's disease is uniquely challenging because it gradually erodes aspects of a person's identity, memory, and independence. For people living with dementia and families, even modest therapeutic possibilities can carry enormous emotional weight. Hope can sustain resilience, but it can also distort decision-making. Patients may overestimate likely benefits, underestimate risk, or interpret participation in trials as a greater promise than

the evidence supports. This is why truly informed decision-making requires communication that is honest, nuanced and emotionally intelligent.

Clinicians therefore carry an enormous responsibility. They must communicate uncertainty without extinguishing hope, and discuss risks without overwhelming patients already facing profound emotional strain. This balancing act becomes increasingly difficult as treatments become more complex and regulatory decisions more contested.

The ethical challenge also extends into a broader question of fairness. Alzheimer's disease is overwhelmingly a disease of older age, and that reality raises uncomfortable questions about ageism in clinical trials and regulation. Ageism in medicine is often subtle, embedded in systemic assumptions about whose health, risk, and quality of life matter most. In Alzheimer's trials, this often manifests through eligibility criteria that favour healthier, less complex patients.

From a scientific perspective, the logic is understandable. Trials often seek relatively homogeneous populations to reduce variability and improve statistical clarity. Patients with multiple comorbidities, vascular disease, frailty, polypharmacy, or advanced age may be excluded because they complicate analysis and increase safety concerns. Yet the result is a persistent disconnect between trial populations and real-world populations.

Prof Thirstrup acknowledges this challenge directly. "Fundamentally, we want clinical trials to reflect the population the product is intended for," he says. But he also recognises the scientific trade-off. More heterogeneous populations may better reflect real-world patients, but they also make efficacy harder to detect and safety more difficult to interpret.

This tension creates a subtle form of structural ageism. The very people most likely to receive Alzheimer's treatments in practice – older adults with multiple comorbidities – are often underrepresented in the evidence base used to approve those treatments. That creates significant uncertainty. Do therapies work equally well in frailer older adults? Is ARIA risk higher in patients with cerebrovascular disease? How does polypharmacy affect safety? These are critical questions, yet the trial populations used to generate evidence may not provide clear answers.

Ageism and the politics of risk

But ageism in dementia regulation goes beyond trial inclusion. It also operates in more subtle and politically uncomfortable ways, particularly in how regulators, clinicians, and wider society think about risk. The central question is not whether regulators intentionally discriminate against older adults. They do not. The more difficult question is whether regulatory systems – through their design, assumptions, and evidentiary standards – systematically disadvantage the very people they are meant to serve.

One way this happens is through risk tolerance. Across medicine, society accepts very different levels of risk depending on the disease in question. With cancer, serious adverse events such as toxicity, hospitalisation, and severe side effects are often considered an acceptable price for even modest gains in survival. In Alzheimer's disease, by contrast, regulatory caution often appears much higher – even though dementia is progressive, terminal, and profoundly life-altering.

This raises an uncomfortable question: why is society often willing to accept high risk in younger or middle-aged cancer populations, but markedly more cautious when treating older adults with dementia? Some patient advocates argue this reflects an implicit form of age bias. Cognitive decline in old age is sometimes viewed as tragic but inevitable – something to be managed rather than aggressively fought. That mindset can shape how regulators, clinicians, and policymakers view acceptable risk.

Small gains in dementia are more likely to be dismissed, even though incremental slowing of decline can be profoundly meaningful. As Jim Taylor explained in our opening chapter, a few additional months of independence, preserved memory, or recognition of loved ones may not look transformative in a trial dataset, but will carry enormous value for people living with dementia and their carers. If regulators set an unrealistically high bar for meaningful benefit while maintaining a very low tolerance for risk, the result may be a regulatory environment that unintentionally restricts innovation and access.

Ageism can also persist after regulatory approval. Even when treatments receive authorisation, access barriers often remain steep. Anti-amyloid therapies require specialist clinics, repeated infusions, MRI monitoring, and close surveillance for complications such as ARIA. In practice, these requirements disproportionately disadvantage the oldest, frailest, and most medically complex patients. Older adults living in rural areas, those with mobility limitations, and those without access to specialist centres may be effectively excluded from treatment even after approval.

This creates a second form of inequity. Regulatory approval may signal that a therapy is available, but availability does not necessarily mean accessibility. The people most likely to benefit from treatment may still face significant practical barriers to receiving it. For many patients, the limiting factor is no longer regulatory approval itself, but whether healthcare systems can deliver these therapies equitably.

The challenge, then, is not simply to make regulation faster or more flexible. It is to ensure that regulatory systems, trial designs, and healthcare infrastructure genuinely serve the real-world dementia population – including the oldest and most vulnerable adults. These challenges become even greater when regulators are evaluating therapies for less common forms of dementia, such as frontotemporal dementia (FTD), Lewy body dementia (LBD), and vascular dementia. Patient populations are smaller, disease biology is more heterogeneous, and traditional large-scale trials become far more difficult to conduct. This forces regulators to confront a difficult question: should evidentiary standards remain identical when diseases are rarer, more complex, and harder to study? Increasingly, the answer appears to be no.

Regulators are showing greater willingness to consider smaller studies, adaptive trial designs, surrogate biomarkers, and real-world evidence in areas of high unmet need. The FDA's evolving openness to approving therapies on the basis of a single highly persuasive trial reflects this broader shift.[30] That flexibility could accelerate innovation and reduce costs, but it also carries risk.

Jeff Cummings supports regulatory flexibility in principle, but with caution. "A single well-conducted study with a robust outcome? I'm with the FDA on this because we want to get these new drugs to patients as quickly as we can." But he remains uneasy about lowering evidentiary thresholds too far. "I'd not want to see approval based on a single marginal study."

Trial integrity and maintaining public trust

Regulatory flexibility can only succeed if it is underpinned by public trust – trust that approved therapies genuinely work, that risks are communicated transparently, and that the evidence itself is reliable. This is where another emerging concern enters the regulatory conversation: trial integrity.

> **For many patients, the limiting factor is no longer regulatory approval itself, but whether healthcare systems can deliver these therapies equitably.**

Prof Cummings has become increasingly vocal about the risks posed not only by safety controversies, but by data fraud. "I'm very concerned about fraud in trials," he says. His concerns intensified following allegations of falsified data at several Alzheimer's clinical trial sites in the United States, where sponsors identified statistically improbable data patterns, including unusually consistent participant outcomes and concerns that some assessments may not have reflected genuine patient visits. The affected datasets were investigated and, where appropriate, excluded from analyses, prompting renewed discussion about site monitoring and quality assurance across dementia research.[31]

"That will undermine my faith in clinical trials, let alone the general public's," Prof Cummings says. "As people involved in this system, we have to be continuously vigilant about that possibility, which we never considered seriously before. I couldn't imagine people faking data, but it's absolutely true that it's happening."

This threat is potentially profound, as clinical trials rely on trust at every level. Patients trust investigators to act ethically, and regulators trust sponsors to generate reliable evidence. The public trusts the overall system to protect safety and scientific integrity. Fraud damages all three simultaneously, which makes rigorous oversight essential. Fortunately, detection tools are improving. Prof Cummings adds: "There are some statistical techniques to identify this: For example, too many patients having the same outcome. There are patterns of falsifying data. And there is more detection of fraud than I would ever have imagined."

Prof Cummings's concerns reflect a broader anxiety within the field. Faster approvals may improve access, but they also risk undermining public confidence if therapies are later found to lack meaningful efficacy – or if confidence in the underlying evidence begins to erode. Trust, once lost, is difficult to rebuild. This concern extends beyond isolated bad actors. The deeper issue is what happens when public confidence in the integrity of research takes a hit. Clinical trials rely on participation. Participation relies on trust. Without trust, recruitment slows, evidence weakens, innovation suffers, and the entire research ecosystem becomes more vulnerable.

Professor Sid O'Bryant, executive director of the Institute for Translational Research at the University of North Texas, argues this is precisely why regulators should be viewed as partners rather than obstacles. "Oftentimes regulators are viewed as the bad guys," he says. "They're not. They are there to protect patients. We need to work more collaboratively with regulators to figure out ways we can do this work."

30 https://www.fda.gov/industry/fda-actions-accelerate-and-modernize-early-and-late-stage-clinical-development
31 https://www.science.org/content/article/alzheimer-s-drug-developers-accuse-clinical-trial-sites-faking-data

Clinical trials rely on participation. Participation relies on trust. Without trust, recruitment slows, evidence weakens, innovation suffers, and the entire research ecosystem becomes more vulnerable.

That collaborative model may prove essential as Alzheimer's research enters a new era shaped by biomarkers, digital tools, and predictive analytics. Blood-based biomarkers are already transforming diagnosis. Artificial intelligence is beginning to influence trial recruitment, imaging interpretation, and risk prediction. Digital endpoints – passive monitoring through smartphones, wearables, or cognitive apps – could reshape how progression is measured.[32] Regulators are being asked to evaluate not only drugs, but entirely new frameworks for evidence generation.

This may ultimately transform what regulation itself looks like. Prof Thirstrup believes one of the most important changes ahead will be the move toward prevention. The long-term goal in Alzheimer's is increasingly clear: intervene before irreversible neurological damage occurs. This means identifying risk earlier and treating earlier, potentially years before symptoms emerge. But prevention creates profound ethical challenges of its own. Prof Thirstrup says: "If you are able to identify patients at risk, but you have nothing to offer them, that diagnosis becomes unethical. If you went to your doctor and were told 'You have hypertension but we cannot do anything about it, go home and take it easy.' That's not acceptable, is it?"

It is one of the most striking observations in modern dementia policy because it captures a central paradox of scientific progress. Better diagnostics are not inherently beneficial if they outpace therapeutic capability. The ability to predict disease years before symptoms emerge may offer extraordinary opportunities for prevention – but it may also create profound psychological and ethical burdens. Who should be told they are at high risk? When should risk be disclosed? What happens if predictive biomarkers indicate future disease, but effective intervention remains unavailable or limited? These questions will define the next phase of dementia regulation.

The future of Alzheimer's clinical trials will likely be faster, more personalised, and more biologically precise. Biomarkers will become central. Trial populations will become increasingly stratified by genetics and risk. Regulators will rely more heavily on adaptive designs, real-world evidence, and post-marketing surveillance. But however sophisticated the science becomes, the central challenge will remain profoundly human. Prof O'Bryant captures this clearly. "The goal is clear. We want better outcomes. The question is: how do we get there?"

That question sits at the heart of every regulatory decision in dementia research. Not simply whether a therapy works or is safe, but whether the evidence is strong enough, the benefit meaningful enough, and the risks acceptable enough to justify moving forward. For millions of people living with dementia and those who care for them, these decisions determine not only who gains access to treatment and when, but how quickly scientific discoveries are translated into meaningful improvements in people's lives. Ultimately, regulation is not simply about approving medicines. It is about balancing hope with evidence, innovation with safety, and urgency with trust.

32 https://pubmed.ncbi.nlm.nih.gov/37295421/

CASE STUDY

'Just keep swimming': Finding purpose in the clinical trial journey

The first time Bill Yeates forgot a student's name, he brushed it aside. School leadership is exhausting work; anyone can lose a word in the middle of a conversation. Then came the forgotten meetings; the strange inability to complete familiar tasks; the creeping sense that something fundamental was slipping away. At first, he blamed stress, then depression, then burnout. By the time he was diagnosed with young-onset Alzheimer's disease in 2019 at the age of 59, his life had already begun to fracture around him.

