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Journal

Alzheimers and Dementia, 19(2)

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Publication Date

2023-02-01

DOI

10.1002/alz.12737

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Alzheimers Dement. 2023 February ; 19(2): 696–707. doi:10.1002/alz.12737.

Recommendations to address key recruitment challenges of Alzheimer's disease clinical trials

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Abstract

Clinical trials for Alzheimer's disease (AD) are slower to enroll study participants, take longer to complete, and are more expensive than trials in most other therapeutic areas. The recruitment and retention of a large number of qualified, diverse volunteers to participate in clinical research studies remain among the key barriers to the successful completion of AD clinical trials. An advisory panel of experts from academia, patient-advocacy organizations, philanthropy, non-profit, government, and industry convened in 2020 to assess the critical challenges facing recruitment in Alzheimer's clinical trials and develop a set of recommendations to overcome them. This paper briefly reviews existing challenges in AD clinical research and discusses the feasibility and implications of the panel's recommendations for actionable and inclusive solutions to accelerate the development of novel therapies for AD.

Keywords

Alzheimer's disease; clinical trials; trial participation; recruitment; retention; diversity in clinical trials

1. Introduction

With 6.2 million people over the age of 65 estimated to be currently living with Alzheimer's dementia in the U.S., a number expected to grow rapidly as the nation's population ages, Alzheimer's disease (AD) is overwhelming older Americans, their care partners, and the healthcare system.[1] In fact, absent effective therapies, the prevalence of dementia is expected to triple over the next several decades,[2] and by 2050 an estimated 12.7 million Americans will be living with Alzheimer's dementia.[1]

Research suggests that interventions for AD could significantly reduce the prevalence of dementia in coming decades,[3] and even a modest delay in disease onset could generate billions in savings to society.[2] Yet only one therapeutic, aducanumab, has come to market in nearly two decades.[4,5] Given the significant unmet treatment need in AD, it is crucial to expedite the development of novel therapies.

The clinical trials required to accelerate the approval of effective therapies are expensive and time-consuming in any disease area, but they are especially challenging in AD. Alzheimer's clinical trials tend to take longer to complete and are more expensive than trials in most other therapeutic areas.[6] Specifically, the recruitment and retention of a large number of qualified, diverse volunteers to participate in clinical research studies remain

key barriers to the successful completion of AD clinical trials.[7,8] Nevertheless, the research community remains committed to developing therapies for AD, and over 120 pharmaceutical agents targeting the disease are currently in the drug development pipeline.[5] A significant increase in the number of volunteers from diverse backgrounds is however required to meet the growing need of AD clinical trials in order to accurately assess how potential therapeutics perform in all populations.[7–10] AD begins years before symptoms appear thus new approaches are particularly needed to improve enrollment into early stage trials that recruit asymptomatic individuals at risk for progression to AD dementia.

In 2020, the University of Southern California Schaeffer Center for Health Policy and Economics, Alzheimer's Therapeutic Research Institute and Gates Ventures convened an advisory panel to assess the critical challenges facing AD clinical trials—particularly those associated with bottlenecks in trial recruitment. The panel considered a wide range of AD clinical trials across the spectrum of disease, including but not limited to trials defining at risk of AD-progression through biomarker evidence as well as other pre-clinical and clinical AD diagnostic evidence. Chaired by three experts—Paul Aisen, Jessica Langbaum, and Julie Zissimopoulos—the advisory panel included more than 35 experts representing a wide range of stakeholders from academia, industry, patient-advocacy organizations, philanthropy, non-profit and government, including several international experts. Over the course of two meetings and several sub-group discussions, hosted by the University of Southern California, as well as panelist surveys and commentary, the panel developed recommendations for actionable, feasible and inclusive solutions to accelerate progress in recruitment for AD clinical trials. Panelists' participation was voluntary, and their recommendations do not necessarily express the views of their affiliated organizations. Although the solutions are predominantly U.S.-focused, many can be adapted to challenges facing AD clinical research globally. This paper briefly reviews existing challenges in AD clinical research and discusses the feasibility and implications of the panel's recommendations for actionable and inclusive solutions to accelerate the development of novel therapies for AD.

