Science disconnected: the translational gap between basic science, clinical trials, and patient care in Alzheimer's disease

Science disconnected: the translational gap between basic science, clinical trials, and patient care in Alzheimer's disease

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Both research and clinical practice have traditionally centred on the dementia syndrome of Alzheimer's disease rather than its preclinical and prodromal stages. However, there is a strong scientific and ethical impetus to shift focus to earlier disease stages to improve brain health outcomes and help to keep affected individuals symptom-free (dementia-free) for as long as possible. We provide an overview of recent advancements in early detection, drug development, and trial methodology that should be utilised in the development of new therapies for use in brain health clinics. We propose a triad approach to Alzheimer's disease clinical trials, encompassing (1) experimental medicine studies to gather greater knowledge of disease mechanisms, (2) a more comprehensive platform of phase 2 learning trials to inform phase 3 confirmatory trials, and (3) precision medicine involving smaller subgroups of patients with shared characteristics. This triad would ensure that treatment targets are identified accurately, trial methodology focuses on at-risk populations, and sensitive outcome measures capture potential treatment effects. Clinical services around the world must embrace the brain health clinic model so that neurodegenerative diseases can be detected in their earliest phase to quicken drug development pipelines and potentially improve prognosis.

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Introduction

Alois Alzheimer discovered the soon-to-become eponymous condition of Alzheimer's disease in 1906, describing misfolded and then aggregated amyloid β and tau, brain atrophy, and a host of cognitive and functional symptoms. Accordingly, clinical symptoms of memory loss formed a prominent, and then core, part of the diagnostic criteria for Alzheimer's disease, alongside functional impairment. With clinical history and neuropsychological assessment forming the basis of Alzheimer's disease investigations throughout the 20th century, Alzheimer's disease became predominantly conceptualised as a cognitive disorder due to its late-stage clinical manifestations. Despite advancements in in-vivo biomarker development to support diagnosis, this legacy of considering Alzheimer's disease mainly in the context of cognition is proving resilient, hampering clinical practice and clinical trials. As such, the majority of clinical trial work has been done with people in the very late, symptomatic or dementia phases of the disease. We now know that there is a long, silent (or preclinical) period of Alzheimer's disease, beginning as early as midlife (40–65 years of age), followed by a shorter prodromal period (3–6 years before symptom onset).[1] Both the preclinical and prodromal periods could represent key windows for interventions to delay or even prevent dementia. Crucially, the period currently conceptualised as being silent (or asymptomatic) is becoming increasingly detectable through biomarker discovery and development. Importantly, during these periods, cognitive symptoms are largely absent. Thereby, it might be time to revisit Alois Alzheimer's original proposal of Alzheimer's as a brain disease, which might be more readily detected in its early stages using new biomarkers, rather than continue its classification as a syndromal cognitive disorder.

There are three overarching considerations for the planning of future trials in Alzheimer's disease: (1) the right disease pathology target; (2) the right time in the disease process; and (3) the right person. The trial population needs to be sufficiently phenotyped to identify individuals at each disease stage. We will discuss recent developments in the field of Alzheimer's disease that inform each of these stages and argue for a triad approach to Alzheimer's disease clinical trials that would further enhance all three. In terms of selecting the right participants, we will also highlight developments in the brain health clinic service, which is a necessary upstream requirement to support more targeted clinical trial efforts.

Recent discoveries in Alzheimer's disease pathology

The field of biomarker discovery for Alzheimer's disease is constantly evolving. Many clinical trials of prodromal Alzheimer's disease now include metabolic measures, such as PET imaging, either as screening tools for study eligibility or as secondary or tertiary outcome measures. Currently, a PET tracer compound is being developed to detect synaptic loss,[2] which is a crucial event in Alzheimer's disease pathology thought to correspond with the start of observable cognitive impairment and other behavioural and neuropsychiatric problems.[3] The early onset of cognitive impairment is also when most patients first present to clinical services and thereafter enter into research studies, albeit in smaller numbers. Although this radiotracer has not yet been verified in autopsy studies, synaptic loss has been well correlated with cognitive decline in previous post-mortem investigations, suggesting that this measure is likely to be a useful biomarker in the future.[4] Regarding neuroimaging, recent focus has been on the thinning of certain brain regions, such as hippocampal subfields[5–7] and the entorhinal cortex,[8] as a highly sensitive measure of structural changes in the pre-dementia stages of Alzheimer's disease.[9] Although promising, robust measurement techniques must be developed before