"I'm one of these people who was misdiagnosed for five years and treated for depression," he tells ADI. "And it wasn't going anywhere. In fact, it was getting worse. Eventually, my psychiatrist said: 'You might have depression, but it's not the underlying cause of your memory issues.' So I had a perfusion test, which showed a reduced blood supply to the brain. Then I had an amyloid PET scan, which showed I had a significant level of amyloid buildup in my brain."

For years, Bill had worked as the deputy principal of a private school in Australia. He was articulate, ambitious, and intensely driven. But while his professional life was unravelling, he was also carrying another burden: the memory of his father's dementia and the impact that had on all the family. Bill and his identical twin brother, Peter, had cared for their father through the final years of his illness, so they knew exactly what the journey with Alzheimer's disease was going to be like.

"I was very much aware of the journey which was now in front of me," he says. "I looked at it and thought: OK, this is where I'm sitting. I only have a couple of years left. That's it."

After the diagnosis, he shut down almost completely. "I talk about this dark phase of my life where I simply gave up on life," he says. "I withdrew myself from the wider community, ate and drank too much, put on all this weight because I felt sorry for myself. Life no longer had any meaning for me."

Then, unexpectedly, came Japan. Seven friends, none of whom knew about his diagnosis, invited him to the 2019 Rugby World Cup. Only Peter, who was also on the trip, knew the truth about his diagnosis. Bill almost did not go, but ultimately decided to treat it as his final trip abroad before dementia took hold. "I saw the trip as my last hurrah," Bill says. "Thirty-five years previously, I'd been in Japan for six weeks. It's my favourite country. And I thought, if this is my last trip, that's where I'm going."

What changed him was not a dramatic revelation, but the simple act of being alive among friends again. "Laughing, carrying on like I was 21 again – you know what a rugby trip is like."

One afternoon, sitting quietly in an onsen [Japanese hot spring], he looked around at his friends and realised how much of his life he had already surrendered to despair. "I thought: there's me. I've been sitting around feeling sorry for myself. And I thought, look, this is the wrong way of looking at life. I should stop feeling sorry for myself and think more about: how can I start enjoying the time I have remaining with the people around me?"

"Initially, I didn't cope well with my diagnosis. But that trip to Japan showed me life was worth fighting for. So, when I came back, a couple of months later, my wife Nicole suggested that I should sit down with my twin brother, and together we talked about how I was going to, let's call it, fight, this disease."

Peter's background in pharmacy and clinical trials became critical. Together, the brothers combed through experimental dementia research opportunities around the world. They became increasingly sceptical of mainstream Alzheimer's approaches that focused almost entirely on amyloid plaques and tau proteins.[33] "Peter said to me they'd been following this path for 25 years and [he thought] they'd got nowhere," Bill says. "So for me, if I were looking for a silver bullet, then I needed to start looking out of left field."

Bill became convinced that stress and inflammation had played a central role in his case. "I saw stress as the main influence or trigger for my Alzheimer's," he says. "So I needed a clinical trial that would give me access to a precision (anti-inflammatory) drug."

At first, he found nothing suitable in Australia and seriously considered travelling overseas for treatment. Then a trial based in his home city of Sydney appeared almost by chance: a Phase 1B trial for XPro1595, an experimental anti-inflammatory drug targeting neuroinflammation rather than amyloid itself.[34]

33 https://med.stanford.edu/news/insights/2025/09/rethinking-alzheimers-tau-protein.html
34 https://www.alzforum.org/therapeutics/xpro1595

'Taking part was never just about me. It was also about being part of something much bigger than myself and helping create a future where others living with dementia might have access to better treatment options than are currently available today,' Bill Yeates says. (Photo by Belinda Cooper)

"I read about neuroinflammation, and I thought: yeah, OK, this is probably left field enough," Bill says. "There weren't too many trials on it at that point in time. And in probably the biggest gamble of my life, I decided: this is the one."

The trial, run through KaRa Minds in Sydney, required extensive screening. Bill underwent genetic testing, MRI scans, blood tests, cognitive assessments, and cerebrospinal fluid analysis. Participants needed to be in the mild to moderate stage of the condition and have a range of specific inflammatory markers.

"I hadn't been taking any other dementia related medications, so I ticked that box. My genetic test revealed that I was heterozygous for APOE4 – I ticked that box. I had long-term or drug-resistant depression, but that was not an exclusion factor, so it all looked good and I was accepted into the trial in February 2020."

Even with Peter's scientific background guiding him, Bill says the process was emotionally overwhelming. At first, his wife, then a friend, would be by his side as he arrived at the private clinic for his weekly injections over an initial 12-month period, later extended to 15 months.

"The walk up the stairs into the room was often filled with uncertainty: What am I doing here? Is it worth it? Am I wasting my time? I needed someone there just to encourage and reassure me as I walked up the stairs and into the room. It's an interesting thing how you go through all these different emotions, because the dropout rate [of Alzheimer's disease clinical trials] is quite high."

Bill soon discovered that the emotional support of clinical trial staff mattered just as much as the support from his family and friends. The people at KaRa Minds, he says, treated him with kindness and humanity.

"At the end of every single injection, the nurse secretary who was looking after me would have my favourite chocolate sitting there on the counter. It's something small, but it's person-centred, and it made the whole process much easier."

Bill believes many early researchers don't fully understand what participation needs to look like for people living with dementia. "There are a hell of a lot of discrepancies between clinical trials across the world," he says. "Some are very good. Others are actually quite unrealistic in terms of what is being expected of people living with dementia."

He argues that people living with dementia need to be directly involved in trial design from the beginning. "How can researchers make sure they're catering for the needs of people living with dementia?" he asks. "Make sure that when you come up with a methodology, it's focused on obtaining accurate data under the best possible conditions."

By the sixth month of treatment, Bill began noticing subtle changes. "Not a lot better," he says, carefully. "But I could detect that something was improving." Early data from the Phase 1 clinical trial shows improvement in white matter tracts – the nerve fibres responsible for network communication. Alzheimer's disease is traditionally viewed as a grey matter

Surfing, along with changing his diet and being more proactively social, has become a big part of Bill Yeate's life since being diagnosed with Alzheimer's disease. (Photo by Belinda Cooper)

disorder, but it also causes significant damage to the brain's white matter tracts. In Alzheimer's disease, these tracts degrade due to demyelination, inflammation, and cellular loss.

The trial itself was small: 18 participants started, six completed it. According to Bill, two participants – including himself – were seen as statistical outliers because of their unusually positive outcomes. Researchers monitoring inflammatory biomarkers believed the drug was reducing swelling in the brain.

The effect on his daily life felt dramatic. Although he says formal cognitive scores were never fully disclosed to him, his psychogeriatrician was recently quite impressed by his overall progress. "She looked at me and said how much I had changed over the past nine months."

At the same time, Bill was transforming his life outside the clinic. He changed his diet, exercised intensely, rebuilt friendships by becoming socially active and consciously reconstructed his identity after diagnosis. "With young-onset Alzheimer's disease, I found that who I was had been taken away from me," he says. "I needed to rebuild myself while doing everything possible to combat my cognitive decline."

Today, Bill, now 66, lectures at the University of West London on how to effectively include people living with dementia in the design of clinical trials. He is on Alzheimer's Disease International's board and co-chairs the organisation's Global Dementia Expert Panel. Bill is also the living experience associate consultant for HammondCare.

Bill now speaks publicly about dementia, mentors others living with the condition, and campaigns for more humane approaches to care and research. "I decided that, whether it works or not, I have an opportunity to be an advocate to show people how to live a more enjoyable and meaningful life with dementia. Don't do what I did: give up and adopt a fatalistic outlook. What you need to do is get on with your life."

For years, XPro1595 appeared to offer stability. After the formal trial ended, Bill successfully applied through Australia's Special Access Scheme to continue receiving the drug – an unusually rare outcome for a Phase 1B participant. He remained on the drug for another three years. Then, in July 2025, everything stopped. The broader clinical programme failed to meet expectations, and the drug supply was then terminated.

"All I got was an email informing me that they were now ceasing supply," he says. "'Please stop using the drug by 27 July 2026 and dispose of any that you have left over.' And that was it… I was left devastated."

The experimental Alzheimer's drug XPro1595, developed by INmune Bio, produced mixed results in its Phase 2 clinical trial, called MINDFuL. In the full study group of about 200 patients, the drug did not meet the trial's main goal: patients taking XPro1595 did not show a statistically significant improvement in overall cognition compared with those receiving a placebo.[35]

However, researchers found something more encouraging in a smaller subgroup of patients who had high levels of inflammation-related markers in their blood. In these patients, XPro1595 showed signs of slowing cognitive decline and of improving some behavioural symptoms such as agitation and hyperactivity. The benefits were modest, but appeared consistent across several measures. One of the most important findings was safety. Unlike several currently approved Alzheimer's drugs that can sometimes cause brain swelling or bleeding, XPro1595 did not produce those side effects in the trial. Researchers highlighted this as a potentially important advantage.

After XPro1595 was withdrawn, Bill faced another anxious wait. Nearly a year later, he underwent a repeat amyloid PET scan to understand what had happened inside his brain after four years of treatment. The results were deeply disappointing. The scan showed that amyloid pathology had continued to progress, including new areas of the brain that had become strongly amyloid positive.

"I left the appointment with my GP feeling empty and completely devastated," he says. "For the first time in many years, I could feel the darkness beginning to return."

A few days later, however, a consultation with his dementia specialist offered a different perspective. Although the scan confirmed the progression of Alzheimer's pathology, Professor Michael Woodward reminded Bill that amyloid tells only part of the story. Looking at Bill's clinical course over the previous seven years, he believed several factors may have contributed to slowing his cognitive decline, including participation in the clinical trial, long-term treatment with XPro1595, sustained lifestyle changes, and ongoing psychosocial interventions.

For Bill, the conversation marked another turning point. "I realised that my journey with dementia can't be measured by amyloid alone," he says.

Rather than signalling the end of the road, the scan became the beginning of another decision. His specialist outlined two possible paths: treatment with one of the new anti-amyloid therapies or participation in another clinical trial targeting tau pathology. At present, Bill believes he is likely to pursue another trial.

"From the very beginning, I believed that if we are ever going to find more effective treatments – or dare I say a cure – for Alzheimer's disease, it will be through research and the willingness of people living with dementia to participate in clinical trials," he says. "Taking part was never just about me. It was also about being part of something much bigger than myself and helping create a future where others living with dementia might have access to better treatment options than are currently available today."

Seven years after his diagnosis, Bill continues to lecture internationally, advocate for better dementia care, and champion the involvement of people with lived experience in clinical research. The advice he received from a past student called Alison, he now gives to others. "Just keep swimming," which serves as a constant reminder that when life becomes challenging, especially on those difficult days, it's important to always move forward with your life. And perhaps this mindset – more than any scan result or biomarker – is what keeps him going.

35 https://www.nature.com/articles/s44400-026-00091-x

Chapter 6:

Global perspectives and solutions: moving toward inclusivity and innovation

In KwaZulu Natal, north of the city of Durban in South Africa, "gogos" (grannies), like the one pictured here in January 2003, volunteer to care for children either living with HIV/AIDS, orphaned, or having left home because of abuse. (Photo by Luca Zanetti)

Summary

Chapter 6 examines one of the defining challenges in Alzheimer's research: ensuring that advances in clinical trials and therapeutic innovation are accessible, inclusive, and globally representative. While Alzheimer's science is progressing rapidly – with breakthroughs in biomarkers, disease-modifying therapies, and novel trial models – the benefits of this progress remain unevenly distributed.