2. Barriers to clinical trials for Alzheimer's disease

The tallest barriers to more efficient AD clinical trials are those which keep potential volunteers from ever reaching them in the first place.[6] These upstream barriers are not unique to AD, but they are exacerbated by the complex nature of the disease and prevent roughly 99% of eligible participants from being referred to or considering trial enrollment.[6] We briefly review some of these barriers below, including limited awareness of early asymptomatic and symptomatic stages of AD, fear of and lack of a clear AD diagnosis, limited access to diagnostics, overstretched healthcare providers and infrastructure, infrequent trial referrals, and inadequate engagement of people from racial and ethnic backgrounds who have historically been underrepresented in clinical research.

The stigma and fear associated with cognitive decline cause many people to downplay or ignore the symptoms of AD.[11] Many also believe that memory loss and other cognitive impairments are a normal part of aging. Thus, they do not discuss memory issues with their families and healthcare providers, and find their way to a clinical trial only after their

symptoms have deteriorated, sometimes years later. Consequently, of the nearly 90 million Americans who may be candidates for a preclinical, prodromal, and mild Alzheimer's dementia clinical trial, only 12.5 million ever reach the healthcare system for AD-related reasons.[6]

Meanwhile, many primary care providers (PCPs) report lacking the resources and time during patient visits to discuss cognitive issues, especially with patients who show no visible symptoms of declining cognitive health.[6,7,12] Physicians may also lack the training to diagnose AD or the screening tools they need for an evaluation.[11] Further, some are reluctant to diagnose AD when they believe there are no effective treatments, or feel unable to support patients through their network's social services post diagnosis.[6,7,9,11,13] As a consequence, many PCPs do not identify AD patients until they are already experiencing observable symptoms.

Even then, confirming an AD diagnosis is still a long, complicated, and expensive process.[11] Currently many patients have limited access to biomarker testing such as positron emission tomography (PET) scans and lumbar-puncture cerebrospinal fluid (CSF) tests, in part due to expense, limited geographic access to healthcare, or lack of health insurance coverage.[6,11] In 2020, the first blood-based biomarker test to predict Alzheimer's brain pathology in the clinical setting was introduced according to the Clinical Laboratory Improvement Amendments (CLIA), but it is not yet approved by the Food and Drug Administration or covered by public and private payers.[14,15] Other reliable methods to precisely quantify amyloid beta or phosphorylated tau in the blood have been developed, but are currently limited to research use only, underscoring the limitations of biomarkers for diagnosing AD in a clinical setting, and the need for robust and scalable in-vitro diagnostics approved by regulatory bodies for predicting the population of persons with AD as well as the at-risk population.[16] Importantly, there is significant heterogeneity in pathology among persons with AD. Among persons with normal cognition or mild impairment and without dementia, older age was associated with greater rates of amyloid positivity. The opposite was true in participants with AD dementia.[17]

Not only healthcare providers may lack reliable information about local clinical trials—leading to infrequent trial referrals[18]—but approximately 80% of patients never consider participating in AD clinical studies despite being aware of or referred to a trial.[6] Further, even when potential volunteers meet the rigorous screening requirements, they may judge the risks or potential side effects of the therapies being tested as outweighing the benefit to future patients.[6,7,9]

Ample evidence shows that people of color, Black and Latinx Americans in particular, are at increased risk for developing AD,[1,19–21] yet they have historically been underrepresented in AD clinical research.[9,22–24] Although Black Americans are twice more likely and Latinx Americans are 1.5 times more likely than White Americans to be living with Alzheimer's dementia,[1] racial and ethnic groups are significantly underrepresented in AD clinical trials.[23,25] Their trial participation has been suppressed by mistrust of clinical research based on historical mistreatment, language and cultural barriers, and limited access to healthcare, among other barriers.[7,9] Moreover, inadequate targeted recruitment of diverse groups has

exacerbated the underrepresentation of high-risk populations and limited our understanding of whether biomarker and pathological changes are similar across groups.[9,23,25–28] These groups are also less likely to receive a timely AD diagnosis, and therefore when they are diagnosed, the diagnosis typically comes in the later stages of the disease when their symptoms are more debilitating.[29] This barrier is particularly important to overcome if we are to advance AD clinical research that is equitable and represents the full range of the AD patient population.[1]