these neuroimaging metrics can be incorporated into clinical trials as primary or secondary outcomes. Historically, the validation of biomarkers for Alzheimer's disease (eg, PET ligands and cerebrospinal fluid [CSF] assays) has been through autopsy studies. The incorporation of these in-vivo PET and CSF biomarkers into the diagnostic criteria for Alzheimer's disease in the National Institute on Aging-Alzheimer's Association Research Framework 2018[10] has led the Alzheimer's Precision Medicine Initiative Working Group to call for the validation of blood-based biomarkers for cognitive impairment.[11] Evidence suggests that blood tests measuring amyloid β_{42} to amyloid β_{40} ratios correlate with cortical amyloid β deposition, with a positive predictive value of 81%.[12] Similarly, plasma amyloid β measurements have been shown to have a high stability and sensitivity, suggesting that this metric could be used to detect Alzheimer's disease in its early stages now and as a screening test in the future.[13] Additionally, measuring phosphorylated tau in the blood can predict tau and amyloid β pathologies, differentiate Alzheimer's disease from other neurodegenerative disorders, and identify Alzheimer's disease across the clinical continuum.[14] As such, blood phosphorylated tau shows particular potential as a less invasive, cost-effective biomarker of Alzheimer's disease pathology.[15] Alongside the more familiar amyloid and tau proteins, neurofilament light polypeptide is increasingly being considered a possible biomarker for Alzheimer's disease pathology.[16] Once these novel neuroimaging and biological biomarkers are validated, there will be no need to access specialists and specialist facilities for pre-screening in clinical trials, which could increase global access to studies. These metrics could also act as sensitive outcome measures.

Detecting change along the Alzheimer's disease continuum

Detecting brain disease will continue to require two broad domains of assessment: first, changes in the brain itself and, second, any behavioural changes that these brain pathologies mediate. These two broad domains are important throughout the Alzheimer's disease process; however, it is unlikely that the psychometric properties of a single cognitive or behavioural test or a battery of tests can cover the range of impairment across the Alzheimer's disease continuum. Equally, biomarkers are validated against dementia as an outcome as standard, rather than against early-stage Alzheimer's disease pathology with no dementia syndrome. Therefore, more specific and sensitive behavioural tests are needed for use in the preclinical and prodromal periods and a new gold standard is needed for validating biomarkers at early disease stages.

Currently, regulators require clinical trials of treatments for Alzheimer's disease to show efficacy with a cognitive outcome, even though common measures are insensitive to change in the preclinical and prodromal stages of pathological disease accumulation. It is crucial that efficacy in clinical trials is assessed by use of outcomes that are sensitive to the presence of disease before more widespread neuronal injury occurs. The development of increasingly reliable, valid, and standardised metabolic brain imaging,[17,18] structural brain imaging,[19,20] protein biomarkers in CSF and plasma,[21] risk prediction algorithms,[22] and brain health services[23] will ensure that, as we progress further into the 21st century, Alzheimer's disease and other neurodegenerative disorders are detected, managed, and treated as brain diseases.

Digital biomarkers, which utilise advances in technology, are promising new tools for detecting Alzheimer's disease pathology early in the disease course. Although research on digital biomarkers is only beginning to emerge, they will undoubtedly have a major role in screening and tracking preclinical Alzheimer's disease in the future.[24] Findings from the PREVENT dementia study of a midlife cohort (aged 40–59 years) suggest that, even decades before any clinical signs of dementia appear, novel cognitive tasks, such as tests of allocentric processing (a person's ability to understand object-to-object spatial relations), might correlate well with midlife risk for Alzheimer's disease.[25] These results are in line with a study concluding that driving ability might serve as an effective and accurate digital biomarker for identifying preclinical Alzheimer's disease (quantified by amyloid β positivity in the absence of cognitive symptoms) among older adults (aged ≥65 years).[26] Speech is also emerging as an important biomarker, with changes to elaboration and attribution associated with symptomatic Alzheimer's disease.[27] A 2020 systematic review found that, when compared with traditional neuropsychological assessment methods, speech and language technology were at least equally discriminative between pre-dementia stages of Alzheimer's disease, such as preclinical Alzheimer's disease, subjective cognitive impairment, and mild cognitive impairment.[28] Eye-tracking is increasingly considered a useful tool to differentiate between healthy controls, people with mild cognitive impairment, and people with Alzheimer's disease dementia.[29] Further efforts are needed to validate these novel tools against standardised Alzheimer's disease biomarkers (in either traditional autopsy studies or against PET and CSF biomarkers). Such methods of capturing change along the Alzheimer's disease continuum could be considered for use as screening tools to identify potential participants among seemingly healthy volunteers and as potential outcome measures for clinical trials.