Significant disparities persist between high-income countries and low- and middle-income countries (LMICs), shaping who can access diagnosis, specialist care, and clinical trial participation.[1] In many parts of the Global South, barriers such as limited diagnostic capacity, underdeveloped research infrastructure, workforce shortages, financial constraints, and low public awareness continue to restrict participation in trials. These gaps not only limit access to potentially beneficial interventions, but also risk producing evidence that does not fully reflect the global population affected by dementia.

Yet this chapter also highlights growing momentum toward more equitable solutions. Across LMICs, researchers, healthcare systems, community organisations, and industry partners are developing innovative approaches to improve participation and inclusion. Public–private partnerships, community-led engagement strategies, mobile health technologies, and digital tools are expanding reach and improving recruitment. At the same time, decentralised and virtual trial models are reducing geographic and logistical barriers for participants and caregivers.

The examples presented in this chapter demonstrate that progress is possible. Success depends not only on scientific innovation, but on building systems that are locally relevant, culturally responsive, and person-centred. Creating a truly inclusive global clinical trial ecosystem will be essential to ensuring that future Alzheimer's treatments benefit all communities, not only those in well-resourced settings.

The global divide in Alzheimer's clinical trials

In the mountains outside Medellín, families have spent generations living with a devastating inheritance. Entire bloodlines in parts of Colombia carry rare genetic mutations that all but guarantee the development of early-onset Alzheimer's disease. For decades, clinicians followed the same grim pattern: memory slips in middle age, progressive cognitive decline, and, eventually, profound disability.

Then something changed.

These families became central to one of the most important Alzheimer's prevention studies ever conducted. The landmark Alzheimer's Prevention Initiative (API) trial in Colombia[2] tested whether intervening years before symptoms appeared could alter the course of the condition. The drug itself ultimately failed to meet its primary endpoint.[3] In conventional pharmaceutical terms, it was a negative trial; but that description tells only a fraction of the story. For researchers in Colombia, the trial transformed what was possible. It built infrastructure, trained staff, expanded diagnostic capability, and turned the country into one of Latin America's most important Alzheimer's research hubs.

"The result was negative in the sense that the drug in question [crenezumab] failed to significantly slow or prevent cognitive decline in cognitively healthy individuals with a rare genetic mutation," David Aguillón, a clinician and researcher working in Colombia's neurogenetics landscape, tells ADI. "But for our group, the result was very positive. For us, API is the most important trial. We learned a lot. We updated our data. We continued understanding the disease process in these families. And we grew in capacity. At the start of the trial, we only had 60

1 https://pmc.ncbi.nlm.nih.gov/articles/PMC12491904/
2 https://alzheimerspreventioninitiative.com/api-studies/adad-colombia-trial/
3 https://www.alzforum.org/news/research-news/api-colombian-trial-crenezumab-missed-primary-endpoints

or 70 people [in our research team]. Now we have 150 people and have discovered 14 different genetic forms of Alzheimer's disease in Latin America."

The trial trained clinicians, coordinators, nurses, and laboratory teams. It expanded infrastructure. It strengthened regional collaboration with centres in Argentina, Brazil, and beyond. Most importantly, it proved something critical: with sustained investment, sophisticated Alzheimer's trials can succeed in LMIC settings even when the trial endpoint is not reached.

That distinction – between a failed drug and successful capacity-building – captures the central tension in global Alzheimer's research today. The science is moving faster than ever before, and the approvals of anti-amyloid therapies have fundamentally altered the field. After decades of repeated disappointment, Alzheimer's research is no longer defined purely by failure. The arrival of disease-modifying therapies, blood-based biomarkers, and increasingly precise risk stratification has brought cautious optimism. Researchers now speak openly about precision medicine, combination therapies, and prevention strategies in ways that would have felt aspirational only a decade ago.

"It's a really exciting time," Professor Miia Kivipelto, architect of the influential worldwide FINGER network, which has now spread to more than 70 countries, tells ADI. "We have biomarkers, we have prevention trials, we have new treatments. When you put all these pieces together, we are really seeing dementia milestones."

And yet this optimism is profoundly uneven. The future of Alzheimer's care is arriving first in wealthy countries with strong research infrastructure, advanced diagnostics, and specialist memory services. For many LMICs, that future remains distant. This growing divide is becoming one of the defining ethical questions in dementia care: as Alzheimer's science accelerates, who gets left behind?

The answer increasingly depends on geography. More than 60 percent of people living with dementia already reside in low- and middle-income countries (LMICs), and this proportion is expected to rise to over 70 percent by 2050.[4] The steepest growth in dementia prevalence is projected in regions such as Latin America, sub-Saharan Africa, and South Asia.[5] These are precisely the parts of the world that remain least represented in Alzheimer's clinical trials.

There are now 158 drugs in 192 active clinical trials, requiring approximately 55,000 participants globally to populate ongoing studies, according to Professor Jeff Cummings and colleagues' 2026 Alzheimer's disease drug development pipeline report. There are 3,156 unique active clinical trial sites in North America and 3,607 in non–North American regions, including 1,363 in Western Europe/Israel, 661 in Eastern Europe/Russia, 571 in Asia (not including Japan), 516 in Japan, 321 in Latin America, and 175 in South Africa, Australia, or New Zealand.[6]

On paper, this looks like a scientific revolution. In reality, it is also exposing a fault line that has long existed in global health but is becoming increasingly visible in dementia care: the widening divide between the countries driving Alzheimer's innovation and those most likely to shoulder its future burden. Large parts of Latin America, Africa, South and Southeast Asia remain dramatically underrepresented in Alzheimer's drug development. That imbalance matters not simply because of fairness or representation, but because it raises increasingly urgent scientific questions about whose biology is being studied, whose disease trajectories are being modelled, and whose outcomes are shaping the next generation of therapies. This imbalance becomes even more striking when viewed against the projected disease burden. The countries facing the steepest future increases in Alzheimer's prevalence are not, in most cases, the countries where clinical infrastructure is expanding fastest. In other words, the populations likely to experience the largest growth in dementia are often the ones least included in building the evidence base for future treatments.

That imbalance matters for reasons that go far beyond fairness. Clinical trials shape the future of medicine. They determine which drugs are approved, while observational and validation studies establish which biomarkers can reliably identify disease or predict treatment response, and which populations benefit from scientific progress. If entire regions remain absent from the evidence base, treatment pathways risk being built around incomplete biology and narrow populations.[7] There is still caution, and plenty of scientific disagreement, but there is no longer serious debate about whether disease-modifying therapies for Alzheimer's are possible. They are. The question now is not whether the field is moving forward, but how fast, and crucially, for whom. This is not merely a representation problem; it is a scientific problem.

Alzheimer's disease does not manifest identically across populations. Genetics, cardiovascular risk, metabolic health, environmental exposures, and social determinants all influence disease expression. If clinical trials and biomarker research are concentrated largely in people of European ancestry, scientists risk developing diagnostic tools, biomarker thresholds, and treatments calibrated to only a subset of the world's population.

4 https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/
5 https://pmc.ncbi.nlm.nih.gov/articles/PMC11922445/
6 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70251
7 https://www.ncbi.nlm.nih.gov/books/NBK584396/

The populations likely to experience the largest growth in dementia are often the ones least included in building the evidence base for future treatments.

Those consequences are already becoming apparent. Participation in modern Alzheimer's drug trials increasingly depends on access to sophisticated diagnostic technologies. Whereas earlier dementia trials often relied on clinical assessments, cognitive testing and MRI imaging, today's studies typically require confirmation of amyloid or tau pathology through PET imaging, cerebrospinal fluid analysis, or advanced blood biomarkers. These advances have improved trial precision, but they have also introduced new barriers for countries with limited diagnostic infrastructure.

Dr Phyllis Ferrell, who leads health system preparedness work at the Davos Alzheimer's Collaborative (DAC), believes this growing biological knowledge gap is now one of the field's most pressing challenges. "Most biomarker studies and most research done to date are in high-resource countries of European descent," she tells ADI. "The Global South is where you really get into trouble [over research]. You can probably get things done in Brazil, Argentina, and now Colombia, because they did that API study, [but] the big problem is the disease state understanding. You're just not getting the biology. And what it also means is in the countries where you have some of the largest growth rates, you can't get the medications there."

In the Philippines, neurologist Michelle Anlacan sees this shift in stark terms. "Previously, you could participate in trials by clinical evaluation and MRI," she tells ADI. "Now you need amyloid or tau PET scans. These are very expensive, which effectively excludes us from drug trials."

That exclusion is not unique to the Philippines. Across Latin America, biomarker infrastructure remains limited and uneven. PET scanners are concentrated in major urban centres. Blood biomarker testing remains unavailable or prohibitively expensive in many regions. Laboratory systems for specimen processing, storage, and transport remain underdeveloped. Even where blood biomarkers offer hope as cheaper alternatives, implementation remains difficult. The assumption that blood-based testing automatically solves access barriers can be misleading.

Dr Ferrell offers a sobering example from Jamaica. In one DAC research programme, collecting blood was not the problem. Instead, it was shipping the blood samples when trial developers could not find a logistics provider capable of handling biological export requirements. "So, you think of all the challenges in research, and the one we encountered was a country that didn't have a [logistics and delivery company] that could handle the import export license of biologics," she says.

The bottlenecks multiply quickly: centrifuges, dry ice, export permits, laboratory processing, genetic counselling, and imaging capacity. Even seemingly basic requirements can become insurmountable barriers. Jamaica faced another challenge, having only one genetic counsellor for the entire country. These infrastructural gaps help explain why large parts of the Global South remain all but invisible in Alzheimer's drug trials. The problem is not a lack of patients, nor is it a lack of willingness. In fact, many researchers say patient interest is high – and often higher than in wealthier countries where multiple treatment options exist.

In Alzheimer's disease, scarcity creates a paradox. Where treatment access is poor, clinical trials often represent one of the few opportunities for specialist care, diagnostic work-up, and potential access to emerging therapies. "There are plenty of patients wanting to go into studies," said Greg van Wyk, medical director for Asia-Pacific at IQVIA. "Because there aren't really any other options for them."

The challenge is therefore access rather than demand. Yet access depends on infrastructure, infrastructure depends on money, and money remains perhaps the most powerful dividing line in global dementia research. Clinical trials are expensive everywhere: between 1995 and 2021 cumulative private expenditures on clinical-stage Alzheimer's disease research and development were estimated at $42.5bn.[8] But in LMICs, financial constraints hit at every stage: diagnostics, staffing, training, regulatory approval, transport, data systems, and patient support. Governments in many low-income countries are already struggling to fund basic health services. Dementia research rarely rises high on the political agenda.

In Nigeria, neurologist Temitope Farombi describes a system under enormous pressure. Healthcare spending remains low, and out-of-pocket payments dominate. Specialist services are scarce, and 'brain drain' continues to hollow out clinical expertise. Africa also has particular cultural issues around dementia that provide extra challenges. The implications for dementia care are severe: across much of Africa, formal Alzheimer's drug trials are non-existent, but other forms of research are underway that scientists hope will make a lasting difference.

"I see patients with Alzheimer's disease or dementia coming to my practice, and they're afraid," Dr Farombi tells ADI. "They are struggling, the family is confused because they know nothing about how to manage them, and then you have the cultural nuances around people with dementia in this part of the world.

8 https://pmc.ncbi.nlm.nih.gov/articles/PMC8940715/

So you have individuals not being well taken care of and also being stigmatised, and there's a huge knowledge gap about the disease presentation at the community level."