Additionally, downstream barriers also hinder AD clinical trials. Many potential participants do not meet restrictive trial inclusion criteria, leading to screen-failure rates of 88% in preclinical and 78% in prodromal AD clinical trials.[6] Comorbid conditions often applied as exclusion criteria, such as cardiovascular disease, are more prevalent in some racial and ethnic groups, disproportionately screening out diverse populations as a result.[7,9] Older adults, who are more likely to have exclusionary comorbid conditions and use a higher number of prescription medications, are also more frequently excluded and underrepresented in AD clinical studies.[30,31] Most AD clinical trials also require the enrollment of a study partner—a role often filled by a spouse or domestic partner—who can report on the participant's daily cognition and function.[32–34] The number of potential participants who live alone, do not have a spouse or qualified study partner is growing, leading to the exclusion of an increasing number of otherwise eligible volunteers from AD clinical trials.[7,9] Other barriers to participation include extensive time required for study visits which interfere with employment and other responsibilities, and logistical barriers such as distance to study sites and transportation challenges and costs.[7,9]

3. Recommendations for accelerating clinical trials for Alzheimer's disease

Keeping current barriers in mind, the panel identified 27 solutions that have the potential to accelerate the conduct and execution of AD clinical trials. The panelists then ranked these solutions in terms of their likely feasibility, capacity to meaningfully reduce barriers, and potential to improve diversity and inclusion in AD clinical research. In the remainder of this paper, we spotlight a subset of panel's recommendations with the largest potential to accelerate progress in AD clinical trials, grouped in six broad categories (for the full list of solutions, see Table 1).

3.1 Cognitive screening and early detection

The evidence that the pathological process of AD starts many years before clinical symptoms appear requires shifting the paradigm to early diagnosis of AD, engaging individuals at earlier stages of the disease and improving participation in early stage clinical trials. Although research suggests it is best to modify disease progression long before symptoms appear, AD is often underdiagnosed in early stages. Consequently, the lack of diagnosis deprives patients from access to potentially helpful interventions and social services, as well as the opportunity to make personal decisions while they still have cognitive capacity and to be referred to clinical trials.[35] Below we explore several

approaches to encouraging broader cognitive screening and earlier detection in healthy, asymptomatic as well as symptomatic, early stage, older adults.

3.1.1 Prescreening strategies—To facilitate early screening and trial recruitment, innovative prescreening strategies could be deployed to identify potential prodromal AD and mild AD dementia patients in the community.[36] Individuals whose screening indicates they may have a degree of cognitive impairment could be referred for further clinical evaluation, connected to support services, and offered opportunities to enroll in clinical trials. For example, the Models of Patient Engagement for Alzheimer's Disease (MOPEAD) study tested alternative screening approaches including web-based tools, open house initiatives at memory clinics, and cognitive screening during primary care visits across five European countries.[37,38] Alternative screening strategies could be designed and tailored to meet the needs of different communities, and for preclinical use, and persons with prodromal or mild Alzheimer's dementia. Development and assessment of new screening tools will need to consider factors such as implementation time, levels of specificity and sensitivity across diverse populations, affordability, and for those targeted at the primary care setting, integration with electronic health record systems. The results from testing and validation of the tools will need to be communicated to both health care providers and patients for transparency in the reliability and validity of tools.

A digital screening strategy, combining an outreach campaign and digital self-assessment tools, could be an effective way to identify and engage people concerned about brain health or memory issues. Self-identified individuals who meet the inclusion criteria would be invited to take a digital cognitive test and, if cognitive impairment is detected, be referred to local trial sites, memory clinics, or dedicated registries. A prescreening strategy that leverages technology has the potential to reach a pool of untapped volunteers and efficiently accelerate trial recruitment. Digital self-assessment tools may be well-suited for prevention studies among preclinical persons while other strategies may be better for persons with prodromal or mild Alzheimer's dementia. Existing initiatives—including the Alzheimer Prevention Trials (APT) Webstudy, the Alzheimer's Prevention Registry, the Brain Health Registry, and the Cognitive Health in Ageing Register—provide examples of leveraging technology to accelerate enrollment in AD prevention studies.[39–42] The APT Webstudy, in particular, utilizes demographic information plus longitudinal cognitive and subjective concern data to predict brain amyloid elevation and select individuals for referral to sites for trial screening.