Capturing specific and meaningful outcomes for trial participants

A 2017 systematic review identified 81 different outcome measures used in Alzheimer's disease clinical trials.[30] Commonly used global assessment measures stage symptomatic Alzheimer's disease but are not sensitive to

change years before the dementia syndrome manifests. Furthermore, even in the case of symptomatic disease, there might be many aspects in brain health that are a priority to individuals with Alzheimer's disease that are not captured by commonly used outcome measures.[31]

With the move towards interventions for earlier disease stages comes a fundamental shift in what constitutes treatment success and, therefore, what outcome measures need to capture. In people with preclinical Alzheimer's disease, the aim is to maintain ability by entirely preventing, or considerably delaying, the development of symptoms in the first place. Accordingly, in trials of dementia prevention in which participants do not have symptomatic disease, an outcome measure would need to be sensitive enough to detect change if there were a decline (in the placebo group) but would also need to detect stability (in the treatment group) as the desired outcome.[32]

A treatment's success should be evidenced both by changes in disease pathology and how these changes translate into clinical meaningfulness for the individual. The aim of the electronic person-specific outcome measure development programme[33] is to identify outcomes deemed valuable to the individual and monitor an intervention's success against these personally important outcomes with time. This programme is developing a tool that can capture intervention outcomes tailored to the individual and reflect the maintenance and decline of ability. Initial findings yielded 184 themes of importance, highlighting the necessity of a personalised approach to measuring non-biological changes in brain health.[34] Importantly, results suggest that priorities for brain health shift along the preclinical, prodromal, and overt dementia continuum,[31] which has implications for the development of outcome measures that might be used in studies in which participants pass through different stages of disease.

Treatments and treatment targets for Alzheimer's disease

Currently, there are five drugs licensed for the treatment of Alzheimer's disease in the USA, four of which are also licensed in Europe, representing a drug development success rate of less than 1% in the past two decades.[35] The licensed drugs fall into three classes: acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine), an N-methyl-D-aspartate receptor antagonist (memantine), and a monoclonal antibody (aducanumab), which was licensed in 2021 in the USA. All five compounds were approved through clinical trials with a cognitive primary outcome. Cognition is an appropriate endpoint in symptomatic trials, but disease-modifying treatments targeting earlier disease processes should be tested in trials with appropriate, biologically measurable outcomes as the primary outcome. Given the huge advances in our knowledge of Alzheimer's disease pathology, it is somewhat surprising that changes in amyloid β-targeted PET signal from baseline remained a tertiary outcome measure for aducanumab in its licensing trials,[36] despite the fact that accelerated approval was granted on the basis of the reduction in amyloid plaque burden observed in the treatment group who enrolled in the PET substudy.

Disease-modifying therapies: past and present

Early phase 3 trials of the monoclonal antibodies bapineuzumab, solanezumab, and gantenerumab for the treatment of Alzheimer's disease did not reach significance in their primary outcomes of cognition.[37–39] These studies did evaluate biological measures of underlying disease pathology, with secondary outcomes including changes from baseline in amyloid β, tau, and MRI volumetry. In the bapineuzumab trial,[37] no differences were found between treated and placebo groups on Pittsburgh compound B-PET, CSF phosphorylated tau load, or whole-brain volume loss. However, treated patients had decreased plasma and CSF total amyloid β_{40} and amyloid β_{42} compared with untreated patients in the solanezumab trial, although, as these were secondary outcomes analysed in the context of a non-significant primary analysis, these results were not considered to be statistically significant.[38] The gantenerumab trial[39] identified reductions in amyloid β PET standard uptake value ratio and CSF phosphorylated tau, total tau, and neurogranin in patients given gantenerumab versus placebo. As secondary analyses, these investigations were often done in smaller subsets of the overall population and their results should be interpreted with caution. Nevertheless, given the response in these metrics to treatment in some groups, these findings do suggest that positioning such biomarkers as primary outcomes might be a sensible approach. Because the changes observed in these biomarkers were not associated with changes to cognition or function in these studies, recruiting individuals in the earliest stage of Alzheimer's disease, before overt symptom onset, will be important to understand whether the disease process, and the underlying disease pathology, can be interrupted by amyloid-targeting therapies such as monoclonal antibodies. It is incongruous that disease-modifying therapies are tested for whether they delay symptom progression rather than modify the disease.