Dr Farombi is currently leading one of the first plasma biomarker studies for dementia in sub-Saharan Africa, an NIH-supported effort to establish normative data in Nigerian populations.[9] The study itself is significant precisely because such foundational data remains absent, and without data, investment remains limited. Breaking that cycle is difficult, yet infrastructure is only one barrier. The other major obstacle is awareness.

In many parts of the world, dementia remains under-recognised by the public, underdiagnosed by clinicians, and heavily stigmatised. Globally, around 80 percent of the general public believes dementia is a normal part of ageing.[10] In parts of Nigeria, Dr Farombi says dementia symptoms may still be interpreted as witchcraft. "Symptoms are misinterpreted as spiritual problems," she says. "People are tagged as witches or seen as being under spiritual attack."[11]

In the Philippines, awareness remains similarly low. "Up to now, even among our doctor colleagues with their parents, they won't submit them for diagnostic tests because they think it's a normal part of ageing," Prof Anlacan says. "It's going against the grain when we try saying it is common but not normal to have dementia as you get older."

This matters enormously for clinical trials because Alzheimer's research increasingly depends on early diagnosis. Disease-modifying therapies work best – and often only – in early symptomatic or even preclinical stages. By the time many patients in LMICs present to specialists, they are often already in moderate or advanced stages of dementia. That delay narrows the pool of eligible trial participants and also reinforces another growing global divide.

In high-income countries, the conversation is increasingly about early detection, blood biomarkers, and intervention before symptoms worsen. In much of the Global South, the challenge remains basic diagnosis. That mismatch between scientific progress and health system readiness may be one of the defining challenges facing global dementia care. Yet researchers across Latin America, Asia, and Africa are beginning to show that these barriers are not insurmountable. Some are developing community-based recruitment systems.[12] Others are building regional trial networks,[13] expanding telemedicine to reach isolated populations,[14] or creating digital interventions designed around local realities. Although these approaches differ, they share a common principle: if traditional models exclude too many people, the model itself must change.

Perhaps the most striking theme emerging from conversations with researchers across the Global South is that they are not asking to be rescued – they are asking to be included. Whether in Nigeria, Colombia, India, the Philippines, or elsewhere, researchers are building local trial capacity, creating biomarker cohorts, launching awareness programmes, testing telemedicine models, and developing culturally relevant recruitment pathways. Innovation is happening not despite limited resources, but often because researchers have been forced to design systems that work within real-world constraints.

The future of inclusive Alzheimer's research may not come from simply exporting Western trial models into lower-resource settings. It may depend instead on something more ambitious: reimagining what clinical trials can look like when designed for global inclusion from the beginning. That work has already started. The most interesting question now is whether the rest of the world is moving fast enough to meet it.

Innovation from the margins

For years, the implicit assumption in Alzheimer's research was that meaningful innovation would emerge from a familiar set of places: Washington, London, Tokyo. Scientific leadership was concentrated in a relatively small number of institutions, and the architecture of clinical trials reflected that concentration. Innovation flowed outward from wealthy countries to the rest of the world, often slowly and unevenly.

That assumption is now beginning to break down. Not because the traditional centres of research matter less – they remain critical – but because some of the most interesting and potentially transformative work in dementia science is increasingly emerging from places long treated as peripheral to the field. Across Africa, South Asia, and Latin America, researchers are developing new models for prevention, diagnosis, and participation that do more than improve local access. In some cases, they are forcing the field to rethink what inclusive Alzheimer's research should look like in the first place.

The shift is partly being driven by necessity. Countries with limited specialist infrastructure cannot simply replicate the highly centralised, resource-intensive trial systems used in the US or Western Europe. They have had to innovate differently: by designing around primary care, embedding community

9 https://alamarbio.com/blood-based-alzheimers-biomarkers-african-cohort/
10 https://www.alzint.org/resource/world-alzheimer-report-2024/
11 https://www.theguardian.com/global-development/article/2024/jun/05/they-wanted-her-to-confess-to-witchcraft-ending-the-chilling-effects-dementia-stigma-nigeria
12 https://pubmed.ncbi.nlm.nih.gov/41929959/
13 https://red-lat.com/redlat2-a-new-era-for-dementia-research-in-latin-america/
14 https://pmc.ncbi.nlm.nih.gov/articles/PMC12089872/

engagement at the centre of research, prioritising prevention, and using digital tools to leapfrog structural limitations. Increasingly, these approaches are attracting global attention.

One of the clearest examples comes from Africa, where dementia research is moving through a quiet but important transformation.[15] Historically, Alzheimer's research on the continent has been extraordinarily limited relative to both population size and projected future burden.[16] Yet the demographic and epidemiological realities are changing rapidly. Life expectancy is rising, and the burden of non-communicable diseases linked to dementia risk – including hypertension, obesity, and diabetes – is increasing rapidly. At the same time, researchers continue to confront a striking lack of local scientific evidence.

As Dr Farombi in Nigeria puts it, one of the central problems is that researchers still do not fully understand how Alzheimer's biology manifests across African populations. "Environmental influences on the expression of diseases may not be the same as those in the Western world," she says. "That means those medications or drug trials done on White or Hispanic populations may not be the same in other ethnic groups. But often, since there are no drug trials, we are only just grabbing what is being sent to us. That limits individual care and also limits outcomes, which is a huge concern for me."

That scientific gap helps explain why one of the most significant dementia initiatives in Africa today is focused not on drug development, but on prevention. The African Dementia Consortium's AFRICA-FINGERS programme[17] is among the most ambitious attempts yet to build a culturally grounded, scalable dementia prevention model for the continent. Led by Dr Chi Udeh-Momoh and Professor Miia Kivipelto, and embedded within the World-Wide FINGERS network, the initiative is initially focused on Kenya and Nigeria, with a five-year mixed-methods study designed around region-specific dementia risk factors. Crucially, the programme uses community-based participatory research principles, meaning interventions are being co-designed with local stakeholders rather than imported wholesale from Europe.

That matters because risk reduction in dementia is never culturally neutral.[18] Diet, physical activity, education, vascular health, and social engagement are all shaped by local context. What works in Helsinki may not translate directly to Lagos or Nairobi.

AFRICA-FINGERS acknowledges this explicitly, building interventions around African realities rather than expecting communities to adapt to external models. Dietary advice is based on affordable, locally available foods rather than imported nutritional models, while physical activity programmes incorporate culturally familiar activities such as traditional dance.[19] The intervention has also been co-designed with local communities to ensure it reflects regional priorities and everyday realities. This is where the programme's significance extends beyond Africa itself. It reflects a broader evolution in dementia science, away from the idea that global inclusion simply means expanding recruitment, and towards a deeper recognition that intervention design must itself be culturally adaptive.

Prof Kivipelto sees enormous promise in this approach because it shifts the focus to where African health systems can act most effectively. "Prevention is key if you really want to manage the global dementia epidemic because 45 percent of cases are linked to modifiable risk factors,"[20] she says. "Even postponing onset by a few years will have a huge impact on the patient, their families, and society. I don't think it's a case of prevention or treatments, we need to always do prevention as we do for all chronic diseases – that for me is always the basis. We combine modifiable risk factors, lifestyle, and pharmacological treatments when needed. For me, it's more about precision prevention, getting someone the right treatment at the right time."

The same logic is increasingly driving innovation in India, which occupies a particularly important place in the future of Alzheimer's research. Its large population, rapidly ageing demographics, growing research infrastructure, and rising burden of non-communicable disease make it central to the global dementia landscape. Yet the country also encapsulates many of the contradictions shaping dementia care in LMICs: world-class tertiary hospitals exist alongside enormous gaps in awareness, diagnosis, and specialist access.

This tension has made India a major focal point for prevention science.[21] FINGERS-India is emerging as one of the most important adaptations of the FINGERS model anywhere in the world. Rather than transplanting the Finnish intervention directly, researchers have adapted it to India's social, cultural, and health system realities, focusing heavily on cardiovascular risk management, physical activity, nutrition, and cognitive health in ways that reflect local conditions.

15 https://pmc.ncbi.nlm.nih.gov/articles/PMC12689452/
16 https://www.wits.ac.za/news/latest-news/research-news/2025/2025-10/brain-health-and-africas-future.html
17 https://africandementiaconsortium.org/africa-fingers-project/
18 https://www.alzint.org/resource/world-alzheimer-report-2023/
19 https://africafingers.org/communities-in-kenya-co-create-dementia-prevention-strategies-through-africa-fingers-program/
20 https://www.alzint.org/news-events/news/lancet-commission-identifies-two-new-risk-factors-for-dementia-and-suggests-45-of-cases-could-be-delayed-or-reduced/
21 https://www.thehindu.com/sci-tech/health/dementia-the-urgent-need-for-india-to-invest-in-elder-care/article69605415.ece

The importance of this work lies not only in its prevention outcomes but also in its scalability. India's greatest contribution to dementia science may ultimately come from helping answer one of the field's most urgent questions: how do you deliver meaningful dementia prevention at a population scale in a resource-constrained environment? Across the world, that question is becoming increasingly pressing.

Professor Craig Ritchie, chief executive of Scottish Brain Sciences, believes international collaboration will be essential to answering it. SBS has adopted the "triple helix" model, which deliberately brings together three sectors that have traditionally operated in parallel rather than in partnership: academia, healthcare systems, and industry. In practical terms, this means university-led scientific discovery, real-world clinical delivery through health services, and commercial capability from diagnostics, biotech, and pharmaceutical companies are integrated into a single ecosystem rather than functioning as separate silos – and Prof Ritchie believes it could also be a blueprint for improving clinical trials worldwide.

He tells ADI about the importance of moving beyond narrow, high-income-country models and of building partnerships that allow expertise, data, and infrastructure to grow across borders. By the time dementia symptoms are obvious, he argues, pathology is often decades advanced. "It is the diseases that lead to dementia that we need to be identifying and treating," he previously said, "because by the time people are showing symptoms, their disease is at a very late stage."[22]

The SBS model is designed around that reality. Instead of waiting for patients to enter traditional memory clinics, it builds integrated brain health pathways that combine early screening, blood biomarkers, imaging, biobanking, risk stratification, and rapid matching into prevention or treatment studies. In effect, it creates a continuous pipeline from early detection to clinical research participation.

What makes this especially relevant globally – and particularly for LMICs – is that the triple helix model offers a framework for overcoming precisely the structural barriers discussed throughout this chapter. Countries with limited dementia infrastructure often lack one or more components: research expertise, specialist diagnostic capacity, or commercial investment. The Scottish model suggests that meaningful progress happens fastest when these sectors are deliberately aligned. In places such as Ghana, where Scottish Brain Sciences has begun collaborative discussions on early detection and digital screening, the model offers a highly practical approach: a way to build Alzheimer's research capacity without first requiring a fully mature specialist ecosystem. Instead, capacity can be built through partnerships between local universities, health ministries, healthcare providers, and external diagnostic or pharmaceutical partners.

"We're not geographically bounded," Prof Ritchie tells ADI. "We have a centre open in California, for example, so I think this problem exists all over the world. It's not an NHS problem or a UK problem. It's also not a problem just in neuroscience. I think you can see how the template could be used in oncology, respiratory medicine, and other areas, because, as you dig deeper, people in the 21st century are not necessarily waiting for their doctor or nurse to ask for their permission [to access a clinical trial]. So I think that is important. If you're going to modify the course of any disease, you want to get in early."

That may ultimately be the model's most important lesson. The future of Alzheimer's research is unlikely to be built solely on isolated centres of excellence. It will depend on connected ecosystems capable of moving seamlessly from discovery to diagnosis to intervention. The triple helix model provides one blueprint for doing exactly that – and for creating research systems that are not only faster and more efficient, but more globally inclusive.