Open house initiatives offering free cognitive screening to the community could also be implemented at local study sites and memory assessment clinics. Individuals meeting the inclusion criteria would be screened at local sites by trained staff, and those suspected to be at risk for prodromal AD or mild AD dementia could be referred for further clinical evaluation and offered information about the disease, care planning, and participation in clinical trials. To reduce the burden on clinical sites, off-site screening at community sites or satellite diagnostic centers, particularly in underserved areas, is an alternative approach that could accelerate recruitment. In Georgia, for example, physicians have been able to refer patients to five state-funded satellite memory assessment clinics, supported by ongoing educational campaigns since 2018.[43] New strategies as well as expansion of

existing strategies provide opportunities to better understand the harms as well as benefits of cognitive screening. Newly collected evidence may inform the US Preventive Service Task Force who in 2020 again concluded that more research is needed to make a recommendation for or against screening for cognitive impairment.

3.1.2 Early detection in the primary care setting—Memory issues are often raised first in the context of a primary care visit, and PCPs play an important role in cognitive screening and referring symptomatic populations to dementia specialists, social support services, and clinical research. Yet new approaches are required to reduce barriers to cognitive assessment or develop better tools for PCPs to identify patients who may be at-risk for developing AD and who may be interested in clinical trials as a care option alongside standard-of-care measures. Indeed, less than 40% of surveyed PCPs consider participation in clinical research as an important benefit of early detection.[13] To accelerate trial referral rates, educational campaigns designed for healthcare providers could raise awareness about dementia, the benefits of early detection (similar to screening for other chronic conditions such as diabetes and hypertension), and available screening tools. Additionally, targeted dissemination of information regarding reimbursement options, available social services post-diagnosis as well as local memory specialists and trial sites could be undertaken.

Performing the Medicare Annual Wellness Visit (AWV) with cognitive evaluation provides an opportunity for PCPs to discuss brain health with their patients. Yet screening at the AWV—a benefit available at no cost to any Medicare beneficiary since 2011—is underutilized for many reasons.[13,44] PCPs report lacking the time to screen during visits, the education and training to choose, perform or interpret a screening test, or the wrap-around support in their network to address cognitive and other issues that may be uncovered with screening.[6,7,9,13] They may also be discouraged by the latest U.S. Preventative Services Task Force report concluding evidence is lacking to determine the benefits or harms of screening for cognitive impairment in adults 65 years or older.[45] Meanwhile, more than half of patients age 65 and older report being unaware of the cognitive assessment offered as part of the AWV and fewer than one-third report having a structured cognitive assessment.[13,44] Others have offered solutions to optimize the AWV, with suggestions ranging from setting national benchmarks for improvement, improving provider reimbursement, reducing the burden on physicians by redesigning practices and training other staff to perform evaluations, and providing guidance on available cognitive assessment tools and reimbursement.[1,46–48] Meanwhile, awareness campaigns, such as Go Annual in Georgia, could encourage the general public to take advantage of this free routine visit and speak to their physician about cognitive assessment.[13,49]

3.1.3 Other health system solutions—Prior studies have shown the economic benefits of earlier diagnosis at both the individual and national levels.[35] Yet some key healthcare players, including policymakers and physicians, oppose reimbursement of dementia screening and diagnostics in the absence of effective therapies for AD—which needlessly slows the identification of volunteers for earlier stage clinical trials, essential for the development of new therapies. This suggests an opportunity for a system-wide paradigm

shift recognizing the value of earlier screening and diagnosis—a potential opportunity to lower costs to the healthcare system and for the purpose of accelerating clinical research.