As of Feb 21, 2022, 46 phase 3 clinical trials of pharmacological interventions for Alzheimer's disease that were not yet recruiting, enrolling by invitation, or active (not recruiting) were listed on ClinicalTrials.gov. Of the 25 studies focusing on prevention or early Alzheimer's disease, four (16%) include a biomarker or neuroimaging as a primary outcome, with ten (40%) more including these metrics as secondary outcome measures, showing a shift towards measuring underlying disease pathology. Similar rates were reported by Cummings and colleagues[40] in their 2022 review of the drug development pipeline for Alzheimer's disease. Studies with a biomarker as the primary outcome include

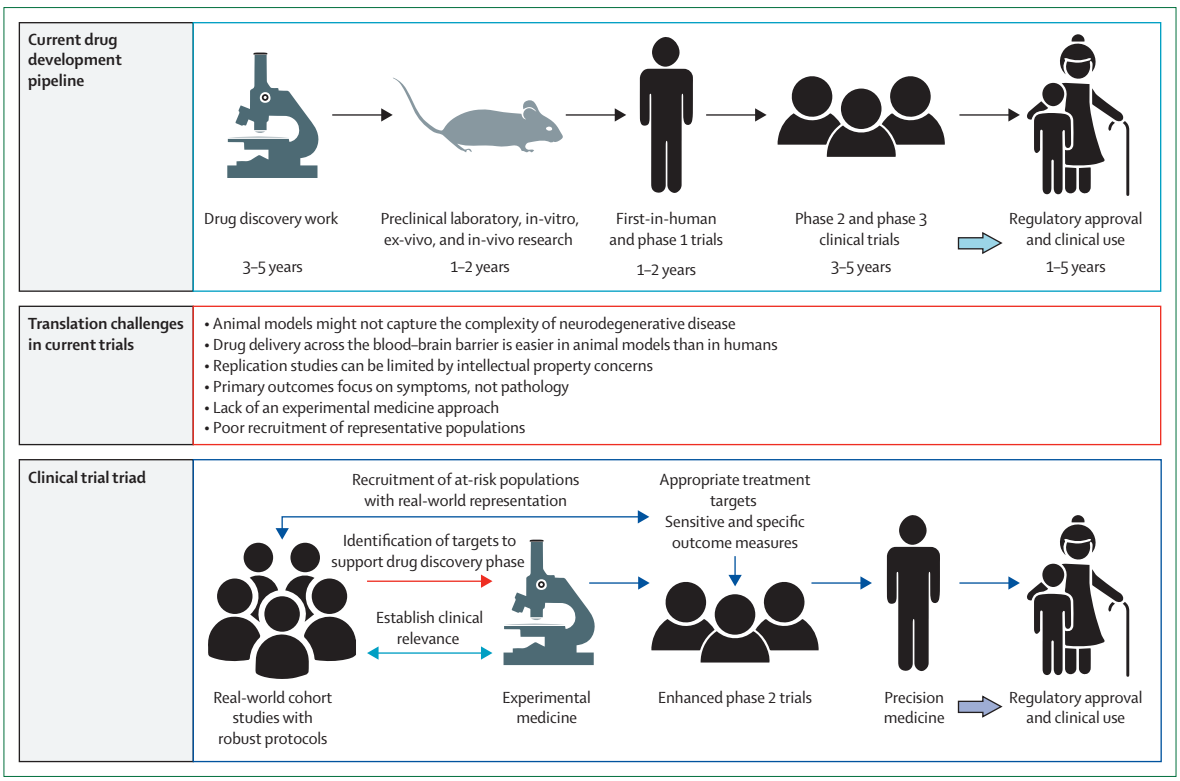

Figure: **Drug development in Alzheimer's disease**

a trial of donanemab versus aducanumab in people with early, symptomatic Alzheimer's disease (NCT05108922) and a trial of lecanemab versus placebo in people with preclinical Alzheimer's disease and elevated or intermediate amyloid load by amyloid brain PET (NCT04468659). Previous trials[41–43] of these compounds have shown their effects on disease biomarkers included as secondary endpoints, and it is encouraging that these compounds are now being tested against primary biomarker endpoints.