Prof Ritchie adds: "There's no reason why we shouldn't be speaking to people in Ghana. I wrote a few papers with Sammy Danso, a Ghanaian [computer science researcher] who worked with me in Edinburgh. We had this notion that African countries and other parts of the Global South could actually leapfrog the Global North because we still have so many legacy issues [in the Global North] when thinking about dementia. What they could do is actually say, 'Well, we're not going to prioritise dementia services but prioritise brain health and early detection.'"

"You can actually make the diagnosis in asymptomatic individuals in Ghana, Kenya, Tanzania. We're working very closely with AFRICA-FINGERS. Pharmaceutical companies want to work in Africa – you just need to have organisations that make it feasible for them to do so. And that's what we're looking to do."

The transformative powers of digital innovation

The attraction is obvious. In health systems where specialist neurologists remain scarce, digital screening tools could allow large numbers of people to be assessed in primary or community settings, with only higher-risk individuals referred onward for more advanced testing. This is where digital innovation may prove genuinely transformative. The future of Alzheimer's inclusion may depend less on replicating specialist-heavy memory clinic models everywhere and more on creating screening systems that identify risk early, cheaply, and at scale.

22 https://brainsciences.scot/dementia-a-treatable-condition-of-midlife/

One of the least discussed barriers in global dementia diagnosis is that many cognitive screening tools were developed and validated in high-income settings, then applied in populations with very different languages, educational backgrounds, and cultural experiences. In countries where literacy levels vary widely, poor performance on a cognitive test may reflect limited formal education or cultural unfamiliarity rather than a neurodegenerative condition. Without culturally appropriate and validated screening tools, people may be misdiagnosed, excluded from care, or overlooked for research. Reliable early diagnosis is also essential for identifying participants for clinical trials and building representative research cohorts.

Few places illustrate this better than Ethiopia, where researchers supported by the Global Brain Health Institute are working on one of the most practical and potentially impactful dementia-diagnosis projects in the Global South: adapting and validating a culturally appropriate brain health assessment tool for local use.[23] The project focuses on translation and validation of the Brain Health Assessment battery into Amharic, ensuring that cognitive screening is not distorted by language, literacy, or cultural mismatch.

Researchers in Latin America are tackling many of the same challenges. In Peru, neurologist Dr Nilton Custodio has spent two decades adapting and validating cognitive screening tools for people with limited formal education and Indigenous Quechua-speaking communities. His work reflects a growing recognition that accurate diagnosis depends on cognitive assessments adapted to local linguistic, cultural, and genetic contexts.

Dr Custodio tells ADI: "The Latin American genetic structure is quite unique. Argentina and Chile have a genetic profile similar to Europe; 80–90 percent [of the population] are of European origin. Meanwhile, Peru has an 80 percent native population, with no more than 10 percent of African or European [ancestry]. So, we need to build capacity to identify people with cognitive impairment. The first task for Peru is to determine which cognitive tools work best for people with lower levels of education and for groups such as the Aymara and Quechua [the two largest and most prominent Indigenous language and cultural families in the central Andes of South America]. We started these activities in 2005, and by 2020, we found what are probably ideal cognitive tools."

This work has included the adaptation and validation of brief cognitive assessments, such as the Rowland Universal Dementia Assessment Scale (RUDAS), and the development of locally adapted screening batteries for Quechua-speaking and low-literacy populations, thereby reducing the educational bias seen with many traditional cognitive tests.[24] Dr Custodio adds: "Ecuadorean people have similar genetics. So in the next three or five years, I hope that Latin America has harmonised cognitive tools that are the best for our genetic makeup."

The implications of creating adapted cognitive screening tools stretch much further. Reliable early screening is foundational not only for care, but also for research, cohort development, and future clinical trial participation. Without scalable, culturally appropriate assessment tools, inclusive research becomes almost impossible. The work of researchers in Ethiopia and Peru demonstrates that sometimes the most important innovation in dementia science is not a new drug or biomarker, but a better front door into the system.

That same principle is driving innovation in poorer parts of Asia, where researchers are increasingly combining digital tools, community engagement, and non-pharmacological interventions to compensate for limited specialist infrastructure.

In the Philippines, Prof Anlacan describes how structural barriers around expensive biomarker-led trials have pushed clinicians to think more creatively about accessible interventions. The emphasis has increasingly shifted towards technologies and therapies that can be delivered at lower cost, including digital tools and non-pharmacological care models. This includes virtual reality-based interventions, telehealth, and remote cognitive support systems – approaches that may not generate the headlines associated with anti-amyloid drugs but could prove highly relevant in lower-resource settings where access to advanced therapeutics remains limited. Prof Anlacan sees these approaches not as substitutes for pharmacological progress but as necessary parallel innovations. "We try to stay away from drug trials in the Philippines because it's an impossible task, so we try to focus on non-pharmacological trials or add-on trials," she says.

Her work currently focuses on two Alzheimer's-related studies. The first explores precision medicine approaches through genetics and the gut microbiome, investigating whether specific genetic variants influence how patients respond to existing Alzheimer's medications. Alongside this, her team is studying microbiome-related metabolic pathways to better understand whether gut health could help predict disease risk, treatment response, and potentially even identify microbiome profiles that improve therapeutic effectiveness. The goal is to move towards more personalised treatment strategies using tools that may eventually be more scalable than high-cost drug trials.

Her second and perhaps most innovative project is a virtual reality-based intervention for dementia care, developed over several years with university and government support. The platform creates immersive therapeutic environments

23 https://www.gbhi.org/projects/cultural-adaptation-and-validation-brain-health-assessment-ethiopia
24 https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.629325/full

where patients, guided by a therapist, engage in a range of non-pharmacological interventions, including art therapy, reminiscence therapy, music therapy, and cognitive exercises.

"We have been working on virtual reality applications for dementia patients for several years already," Prof Anlacan tells ADI. "You can play the game using the headset, and if you are afraid of that, we also have a view which is projected onto the walls – you won't need to wear anything, just bracelets that will track the movements of your hands."

"The participants find themselves in different areas that they want. They will be asked to choose if they want to go to a park, a beach, or in front of a church. Once they are there, they have several activity groups. There is a big vase you can paint and rotate, a car that you can arrange and put together, a sing-along karaoke where you are given virtual maracas, and you can explore the virtual world with the help of the therapist. The patient is seated and safe."

The project has progressed from an initial phase involving healthy participants to a Phase 2 trial involving Alzheimer's patients at all stages of the condition, with around 30 participants in each phase. Recruitment came through university networks and nearby hospitals, reflecting the programme's grassroots nature. Importantly, Prof Anlacan notes that recruitment patterns also revealed stark socio-economic disparities in dementia care: patients at private sites tended to present at earlier stages of disease, while those attending government hospitals were far more likely to have moderate to severe cognitive impairment, highlighting major delays in diagnosis and treatment among lower-income populations.

While Prof Anlacan is realistic about the limitations of small-scale studies in delivering statistically powerful conclusions, she emphasises that clinical meaningfulness extends beyond sample size alone. Patient response to the virtual reality intervention has been overwhelmingly positive, particularly in addressing behavioural and psychological symptoms such as apathy, an area where pharmacological options remain limited. Families and caregivers involved in the development process from an early stage have reported strong enthusiasm for the platform, with many expressing a desire for home-based versions. For Prof Anlacan, this points to a broader lesson for Alzheimer's research in LMICs: meaningful innovation may not always come through blockbuster drug trials, but through practical, culturally adaptable interventions that improve quality of life and can be integrated alongside existing care.

The same pattern is visible across parts of Southeast Asia, where dementia researchers are increasingly focused on scalable screening, prevention, and low-cost intervention rather than immediate access to monoclonal antibody treatment. This shift reflects a broader truth that runs through nearly every successful example emerging from LMICs. Innovation does not always happen where the money is. Sometimes it happens where constraints force researchers to ask sharper questions: How do you screen earlier without specialists? How do you reduce risk before treatment becomes necessary? How do you recruit inclusively when infrastructure is limited? How do you design research around the lived reality of patients and families?

The answers emerging from Africa and Asia suggest that inclusion may require the creation of entirely different systems. This is perhaps the most important lesson from the Global South's recent successes in Alzheimer's research. These initiatives are not simply catching up with the rest of the world. In many cases, they are solving problems that wealthy health systems will increasingly face as demand for dementia screening and treatment grows.

That future will demand scale, efficiency, and inclusion on a level the current clinical trial model is not equipped to deliver. The Global South's most promising research initiatives are beginning to show what that next model might look like: more digital, more community-centred, more prevention-focused, and more culturally adaptive. Innovation shaped by constraint rather than despite it.

Success stories and global lessons

If one lesson emerges clearly from Alzheimer's research in LMICs, it is that inclusion is not simply a moral imperative or a diversity target. Increasingly, it is a scientific necessity. The countries and organisations that have made the greatest progress in recent years are not necessarily those with the largest budgets or most sophisticated infrastructure, but those that have found ways to overcome the practical barriers that have historically excluded so much of the world from dementia science: delayed diagnosis, poor recruitment, weak trial infrastructure, and limited diversity in participant populations.

Nowhere is this clearer than in Colombia, which has fast become one of the most important countries in the history of Alzheimer's prevention research. For decades, the work of Professor Francisco Lopera and the Grupo de Neurociencias at the University of Antioquia transformed a cluster of families in Antioquia carrying the PSEN1 "Paisa" mutation into one of the world's most important cohorts for understanding preclinical Alzheimer's disease. The Alzheimer's Prevention Initiative (API) Colombia trial, run in partnership with Banner Alzheimer's Institute and Genentech, helped shift global thinking away from treating symptomatic disease and towards prevention decades before clinical symptoms appear.

As we said at the start of this chapter, although the original crenezumab trial did not achieve its primary endpoint, its global impact has been profound. The study demonstrated that sophisticated prevention trials could be delivered successfully in Latin America, even in relatively resource-constrained settings. Perhaps even more importantly, it showed what sustained

community engagement could achieve. By year four, participant retention stood at 94 percent, an extraordinary figure for a long and demanding prevention study.

That success was built through trust, family engagement, transport support, and long-term relationships with participants. In effect, Colombia solved one of the hardest problems in Alzheimer's trials: how to keep healthy participants engaged in intensive research for years before symptoms emerge. That lesson now informs prevention trials globally. The next phase, API Colombia 2, is already testing new interventions including donanemab, underscoring Colombia's continuing centrality to the field.[25]

Elsewhere in Latin America, success has increasingly come through collaboration rather than single-site leadership. The ReDLat initiative – Research Dementia in Latin America[26] – brings together researchers across Argentina, Brazil, Chile, Colombia, Mexico, Peru, and beyond to address one of the most persistent weaknesses in global dementia science: the treatment of Latin America as a single, homogeneous population. Led by Professor Agustín Ibáñez, the consortium integrates genetics, biomarkers, neuroimaging, and social determinants of health to better understand how dementia manifests across highly diverse Latin American populations.

Its importance extends well beyond the region. Latin America's genetic diversity and sharp social inequalities make it a uniquely powerful setting to study how biological and environmental factors interact in dementia risk. Insights from ReDLat are increasingly shaping global conversations around biomarker thresholds, genetic risk, and diagnostic equity.[27] In practical terms, this work is helping challenge a longstanding problem in Alzheimer's science: the assumption that data derived largely from white populations can be universally applied.

Africa presents a different but equally important success story. Historically, dementia research on the continent has been severely underfunded and underrepresented, particularly in biomarker-led studies. Yet this is beginning to change. Rather than importing European protocols unchanged, Africa-FINGERS is designing interventions around local realities.