Financial incentive programs for clinical research participation could be designed and implemented through partnerships with the Centers for Medicare & Medicaid Services (CMS) and private payers. Plan enrollees who opt-in to learn about research opportunities and participate in clinical trials could be offered incentive payments or annual premium discounts, similar to healthy lifestyle incentives. Payers in turn may observe lower per-member-per-month costs because of the high-quality care typically provided to clinical trial volunteers.

From a reimbursement standpoint, the value of cognitive screening and early diagnosis in the context of clinical research participation should be considered. Even though Medicare provides reimbursement for visits that entail cognitive and functional assessment and care planning services, only a small fraction of eligible beneficiaries are receiving the benefit.[50] Further, the current reimbursement system lacks incentives for healthcare providers to provide comprehensive dementia care, including referrals to clinical research, for individuals with cognitive impairment.[51–53] To reduce financial barriers for healthcare providers, encourage earlier diagnosis and ultimately referrals to clinical trials, the CMS could consider value-based and alternative payment policies, both in Medicare Fee-for-Service (FFS) and Medicare Advantage. For example, these payment reforms could revise the incentive system by increasing reimbursement in Medicare FFS or implementing quality measures for cognitive care and clinical research participation into the Shared Savings Program for Accountable Care Organizations or the Medicare Star Rating System to reward Medicare Advantage plans.

3.2 Blood-based biomarker testing

Emerging blood-based biomarker tests for the detection of Alzheimer's brain pathology may lead to broader screening in various settings, including primary care, and accelerated recruitment and enrollment of eligible trial volunteers. For example, biomarker research supported by the Alzheimer's Drug Discovery Foundation Diagnostics Accelerator led to an important milestone in blood testing in 2020 when C2N Diagnostics introduced the first commercially available biomarker blood test detecting brain amyloid plaque.[54] The availability of biomarker testing that was highly predictive of AD onset, accurate with respect to discriminating between persons with AD and without AD, standardized, accessible, and cost-effective blood-based biomarker testing will accelerate the detection of the population at risk of AD and biomarker evidence along with AD specific phenotype evidence could eventually be used to establish the eligibility of potential trial participants, assuming the biomarkers are validated in diverse populations. However, there is a gap in accuracy of current tests for predicting who will progress to clinically significant AD that is a significant barrier. When widely available as initial diagnostic tools in primary care, blood-based biomarker tests will allow PCPs to rapidly screen and determine which patients are suspected to be at risk for prodromal AD or mild AD dementia. Referral to specialists for further evaluation also provides opportunity for referral to appropriate clinical trials.[55] To accelerate their adoption in clinical practice, educational campaigns designed for healthcare

providers and the general public could raise awareness about the benefits of blood tests to predict Alzheimer's brain pathology, similar to initial routine testing in other areas such as cholesterol screening. Research is still need on the implications of learning these results across diverse populations.

Blood-based biomarker tests have the potential to overcome many of the challenges associated with PET and CSF biomarker testing.[55,56] PET scans and CSF tests, which are highly accurate with respect to differentiating between persons with AD and without AD, will remain important tools in the diagnostic process but their high cost, invasiveness and restricted availability limits their accessibility and generalizability to those living in remote areas and across diverse populations. Blood-based biomarker tests, however, could be routinely performed and meet the scalability requirements in primary care and community-based settings.[55] Even though blood tests currently require samples to be shipped to a centralized laboratory for analysis, this limitation could be addressed with time as blood testing and sample handling infrastructure becomes better established within clinical practice and may require only minimal training of personnel.

Yet challenges remain with establishing blood-based biomarkers' technical performance, diagnostic accuracy, and prognostic value. Shared resources of neuroimaging, biofluid, digital, autopsy, co-pathology and other types of data could facilitate the development, validation, and generalizability of blood-based biomarkers, and their performance metrics across different populations should be reported and be transparent to researchers, health care providers and patients. In particular, a centralized data-sharing platform could provide shared resources of blood samples with neuropathological validation of different blood-based biomarker assays for AD, as well as blood and CSF samples and imaging data in underrepresented groups to establish the generalizability of blood-based biomarkers across heterogeneous populations. This initiative could explore the feasibility of building upon existing infrastructure and data-sharing platforms such as the Alzheimer's Disease Data Initiative (ADDI) or the Global Alzheimer's Association Interactive Network.[57,58] ADDI, for example, is a cloud-based platform that aims to increase sharing of dementia-related data among researchers and could potentially be expanded to include essential samples and develop capabilities to catalogue and request samples from multiple sources.