Although the main focus of Alzheimer's disease interventional research has traditionally been amyloid, attention is now being paid to a multitude of other therapeutic targets, such as tau, reflecting the known importance of different pathologies in the development and progression of Alzheimer's disease.[40,44,45] Again, trials of interventions targeting tau have mostly used cognition as a primary outcome, with biomarkers included as secondary or exploratory outcomes. Other interesting therapeutic targets include synaptic plasticity (targeted by anavex2-73 [also known as blarcamesine][46] and neflamapimod[47]), the metabolism (targeted by metformin[48]), epigenetics (targeted by ORY-2001 [also known as vafidemstat][49]), and proteostasis (targeted by posiphen[50] and nilotinib[51]). Such varied therapeutic targets highlight the complex pathophysiology of Alzheimer's disease. These therapeutic targets typically aim to modify disease pathology downstream of amyloid β and tau accumulation. As work with current and future therapeutic targets continues, results might be found that shift our perspective on the underlying disease process. An experimental medicine environment offers the opportunity to explore important responses to the modulation of novel therapeutic targets and the ability to update the disease model or models.

A triad approach to Alzheimer's disease clinical trials

A triad approach to Alzheimer's disease clinical trials, encompassing experimental medicine, enhanced phase 2 trials, and precision medicine, has the potential to revolutionise this field, expediting research studies and increasing the chances of a compound moving from bench to bedside (figure).

Experimental medicine

When human disease is modelled at the drug discovery stage, understanding how the target mechanism behaves in vivo[52] and the clinical relevance of the target is crucial. Importantly, in an experimental medicine approach, the efficacy of a drug itself in the treatment of a disease is not tested, but rather a drug with known properties is used to affect a disease process and then the biological response is studied. Manipulating the disease process with known drugs could define the link between pathologies (eg, amyloid and tau) and reveal how disease

processes differ by phenotype. There are already vast amounts of data that can be repurposed for experimental medicine analytical approaches. For example, although trials have shown the efficacy of certain compounds in clearing amyloid,[38,39,53] research on the effect that normalising amyloid has on tau pathology, and whether effects differ by sex or *APOE* ε4 status, has not been done. Scopolamine and mecamylamine in-vivo challenge studies, which embrace the experimental medicine approach, have investigated the effect of donepezil on reversing scopolamine-induced and mecamylamine-induced cognitive deficits, with results suggesting that donepezil gives rise to no or partial reversibility.[54,55] These findings have resulted in important discussions about donepezil's mechanism of action.[54,55]

We recognise that an experimental medicine approach is costly and time-consuming, but it will arguably lead to new drugs getting to the market more quickly. National approaches should be used to build a research and clinical ecosystem to reduce barriers to clinical trial entry and create cost-effective environments for experimental studies. Furthermore, as a growing number of studies have highly phenotyped cohorts with multiple clinical, cognitive, and behavioural datapoints and components (eg, EPAD,[56] PREVENT,[57] ADNI,[58] and AIBL[59]), a considerable burden of cost in terms of screening eligible participants has been addressed. These cohorts are not without bias, typically recruiting participants who are White, highly educated, and represent affluent socio-economic groups, but they offer a platform from which successful experimental medicine programmes can be built and more inclusive cohorts can be developed. The incorporation of novel biomarkers is integral to this discovery work to maximise our understanding of the earliest pathological changes that occur in Alzheimer's disease. Drug discovery work done in human versus preclinical studies might also be less restricted by intellectual property concerns, which are a contributing factor to the reproducibility crisis.[60]

Enhanced phase 2 trials

Translating findings from basic science and experimental medicine approaches into clinical trials is the crucial next step in our proposed triad. Designing phase 2 trials informed by the results of experimental medicine and in-vivo observational studies will enhance phase 2 trials beyond their current state. Experimentally informed phase 2 trials should include more appropriate treatment targets, matched with sensitive and specific outcome measures, with appropriate inclusion criteria to recruit participants with early-stage disease who are likely to be amenable to the intervention. A continued broadening of treatment targets beyond amyloid for a multifaceted disease such as Alzheimer's disease is likely to be an apt approach. Incorporating novel outcomes into phase 2 trials, particularly when well defined at the preceding discovery stage, will help to progress the field.