The importance of this shift is difficult to overstate. Prevention strategies only work when they fit the social and healthcare context in which they are delivered. Africa's contribution to Alzheimer's science may therefore prove especially important not because it replicates existing models, but because it forces the field to design better ones.

In India, a different model of success is emerging. Rather than focusing primarily on monoclonal antibody trials, researchers have increasingly concentrated on scalable dementia prevention and early detection models that can operate within an overstretched health system. FINGERS-India has attracted growing attention because it asks a question that will become increasingly relevant worldwide: how do you deliver brain health interventions at a population scale in a country with huge socioeconomic and geographic variation?

That question matters far beyond India because even high-income countries are beginning to confront similar capacity problems. Specialist memory services are overwhelmed, referral pathways remain slow, and identifying eligible patients early enough for intervention remains one of the biggest bottlenecks in modern Alzheimer's care. This is where some of the most interesting innovations are emerging – not from drug trials alone, but from trial redesign.

Researchers in LMICs are increasingly pioneering decentralised, community-led, and digitally enabled models that reduce dependence on specialist centres. In the Philippines, Professor Michelle Anlacan has shown what this looks like in practice. Faced with the high costs and infrastructure barriers associated with conventional biomarker-driven drug trials, her research has focused instead on practical interventions that improve care within local constraints. These interventions may not attract the same attention as anti-amyloid drugs, but they address an equally important goal: improving quality of life in settings where access to advanced therapeutics remains limited.

The global significance of these success stories lies in what they reveal about the future of Alzheimer's research. The central challenge facing the field is no longer simply scientific discovery, but implementation. How do we recruit earlier? How do we improve retention? How do we ensure safety while expanding inclusion? How do we build research systems that reflect the populations most affected by dementia? The Global South has become an increasingly important source of answers.

Latin America has demonstrated that long-term prevention trials with exceptional retention can succeed outside traditional research centres. Africa is helping redefine culturally adaptive prevention science. Asia is showing how digital and community-led models can expand access while reducing costs. Together, these efforts are reshaping a fundamental assumption in dementia research. For too long, inclusion has been treated as something to improve once scientific progress has been secured. Increasingly, the opposite is proving true. Better science depends on broader inclusion from the outset.

25 https://alzheimerspreventioninitiative.com/api-studies/adad-colombia-trial-2/
26 https://red-lat.com/redlat2-a-new-era-for-dementia-research-in-latin-america/
27 https://www.nature.com/articles/s41591-026-04433-3

CASE STUDY

'Diagnosis shouldn't be a luxury, it should be a human right': the race to build Africa's Alzheimer's future

In parts of rural Kenya, dementia is still explained through whispers. An older woman begins forgetting names. She wanders from home and talks to people who are no longer there. Families fear she has been cursed, possessed, or bewitched. Some hide sick relatives away from neighbours, others seek help from faith healers before doctors. A few patients, Professor Zul Merali says quietly, are beaten or abandoned.

"People feel that when you start acting strange, maybe you are possessed by evil spirits," he tells ADI. "And very often, people are not very kind to those suffering from dementia because they think they have been possessed."[28]

Professor Merali has spent the last five years trying to change that. At the Brain and Mind Institute (BMI) at Aga Khan University in Nairobi, the neuroscientist and pharmacologist is leading one of Africa's most ambitious efforts to prepare not only that continent but also South and Central Asia for the inevitable surge in dementia cases. Projections are that the number of people over 60 is going to triple or quadruple in size by 2050 in the Global South[29] – and with it an inevitable surge in dementia cases.

The BMI is therefore not only researching Alzheimer's disease but also building the infrastructure that could allow Africa to participate meaningfully in the next generation of global Alzheimer's clinical trials, so it is not left behind in the race for new treatments. That means constructing large data hubs, creating culturally adapted diagnostic tools, training young scientists, collecting biomarkers, mapping community risk factors, and building relationships with populations historically excluded from neurological research. It also means confronting one of the starkest inequities in global medicine.

"Less than 2 percent of the information in dementia research is coming from the Global South," Prof Merali says. "Despite the fact that two-thirds of people with dementia and Alzheimer's disease are going to be residents of the Global South."[30]

Alzheimer's research is entering a transformative new phase. Drugs targeting amyloid plaques, including lecanemab and donanemab, have opened the possibility of slowing cognitive decline for some patients – especially if treatment begins early enough. But nearly all the underlying research, biomarkers, and trial populations used to develop those drugs have come from Europe, North America, and wealthy parts of Asia. Africa, despite containing the greatest human genetic diversity on Earth, remains dramatically underrepresented in clinical trials for Alzheimer's disease and other forms of dementia.

Prof Merali worries the consequences could be profound given the different genetic makeup of populations between ethnicities. One well-known gene that influences Alzheimer's risk is the apolipoprotein E (APOE) gene, which encodes a protein that helps transport cholesterol and other lipids in the bloodstream. Problems in this process are thought to contribute to the development of Alzheimer's.

"APOE is very predictive of dementia development in the Global North," he says, referring to the APOE4 gene variant long associated with increased Alzheimer's risk. "Yet if you look at Black populations, such is not the case."

The presence of APOE4 carries a significantly lower statistical risk for developing Alzheimer's disease in people of African ancestry compared to those of European or East Asian descent.[31] "So are we getting on the wrong track to develop drugs that may fail in the world's health?" Prof Merali asks. "I think that the correct way of doing it is to make sure that we recruit more diverse populations in research. And I think the Global South needs to contribute a lot more to that pool of knowledge that is being developed."

The BMI was founded precisely because Africa's brain-health crisis was being overlooked. "Brain and mental health conditions are amongst the largest and fastest-growing challenges in Africa and in the Global South, period." Professor Merali says. "Yet they remain dramatically underfunded and understudied."

28 https://www.independent.co.uk/news/world/africa/africa-dementia-witch-nigeria-uganda-b2818333.html
29 https://www.who.int/news-room/fact-sheets/detail/ageing-and-health
30 https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.71269
31 https://www.nature.com/articles/s41467-026-68808-3

The institute's vision, he explains, is a "neuron to neighbourhood" approach: connecting neuroscience, dementia, psychiatry, technology, and community care into a single integrated system. It is an unusually expansive model. Anthropologists work alongside neurologists. Social scientists collaborate with geneticists. Community healthcare workers sit with digital-health specialists. One moment, researchers are discussing blood-based biomarkers; the next, they are examining stigma, isolation, and cultural beliefs surrounding ageing and memory loss.

"We are very embedded in the communities that we serve," Prof Merali says. "We have teams of anthropologists and social scientists who actually work with the communities to fully understand what their perceptions are, and we're learning that they're very keen on participating in research. They are willing to share samples of all kinds. They're happy to be imaged, they're even willing to allow CSF [Cerebrospinal Fluid – a clear, colourless bodily fluid that acts as a protective cushion or shock absorber for the brain and spinal cord] collection. But they're not too keen on collecting some body samples, such as hair, which has a very special significance to the geographies where we are."

Such findings shape whether clinical trials succeed or fail. Many believe you can't simply parachute Western science into communities and expect trust to follow. And trust, in fact, may become Africa's greatest contribution to future dementia science. As Alzheimer's drug development accelerates globally, researchers increasingly recognise the need for more diverse trial populations. Blood biomarkers, digital diagnostics, and AI-driven risk models all require broader datasets to work equitably across populations.

That embeddedness may prove essential if Africa is to become a serious player in Alzheimer's clinical trials. For decades, dementia research in many African countries has been constrained by an absence of foundational infrastructure.[32] There are too few neurologists and neuropsychologists. Imaging technology is concentrated in urban centres. Longitudinal cohort studies are rare. Patient registries are fragmented or non-existent. Standardised cognitive tests often fail outside Western educational contexts.

Professor Merali gives a simple example.

"The gold-standard cognitive test is the MoCA," he says, referring to the Montreal Cognitive Assessment widely used to detect cognitive decline.[33] "Yet when you go to rural areas of Kenya, you can't ask somebody who has never been to school to use paper and pencil to draw a clock face and show the time when they've never even seen an analogue clock face."

Douglas Nyankira, a lab technologist at the Brain and Mind Institute in Nairobi, Kenya, analyses samples in June 2026. (Photo by Muthoki Kithanze)

The implications ripple through every stage of Alzheimer's research. If screening tools are culturally inappropriate, early symptoms are missed. If the condition is diagnosed late, clinical trials recruit patients too far along the disease pathway. If populations remain poorly characterised genetically and socially, therapies developed elsewhere may prove less effective. So the BMI began by building from the ground up.

Over the past five years, researchers have developed contextually sensitive cognitive tests adapted for African populations, cross-validated against deep phenotyping and international standards. They have established a blood-based biomarker infrastructure designed to bypass some of the logistical limitations of expensive neuroimaging. They are conducting deep phenotyping studies, collecting longitudinal risk data and identifying people at risk of dementia before symptoms become severe.

"We want to be able to screen in the communities," Professor Merali says. "You can't screen communities when you don't have clinical neuropsychologists or neurologists. They are very few and far between in Africa."

Instead, the BMI is designing tools that can be administered by other healthcare workers in community settings, allowing earlier screening, identification, and referral. The goal is not merely diagnostic. It is strategic. "Part of our strategy is to be out in the community, identify people who are at risk, and then develop a spectrum of people who are in early stages of disease. So that if and when we do clinical trials, we already have identified populations that we can begin our work on," Prof Merali says.

Historically, dementia trials often begin too late, he adds. "It's like testing anticancer drugs when you have Stage 4 cancer. You need to start early."

32 https://pmc.ncbi.nlm.nih.gov/articles/PMC11923557/
33 https://mocacognition.com

That philosophy now sits at the centre of the institute's work. At Aga Khan University's Nairobi campus, the BMI is creating what researchers hope will become one of the most important dementia data hubs in the Global South. The hub stretches across East Africa – particularly Kenya and Tanzania – while a second centre in Karachi, Pakistan, collects comparable data from South and Central Asia.[34] Together, they are generating large datasets linking genetics, vascular risk factors, lifestyle factors, biomarkers, neuroimaging biobanks, and culturally adapted cognitive assessments. For pharmaceutical companies and global researchers, those datasets could eventually become invaluable.

"Africa has historically been light on large-scale clinical trials," Prof Merali says. "So we are building a strong foundational infrastructure."

The institute's work has attracted major international partnerships. One of the earliest came through the Davos Alzheimer's Collaborative (DAC), which helped fund the BMI's early diagnostic research. The partnership evolved into something larger: an attempt to place African dementia research at the centre rather than the margins of global scientific discussion.

"With DAC, we were able to convince the journal *Nature* to host one of our major conferences in Africa dealing with dementia in Africa," Prof Merali says.[35]

The symbolism mattered. For decades, Africa's role in global neuroscience has often been reduced to that of a data source rather than an equal research partner. Prof Merali is determined to reverse that dynamic. "Africa is not just a recipient of knowledge. We are generating much-needed data and collaborations where everybody grows."

The BMI's network now includes partnerships with Harvard University, the Global Brain Health Institute, the US National Institute on Aging, and multiple international dementia-prevention initiatives. One collaboration sends early-career African researchers to Harvard for postdoctoral training in global mental health before bringing them back to Kenya and neighbouring regions. "The idea is that they would plant themselves and develop roots locally to build capacity," Prof Merali says.