3.3 Public awareness and outreach

The general population does not fully understand AD, and most do not yet know that the disease begins to develop 10–20 years before symptom onset, making it crucial to intervene years before symptoms appear. This lack of awareness and understanding of AD and the benefits of early detection remain critical barriers to recruiting qualified volunteers. While one of the main reasons a person joins a clinical trial is because their physician recommends it, preclinical individuals who do not present with symptoms are not effectively recruited through their interactions with the healthcare system. Yet community-based recruitment programs could be designed to engage asymptomatic, at-risk individuals through alternative outreach channels.

While several public awareness campaigns have been conducted to date, more effective approaches are needed to reach diverse populations and fill the growing need for trial

volunteers. Programming is needed to increase awareness among potential trial participants and to build relationships and trust between clinical research sites and local communities. An effective awareness campaign encouraging individuals to seek care for brain health could steer a large, currently untapped pool of potential participants into AD clinical trials. Outreach campaigns should raise awareness, encourage individuals to differentiate between normal aging and actual cognitive issues, and educate about the benefits of early diagnosis as well as the limitations of biomarkers in preclinical disease. Consequently, these initiatives can lay the groundwork for conversations about participation in clinical trials, providing potential participants with the relevant information they need to present to local studies.

Community outreach has the potential to address inclusion and health equity in underserved communities, but trial recruitment necessitates a long-term commitment to understanding cultural barriers and establishing rapport with individuals and community leaders. Outreach campaigns should target diverse communities and work with local community organizations, in addition to national advocacy organizations, to reach underrepresented populations and be seen as trusted sources of information. No single recruitment strategy will work in all communities—outreach efforts must work with local leadership and understand the opportunities and the barriers of each community to engage in research. For example, if access to technology is a barrier, solutions must provide access in local spaces.

Because many awareness campaigns today are implemented locally as outreach for individual trials, some have called for a national public campaign to convey the value of participating in AD clinical trials broadly. A national awareness campaign with a broader reach may be effective if focused on patient activation with clear messages, tailored to diverse communities, and implemented with the alignment of disparate stakeholders including trial sponsors and registries. Yet national awareness campaigns should consider who will listen to the messages and what call to action the audience will hear. Clinical trial messages are most salient when a person or a loved one is facing a health concern in the moment. Investing significant resources on a broad, national message to have it resonate with only a subset of people might not be the best approach. Further, access to clinical trials is not equally distributed, and there are research deserts across the U.S. and within underserved communities where no trials are available regardless of the population's level of interest. A national campaign risks raising interest in trial participation among people for whom trials are not available. Instead, efforts should focus on bringing clinical research directly to those at risk by facilitating clinical trial architecture in the communities where people are affected by AD.

3.4 Clinical trial architecture in the community

To build a diverse cohort of trial participants, clinical trial architecture should be scaled in local communities. Clinical studies could leverage health systems' satellite sites, mobile clinical trial units or local networks of diagnostic clinics to take AD trials to the community. Because no single solution will serve the needs of all communities and trial populations, different approaches to recruitment and trial architecture should be applied in the asymptomatic population versus the dementia populations.

In the asymptomatic population, the focus should be on raising awareness through outreach and providing potential participants with the information they need to consider enrolling in early intervention trials. These individuals are not seeking care for brain health or connected to advocacy organizations, and must be recruited outside the healthcare system. Public awareness and educational programs, collaboration with local community leaders in faith- or culturally-based organizations, and referrals to registries are among the solutions that could encourage this group to present to trials. Despite the lack of a national AD/ADRD registry in the U.S., a few state-level registries of persons living with dementia exist. There are also dementia research registries that included persons in preclinical stages that may be utilized for accelerating trial recruitment. Further assessment of usefulness of myriad registries for trial recruitment may provide insight and lessons learned to support community based clinical trial architecture.