***Panel*: Using analogies in discussions of Alzheimer's disease**

Debates and discussions about the modernisation of the field of neurodegenerative disease have often been supported by analogies to other chronic diseases. Analogies can be helpful to illustrate and support an argument, grounding discussions of Alzheimer's disease within branches of medicine that are much more developed than the field of neurodegenerative disease. The reason that this field is not as advanced is simply due to the fact that tissue diagnosis in the brain is not possible. However, multi-modality biomarker detection methods coupled with risk factor (eg, genetic) analyses and machine learning could act as pseudo-biopsies and give accurate and precise clarity as to what is happening in the brain without recourse to a biopsy. Comparing Alzheimer's disease with cancer is a favoured analogy that is applicable at both the drug development level and the intimately linked clinical practice domain. Although Alzheimer's disease does not spread throughout the body like cancer, it does spread through the brain, affecting various cell types in addition to neurons (eg, inflammatory cells and the neurovascular unit) and varied brain regions via tau seeding and other mechanisms that are perhaps underpinned by cerebrovascular disruption. With the passage of time, cancer types and subtypes have been refined, aiding a precision medicine approach and changing trial design. The cancer field has recognised that several disease processes might be concurrently affecting normal physiology and survival, meaning that patients with cancer require multimodal interventions that involve combination drug therapy. Moreover, cancer clinical practice has almost entirely focused on early detection, especially in populations with cancer risk factors (eg, depending on age, family history, sex, and lifestyle), and these facilities and programmes for screening and early detection are based in community settings, serving otherwise healthy individuals. Dementia can be considered the palliative care stage of the Alzheimer's disease spectrum, in which reversing a disease that has already spread extensively in the brain and recruited multiple pathological processes is near-impossible. Therefore, to run brain health services for early detection, risk profiling, and personalised prevention in a dementia service (memory clinic) would be akin to running mammography services as end-of-life cancer care in a hospice. A new care pathway is required in the neurodegenerative field to unlock all the possibilities that detecting Alzheimer's disease early will generate.

Precision medicine

In the last 10 years, trials of preclinical Alzheimer's disease have struggled to recruit participants because they have focused on traditional services specialising in late-stage Alzheimer's disease (eg, memory clinics). With the opening of brain health services,[61] which offer clinical support to maintain brain health throughout life, a precision medicine approach will become more feasible because of improved data capture at the individual level. Targeting and treating underlying pathology and thereby ameliorating toxic disease processes in Alzheimer's disease will become akin to the well established management of hypertension or cholesterol in preventing heart disease. Indeed, comparing Alzheimer's disease with other, more well studied chronic diseases might prove helpful in debates about its pathology and treatment (panel). Given the diversity of risk factors involved in Alzheimer's disease,[62] differential trajectories of cognitive and functional decline,[63] and disparate responses to current treatments,[64] it is reasonable to assume that the future of Alzheimer's disease treatment will involve individualised risk reduction, prevention, and treatment plans with one or more pharmacological compounds alongside lifestyle modifications and psychosocial

interventions. Translating clinical trial results into clinical practice will be crucial in showing the anticipated meaningful benefits of disease-modifying therapies.[65]

Conclusion

The development of increasingly reliable and valid biomarkers, risk prediction algorithms, and brain health services supports a shift towards understanding Alzheimer's disease as a brain disease that is detectable and manageable decades earlier than the current symptomatic focus allows for. Knowledge emerging from midlife cohort studies, a greater understanding of interactions between risk factors and pathology mechanisms, and the societal and economic costs of dementia are fuelling the brain health revolution. This revolution had as its spark the irrefutable fact that Alzheimer's disease is a disease that starts in midlife and ends with dementia at a very late stage, meaning that research should turn to individuals who have no outwardly observable symptoms of cognitive decline or functional impairment. The brain health revolution will facilitate the development of new clinical services and advocate for the right clinical trials to be done in the right population with the right (combination of) drugs.

Decades of repeating the same clinical trial methodologies for Alzheimer's disease has meant a failure to identify the new treatments that are so desperately needed. While biomarker discovery work is constantly advancing, our clinical trial primary outcome measures remain stuck in a past that does not align to our new understandings of Alzheimer's disease. If we revolutionise our approach to Alzheimer's disease clinical trials, we will maximise our chances of finding treatments that can really impact patients.

Contributors

SG, SS, and CWR all contributed to the conceptualisation of this manuscript. SG and SS contributed equally to writing the original draft and to responding to reviews and edits. CWR was responsible for supervision and for reviewing and editing the original draft of the manuscript. SG, SS, and CWR all agreed on the final manuscript to be submitted.

Declaration of interests

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