The issue of capacity-building looms over every conversation about dementia research in Africa. Yet neurological diagnostic and care systems remain fragile. Funding for dementia still pales beside financing for infectious diseases such as HIV, tuberculosis, and malaria. Governments face competing crises. Brain-health specialists continue to migrate overseas. Many patients seek medical help only after exhausting religious or traditional pathways first, Prof Merali says. "We are very dependent on people who show up at the door of the hospital. And I think we need to shift that."

The BMI's answer is to build what he calls a "pipeline" connecting communities to specialist urban healthcare. Researchers work directly in communities to identify risk, educate families, and reshape pathways into formal care systems. That community-based work has also revealed important social realities often absent from Western Alzheimer's literature.

Africa's enormous genetic diversity could reveal entirely new pathways of disease risk and resilience.[36] The question is whether the world will invest quickly enough. Prof Merali speaks carefully when discussing international funding. "I think the Global North should be participating more actively in promoting work in the Global South," he says. "But all the responsibility doesn't rest on the shoulders of the Global North. Governments in the Global South need to step up as well. That's a gap that we need to address."

Prof Merali acknowledges recent anxieties surrounding changing funding priorities within major US institutions such as the NIH,[37] although the BMI itself recently secured a grant from the US National Institute on Aging. For now, much of the institute's optimism lies in prevention science. One of the BMI's most important upcoming projects is African FINGERS,[38] an adaptation of the international FINGERS dementia-prevention model that has shown promise in Europe through lifestyle interventions. The clinical trials linked to African FINGERS are expected to begin soon, but prevention strategies cannot simply be imported wholesale.

"If I say exercise is important, I can't tell people to go to the gym because there are very few gyms available," Prof Merali says. Instead, researchers are exploring locally sustainable interventions rooted in community life: dancing programmes, community movement activities, and regionally appropriate and available nutritional diets.

Like many colleagues, Prof Merali believes Africa could eventually become one of the most efficient environments globally for Alzheimer's recruitment. "The populations are there," he says. "It'll be easy to recruit individuals for clinical trials."

34 https://www.aku.edu/bmi/research/Pages/hubs.aspx
35 https://www.aku.edu/news/Pages/News_Details.aspx?nid=NEWS-003259
36 https://theconversation.com/africa-has-the-worlds-greatest-genetic-diversity-yet-its-missing-from-research-were-filling-the-gap-278809
37 https://www.nature.com/articles/d41586-026-01426-7
38 https://africandementiaconsortium.org/africa-fingers-project/

Professor Zul Merali, founding director of the Brain and Mind Institute, is confident that Africa could host a fertile environment for dementia clinical trials. (Photo by Muthoki Kithanze)

What frustrates him is the continuing reluctance of many pharmaceutical and research institutions in wealthy countries to fully embrace African trial sites. "We have the infrastructure to do proper clinical trials," he says, pointing to Aga Khan University's dedicated clinical trials unit.

Still, the BMI's progress over five years has been remarkable. The institute has already developed culturally sensitive screening tools, established robust biomarker infrastructure, and built a growing network of international collaborations. Researchers are beginning to identify at-risk populations before severe disease develops. Young African neuroscientists are being trained locally and internationally. Perhaps most importantly, a different vision of global brain-health research is emerging. Prof Merali rejects the idea that advanced dementia diagnostics and therapies should remain luxuries available only to wealthy countries.

"Diagnosis and interventions for dementia and brain health in general shouldn't be a luxury," he says. "It should be a human rights issue. And we need to make sure that our people get access to state-of-the-art treatments and diagnostics, no matter where they are in the world. So I think that our intention at the Brain and Mind Institute is to realise that and bring solutions to fruition."

Outside the Aga Khan University campus, Africa is ageing rapidly, even as it remains the world's youngest continent. The future burden of Alzheimer's disease across the continent remains uncertain. So, too, does the future of Alzheimer's science itself. But within a growing network of clinics, laboratories, and community partnerships stretching from Nairobi to Karachi, researchers are trying to ensure that when the next era of dementia medicine arrives, Africa will not simply be waiting for answers developed elsewhere. Instead, it may help shape the answers from the start.

Chapter 7:

Conclusion and recommendations

Passengers on a train through Myanmar's green highlands share a laugh (and a mango) in July 2016. (Photo by Domenico Pugliese)

The global dementia clinical trial landscape in 2026 reflects a field undergoing profound transformation. After decades marked largely by frustration and slow progress, dementia research has entered a new phase – one characterised by tangible scientific progress, expanding therapeutic ambition, and cautious but genuine optimism. The central finding of this report is that clinical trials in Alzheimer's disease and other dementias are no longer defined solely by uncertainty over whether disease modification is possible. That question, while not fully resolved, has shifted. The more pressing challenge now lies in ensuring that scientific progress translates into equitable, meaningful, and globally accessible advances for all people affected by dementia.

The progress seen over the past five years is significant: that is the key message experts across the world emphasised during interviews for this report. Alzheimer's disease remains the dominant focus of therapeutic development, and the emergence of disease-modifying therapies has fundamentally changed the direction of the field. These developments have altered both scientific expectations and regulatory frameworks, while reshaping discussions around trial design, endpoints, safety, and long-term treatment delivery. Yet perhaps more significant than the arrival of these therapies is what they represent: a clear signal that dementia is no longer viewed as therapeutically intractable.

At the same time, this report highlights that the field is rapidly moving beyond a narrow focus on amyloid. While anti-amyloid therapies have dominated recent discussion, the pipeline in 2026 is considerably broader and more sophisticated than at any previous point. Clinical trials increasingly target tau pathology, neuroinflammation, synaptic dysfunction, vascular injury, mitochondrial biology, and neuroprotective mechanisms, reflecting growing recognition that dementia is biologically complex and heterogeneous. This evolution is important because dementia is not a single disease, and even within Alzheimer's disease, there is substantial biological variation in disease progression, symptom expression, and treatment response.

The future of dementia therapeutics is therefore unlikely to depend on any single intervention or biological pathway. Rather, it is increasingly expected to resemble other complex chronic disease areas, where successful treatment depends on earlier intervention, combination therapies, and more precise targeting based on biological profile. In practical terms, this points toward a future of precision medicine in dementia care, in which therapies are tailored to underlying pathology, stage of progression of the condition, and individual risk profile.

However, our findings also reveal a growing tension between scientific capability and healthcare system readiness. Put simply, the science is advancing faster than the systems required to support it. This tension is most visible in the area of diagnosis. Across all regions and across multiple forms of dementia, early and accurate diagnosis remains one of the most significant barriers to trial participation and therapeutic access. Modern dementia trials increasingly focus on early-stage disease or even presymptomatic populations, reflecting growing evidence that intervention is most effective before significant neurodegeneration has occurred. Yet for millions of people worldwide, diagnosis remains late, inconsistent, or entirely inaccessible.

The implications are substantial. Delayed diagnosis not only limits access to care and support but also restricts access to clinical research and emerging therapies. Participants are often identified too late to meet trial eligibility criteria, while many others are excluded due to limited access to specialist assessment, biomarker testing, or appropriate referral pathways. These barriers are particularly acute in low- and middle-income countries, although they remain highly relevant in high-income settings where specialist capacity is often constrained by workforce shortages and long waiting times.

The rapid development of biomarkers – particularly blood-based biomarkers – offers one of the most promising opportunities to address these challenges. Biomarkers are increasingly central to dementia clinical trials, supporting participant selection, diagnostic confirmation, disease staging, and monitoring of treatment response. If implemented effectively, blood-based biomarkers could significantly expand access to earlier, cheaper, and more scalable screening. However, technological progress alone will not resolve access disparities. Questions of affordability, implementation, and healthcare infrastructure remain central to whether these innovations deliver meaningful global impact.

Recruitment remains another major challenge facing dementia clinical trials. Despite advances in trial design and diagnostics, recruitment remains slow, costly, and operationally difficult. These challenges affect all stakeholders. For sponsors, delayed recruitment increases cost, prolongs development timelines, and introduces significant uncertainty. For participants and their loved ones, trial participation often involves considerable practical and emotional burden, including repeated travel, invasive procedures, frequent monitoring, and substantial caregiving demands.

The findings in this report make clear that recruitment challenges are rarely explained by lack of interest alone. Rather, they are shaped by a combination of logistical barriers, limited awareness, financial constraints, lack of trust, and hurdles to access to research centres. Participation is frequently easiest for those already embedded in well-resourced healthcare systems and living close to major academic or specialist sites. As a result, the current recruitment model often favours populations with greater structural advantages.

This leads directly to one of the most persistent concerns identified throughout this report: the continued lack of diversity, equity, and inclusion in dementia clinical trials.

Despite widespread recognition of the issue, progress remains inconsistent and insufficient. Trial populations continue to underrepresent many communities disproportionately affected by dementia, including ethnic minority populations, rural and disenfranchised communities, and those living in low- and middle-income settings.

This underrepresentation presents both ethical and scientific concerns. From an ethical perspective, it limits equitable access to research participation and emerging innovation. From a scientific perspective, it reduces confidence that trial outcomes will translate effectively across populations with differing genetic backgrounds, comorbidities, environmental exposures, and healthcare contexts. As therapeutic development becomes more sophisticated, ensuring representative trial populations becomes increasingly important.

This report also highlights a difficult but important reality: inclusion often requires sustained investment, time, and structural change. Building trust within underserved communities, developing local research infrastructure, and supporting more inclusive recruitment models cannot be achieved through aspirational commitments alone. Diversity must move beyond being treated as a nice-to-have and become a measurable standard of trial quality.

Safety has also emerged as a defining issue in the next generation of dementia therapeutics. As disease-modifying treatments move into broader clinical use, benefit-risk evaluation has become increasingly central to both trial design and regulatory decision-making. This is particularly evident in Alzheimer's disease, where amyloid-related imaging abnormalities (ARIA) have become a major consideration in discussions around treatment eligibility, monitoring, and long-term safety.

The findings of this report suggest that perceptions of acceptable risk vary considerably across stakeholders. Regulators, clinicians, researchers, patients, and carers may all weigh benefits and risks differently. Many people living with dementia are willing to accept significant risk in exchange for the possibility of slowing disease progression or preserving independence. These perspectives are important and must be meaningfully incorporated into regulatory and research decision-making.

At the same time, robust safety systems remain essential. Monitoring protocols, risk stratification, imaging surveillance, and transparent communication will all be critical to maintaining trust in emerging therapies and the clinical trial process more broadly. The long-term success of dementia therapeutics will depend not only on efficacy, but also on confidence that risks are well understood and appropriately managed.

Perhaps the strongest theme to emerge from this report is the growing importance of clinical meaningfulness. As therapeutic development accelerates, there is increasing recognition that trial success cannot be defined solely by biomarker changes or traditional cognitive endpoints. These measures remain important, particularly for regulatory purposes, but they do not fully capture what matters most to people living with dementia and their families.

For many, meaningful benefit is defined by preserved independence, daily functioning, emotional well-being, quality of life and reduced caregiver burden. It is measured in additional time spent living well, maintaining relationships, and sustaining autonomy. The future of dementia clinical trials must therefore become more person-centred, with outcome measures that better reflect lived experience alongside biological and cognitive measures.

Taken together, the findings of this report point to a defining challenge for the next decade. Scientific progress in dementia research is real and accelerating. Yet without equal progress in infrastructure, access, inclusion, diagnosis and trial design, these advances risk remaining unevenly distributed. The central challenge is no longer discovery alone. It is delivery. To that end, here are ADI's key recommendations:

For governments and policymakers

1. Invest in national diagnostic capacity and early detection pathways

Early diagnosis and risk assessment are foundational to both treatment access and clinical trial participation. Governments should strengthen specialist memory services, improve referral pathways from primary care, and expand access to biomarker testing, including blood-based biomarkers as they become clinically validated and widely available. Practical implementation should include investment in workforce training for general practitioners and frontline clinicians, alongside national diagnostic strategies that reduce waiting times and improve referral consistency. Without stronger diagnostic systems, many eligible participants will continue to be identified too late for clinical trial participation.