In the dementia population, the focus should shift from providing information to providing comprehensive care and wrap-around services to patients and their families within the healthcare system. Patients living with cognitive impairment and their care partners are often connected to advocacy organizations and these relationships could be leveraged for outreach and trial recruitment. Further, it is important to provide infrastructure for screening and social support services to dementia patients and their families. Healthcare system engagement needs to be centered on accessible clinical trial architecture in the communities where patients live to bring research to participants. Mobile facilities could be used to bring screening to people in remote areas who have limited access to diagnostic tools such as PET scanners. For instance, to overcome transportation challenges to screening and enrollment, a mobile clinical trial unit has been serving diverse communities in remote areas in Florida since 2016.[59,60] Bringing the mobile unit to the community increased trial participation of underrepresented populations and doubled the number of screenings over three years. Further, leveraging community-based participatory research, health systems could utilized satellite clinics and sites to make clinical trials available in underserved communities and facilitate recruitment from racially and ethnically diverse populations.[10]

3.5 Screen-fail registry and digital engagement

Many people indicate they are interested in advancing AD clinical research by enrolling in registries, but only a fraction of registry enrollees are recruited into clinical trials.[61] Additionally, many who fail a screening for one trial may be discouraged to apply to other clinical studies. Yet these are the people who registries should engage further: they have already self-identified as interested in research participation and have clinical, biomarker and other data on file that were generated during screening. Many who fail a screening today for one trial may pass the screen in the future or be eligible for other trials. Digital technology provides a cost- and time-efficient opportunity to screen for multiple clinical studies simultaneously, reduce the number of people who are turned away, and ultimately reduce the burden on their journey through clinical research. Digital sharing of information across clinical trials may increase recruitment from one trial into another and will require implementation of best practices for maintaining privacy and trial integrity.

A digital screen-fail registry could capture longitudinal digital screening and assessment data and become a repository for sharing screen-fail data. The platform could allow participants to own their data and share it with other registries and across multiple studies. Ongoing engagement through this platform could provide feedback loops that allow for more sustained retention of those not specifically enrolled in clinical studies and those who have failed screening for other trials to create an online community-based cohort, with the potential to grow into a large data repository needed to accelerate digital biomarker discovery.

A digital-engagement strategy and platform, linked to a screen-fail registry, could be designed to collect and share participant data across multiple trials at once. The platform could raise awareness and activate participants to seek care and receive information about clinical trials. The use of web-based social engagement strategies and precision marketing tools should be explored to develop sustained engagement strategy and registry recruitment. We can take lessons from other industries that excel at attracting large numbers of people and keeping them engaged, such as social media platforms. Next, digital assessment protocols could be leveraged to rapidly triage community-based candidates and identify those who may qualify as study participants. Following the initial contact, cognitive screening protocols could be administered to further assess candidates. Stratification analytic methods could be deployed to direct candidates to multiple clinical trials simultaneously rather than recruit for one study at a time. Further, best practice methods for trust building, powered by social psychology principles, should be integrated to effectively build relationships with historically underrepresented populations and develop automated high-touch methods that can provide interim connectedness between, or potentially in lieu of, direct person-to-person contact, particularly in regions where there are too few appropriate personnel to meet demand.

Lastly, this digital platform presents an opportunity for creating a large data repository needed to accelerate digital biomarker discovery.[62] Although research efforts have shifted to targeting AD earlier in its onset trajectory, researchers continue to rely on cognitive measures developed decades ago. While there has been significant innovation in detecting early biomarkers of AD, similar efforts to identify new primary cognitive outcomes to fit these earlier disease biomarkers have been lacking, particularly at the preclinical stage. Digital assessment methods that can reliably measure cognitive performance continuously would allow baseline metrics and real-time continuous monitoring of cognitive performance to determine drug impact at the time of treatment and at defined timepoints after each treatment. Parkinson’s disease symptom monitoring offers an example of the potential value of using wearables, internet-connected devices, and smartphone applications to monitor treatment effects.[62,63] Adaptive AD clinical trials could particularly benefit from these digital assessment approaches to reduce trial duration and cost. In the long run, the platform could leverage data science and artificial intelligence to process and analyze raw digitized signals such as recorded speech—instead of the currently used derived measures such as verbal memory—to identify pattern changes and activate participants to seek care.