2. Create incentives for clinical trials in underserved regions

Governments should introduce targeted policy mechanisms to encourage clinical trial participation in underserved and understudied populations, including rural communities, low- and middle-income countries, and regions with limited research infrastructure. These mechanisms may include tax incentives, grant funding, streamlined regulatory pathways, and public-private partnerships designed to reduce operational barriers for sponsors. Policymakers should also consider co-investment models that incentivise pharmaceutical companies and

academic institutions to establish long-term research capacity in underserved areas rather than relying solely on short-term trial delivery.

3. Invest in dementia research infrastructure, diagnostic pathways, and public trial readiness globally

Sustained investment is needed to expand the infrastructure required to support high-quality dementia clinical trials, including imaging access, laboratory capacity, data systems, specialist workforce capacity, and regional research networks. Governments should prioritise funding for clinical research networks, digital health infrastructure, trial registries, and technologies that enable efficient data collection, remote monitoring, and broader participation.

Long-term infrastructure planning is particularly important in regions currently underrepresented in global dementia research, where limited research capacity remains a major barrier to inclusion. Building research infrastructure must ultimately be matched by equitable access to successful interventions, ensuring that populations contributing to research are also able to benefit from the treatments they help develop.

Governments should also invest in building trial-ready populations through sustained public education about dementia, clinical research, and emerging treatments. Responsibility for improving awareness should not rest solely with pharmaceutical companies. Governments, health systems, advocacy organisations, and research institutions should work together to develop coordinated public education campaigns that improve understanding of dementia, reduce stigma, and explain clinical trial participation in clear, balanced, and accessible terms.

The scale of this challenge should not be underestimated. As the global pipeline of dementia therapies expands, clinical trials will require substantially larger numbers of people to enter diagnostic and screening pathways to identify those eligible for clinical trials. Because many people will ultimately prove ineligible through biomarker testing, clinical assessment, or other eligibility criteria, recruitment efforts must extend far beyond the number of participants eventually enrolled. Stronger public understanding, earlier diagnosis and well-connected referral pathways will therefore be essential to building more informed, diverse, and trial-ready populations worldwide.

For national Alzheimer's associations

4. Strengthen the role of national Alzheimer's associations in dementia research and innovation

National Alzheimer's associations should proactively adapt their role within the rapidly changing dementia research landscape. As disease-modifying therapies and clinical trials become an increasingly important part of dementia care, associations should develop the knowledge, skills, leadership, and organisational capacity needed to provide accurate, balanced, and accessible information about clinical trials, emerging treatments, benefits and risks, regulation, value, reimbursement, and access.

Associations should strengthen their role in supporting informed decision-making, improving public understanding of research, encouraging equitable participation in clinical trials, and advocating for policies that improve access to diagnosis, research, and future treatments. This should include investment in staff training, organisational leadership, partnerships with researchers, healthcare providers, and policymakers, and clear engagement pathways for people living with Alzheimer's disease and other forms of dementia, those at increased risk, and their carers. As trusted voices within their communities, national associations will play a critical role in ensuring scientific advances translate into meaningful opportunities for everyone affected by dementia.

For trial sponsors and regulators

5. Embed diversity and inclusion into trial design from the outset

Diversity and inclusion should be recognised as core components of trial quality rather than secondary recruitment objectives. This requires action at two levels. First, trials should better reflect the diversity of populations within participating countries, including differences in ethnicity, socioeconomic background, geography, and underserved communities. Second, the global geography of dementia research must itself become more inclusive, with substantially greater investment in clinical trial capacity across low- and middle-income countries that remain underrepresented despite carrying a growing share of the world's dementia burden.

Sponsors should build diversity targets into protocol design, site selection, and recruitment planning from the earliest stages of development, with clear accountability mechanisms and regular reporting. Practical steps may include expanding site locations beyond major academic centres, partnering with community organisations, and funding local engagement initiatives that improve trust and awareness among historically underrepresented populations. More representative trials will strengthen the scientific validity, global applicability, and real-world relevance of future dementia interventions, ensuring that discoveries are relevant to the populations most affected by the disease.

6. Reduce participant burden and strengthen participant-centred trial models

Trial participation remains demanding for people living with dementia and their care partners, and reducing this burden should be a strategic priority. Trial sponsors should adopt hybrid and decentralised trial models where feasible, incorporating remote assessments, telehealth consultations, local laboratory testing, and mobile research services. Protocol simplification should also be prioritised, with careful review of whether visit frequency, testing burden, and procedural requirements are clinically necessary or could be streamlined without compromising scientific integrity.

Participant-centred trial design should also consider how people who contribute to research can benefit when meaningful treatment advances emerge. Where a therapy demonstrates a favourable benefit-risk profile, sponsors and regulators should explore ethical mechanisms that enable participants initially assigned to a placebo to access the active treatment, where scientifically and clinically appropriate. These may include open-label extension studies or other transition pathways that preserve the integrity of long-term safety and efficacy assessments. Ensuring that participants are not excluded from the benefits of successful research is essential to maintaining trust and encouraging future engagement with clinical trials.

7. Continue strengthening safety standards and communication

Robust safety systems are fundamental to the design, delivery, and long-term success of dementia clinical trials. Sponsors should continue investing in risk-stratification tools, enhanced monitoring protocols, and real-world pharmacovigilance systems to better identify, predict, and manage adverse events such as ARIA. These investments not only improve participant safety but also strengthen confidence among regulators, clinicians, and participants, supporting more efficient trial delivery and the responsible evaluation of emerging therapies. Equally important is transparent communication with participants and families, ensuring that risks, uncertainties, and expected benefits are clearly explained in language that supports informed decision-making.

Regulators and health technology assessment (HTA) bodies should also continue evolving their evaluation frameworks to reflect the realities of dementia. Decisions should take account not only of traditional clinical endpoints but also of outcomes that matter to people living with dementia and their families, including independence, quality of life, and the wider societal impact of delaying disease progression. Where appropriate, regulatory pathways that enable timely access to promising therapies while maintaining robust post-marketing evidence generation should continue to be supported.

For researchers and clinicians

8. Prioritise clinically meaningful outcomes

Dementia clinical trials should be designed from the outset to evaluate outcomes that matter most to people living with dementia and their loved ones, rather than relying solely on traditional cognitive and biomarker endpoints. Independence, daily functioning, behavioural symptoms, communication, quality of life, and caregiver burden should increasingly be incorporated into trial protocols as key measures of success alongside biological and cognitive outcomes. Researchers should work closely with people living with dementia, care partners, and regulators to develop, validate, and agree on outcome frameworks that better reflect clinically meaningful benefit. Embedding these measures into trial design from the earliest stages will help ensure that future therapies demonstrate not only biological effects but also meaningful improvements for everyday life.

Researchers should also continue expanding investment in high-quality non-pharmacological clinical trials, including interventions focused on risk reduction, rehabilitation, psychosocial support, and lifestyle changes. Drug development remains essential, but improving dementia care will also depend on generating robust evidence for interventions that can enhance quality of life, maintain function, and support people living with dementia throughout the course of the disease.

9. Further embed people living with dementia and carers in trial design and strengthen clinician referral pathways

People living with dementia and care partners should always play a meaningful role in shaping protocol design, endpoint and outcome measure selection, and participant experience. Their active involvement has become increasingly common in recent years, as it can improve trial feasibility, reduce unnecessary participant burden, and ensure research reflects real-world priorities. Practical approaches include formal advisory panels, patient review groups, and co-design workshops at the earliest stages of trial development, rather than limiting engagement to consultation after protocols are largely finalised.

Healthcare professionals, particularly those working in primary care, will be central to improving access to dementia clinical trials as earlier diagnosis and dementia risk assessment become increasingly important. Yet awareness of active dementia trials remains limited outside specialist research centres, and discussion of research opportunities is rarely embedded within routine clinical care. Health systems and research organisations should strengthen clinician education through training programmes, referral tools, and accessible trial registries integrated directly into clinical workflows.

They should also develop systems that make the discussion of relevant clinical trial opportunities routine and expected in the diagnostic and referral pathway, rather than relying on individual clinician knowledge or initiative. Stronger links between research sites, hospitals, and community-based care providers will be essential to improving referrals, widening participation, and ensuring that eligible patients are consistently offered the opportunity to consider research alongside standard clinical care. This will also strengthen the ability to articulate the real-life impact of treatment on both people living with dementia and carers.

10. Expand investment beyond Alzheimer's disease

Although Alzheimer's disease continues to dominate research investment, greater attention must be directed toward other forms of dementia, including vascular dementia, frontotemporal dementia, Lewy body dementia, and mixed dementias. These conditions remain significantly underrepresented despite substantial unmet clinical need. Governments, funders, industry, and academic institutions should work together to develop targeted research programmes, incentivise investment, and support trial infrastructure for these underserved disease areas.

For people living with dementia and care partners

People living with dementia and their care partners also have an important role to play in shaping the future of dementia research. Individuals should feel empowered to ask their healthcare professionals whether clinical trials may be appropriate for them, seek information from trusted organisations, and consider research participation where it aligns with their values and circumstances.

Participation in research is always a personal choice, but informed conversations can help ensure people are aware of opportunities that might otherwise never be discussed. Beyond participation itself, people living with dementia and carers can help improve future trials by contributing their lived experience to study design, advisory groups, and advocacy initiatives.

Final reflections

Dementia clinical trials stand at an important moment in history. Recent scientific breakthroughs have offered genuine cause for optimism, but scientific progress alone will not define success. Success will ultimately be measured by whether innovation becomes accessible, equitable, and meaningful for all people affected by dementia, regardless of geography, background, or diagnosis. The future of dementia research must be global in ambition, inclusive in design, and centred on the realities of lived experience. The opportunity is substantial. The responsibility to deliver on it is greater still.

Bill Gates recently observed that the pace of progress in Alzheimer's research has accelerated dramatically over the past decade. The Microsoft cofounder said: "Alzheimer's research has historically faced problems with scale: not enough people diagnosed early enough, not enough people in clinical trials, not enough data sharing to learn more."

Gates, who lost his father to Alzheimer's disease in 2020, added: "I'm optimistic that game-changing breakthroughs in the fight against Alzheimer's will soon be here – and while my dad never got the chance to benefit from these innovations, I'm hopeful that future families will. Consider this: For the first time, we have simple, accessible blood tests that can detect Alzheimer's earlier. Because of these tests, researchers will be able to screen hundreds of patients instead of just one or two a day and hopefully accelerate enrolment in clinical trials. We're entering a period where progress against the disease is taking huge strides. If the last couple of years is any indication, I can't wait to see what the next ten brings."[1]

The challenge for the next decade is to ensure that taking part in dementia research no longer depends on persistence or good fortune, but becomes a realistic opportunity for everyone who wishes to consider it. For Julie Stauffer Moore (see page 67), who enrolled in a Phase 2 Alzheimer's clinical trial after her own diagnosis, the reason for participating was simple: "I felt very supported and I felt very optimistic… If there is going to be progress, then I'm glad to have participated."

1 https://www.linkedin.com/feed/update/urn:li:activity:7469496437156925441/

Alzheimer's Disease International: The International Federation of Alzheimer's Disease and Related Disorders Societies, Inc. is incorporated in Illinois, USA, and is a 501(c)(3) not-for-profit organisation

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