3.6 Virtual clinical trials

The COVID-19 pandemic accelerated the shift toward remote assessment in clinical trials, enabling a growing number of trial activities in the participant's home. While the virtual transformation of clinical studies was already underway, the pandemic forced clinical trials to adapt their digital capabilities quickly. Before the pandemic, technology enabled trials to transition from hardcopy to electronic capture, use digital platforms to collect and access data using tablets and smartphones, move databases to cloud storage, centralize data monitoring, and access safety data in real time. In the age of COVID-19, clinical trials adapted to remote cognitive and clinical assessments, eConsent for remote consenting, web-portals for remote data access, telemedicine to monitor participant safety and maintain engagement, nurse home visits to perform infusions and examinations, and video conferencing for community outreach programs.

While virtual trial settings are not feasible for every type of clinical trial, some trial sites could leverage these innovations going forward to recruit more widely, improve clinical trial experience, and reduce the burden on participants and study partners.[64] Integrated, home-based computerized cognitive assessments and video conferencing could reduce the burden (e.g., travel cost and time loss) on potential participants during trial enrollment and increase retention.[65] Where appropriate, trial sites could increase use of virtual procedures for safety monitoring and remote outcome assessments. Along with remote procedures, virtual or hybrid clinical trials could utilize in-home nursing care to administer therapy, perform key lab tests and physical exams, and ensure the integrity of data collected remotely.[66,67] The use of mobile nursing has increased over the last two decades, providing a participant-centric alternative to on-site visits, and—in conjunction with virtual approaches—has the potential to offset the cost associated with trial delays due to slow enrollment and high dropout rates.[66,67] Further, virtual trials provide opportunities to recruit and retain participants in remote areas, and reach underrepresented populations. Yet some candidates may have limited access to technology and the internet, underscoring the importance of providing access to technology to ensure equitable access to clinical trials.

4. Conclusion

The engagement, recruitment and retention of qualified, diverse volunteers to participate in clinical research remain among the key barriers to the successful completion of AD clinical trials. More effective approaches are needed to reach diverse populations, engage patients and their families at earlier stages of the disease, and improve enrollment in early stage clinical trials that recruit from the asymptomatic population. Potential solutions should encourage broader cognitive screening and earlier AD diagnosis, leverage emerging blood-based biomarker testing, digital technology and public awareness campaigns, and scale clinical trial architecture in the communities affected by AD. Unique strategies to increase diversity and inclusion are urgently needed to recruit people from racial and ethnic backgrounds that have historically been underrepresented in clinical research.

Since the advisory panel convened, the FDA approved aducanumab in 2021, and in April 2022, the CMS released its final National Coverage Determination decision memorandum for approved monoclonal antibodies (mAbs) as treatment for AD. The decision differentiates

coverage based on accelerated approval with coverage for treatments within randomized controlled trials conducted under FDA Investigational New Drug application, and traditional approval with coverage under evidence development for patients participating in CMS-approved or National Institutes of Health (NIH)-supported clinical trials. Both add to the urgency of solutions for engaging, recruiting and retaining diverse participants in Alzheimer's clinical trials. Meanwhile, a few of the panel's proposed solutions are already being implemented, however many remain to be addressed and evaluated. For example, some activities of the Alzheimer's Drug Discovery Foundation Diagnostics Accelerator and the Alzheimer's Association Global Biomarker Standardization Consortium are addressing challenges associated with the technical performance, diagnostic accuracy, and prognostic value of promising blood-based biomarkers. ADDI is continuously developing their data-sharing platform to expand data collection and research collaborations. The Davos Alzheimer's Collaborative has launched an initiative to increases cognitive assessment rates for older adults. Trial sponsors are leveraging home-based computerized cognitive assessments and video conferencing to reduce participant burden.

Future studies and panels should consider the cost implications of the proposed solutions as well as specific actionable steps for implementing solutions and a framework for markers of success. Extensions should consider the applicability of the recruitment strategies to various targets of AD trials, for example those that target the functional and behavioral symptoms of dementia. These additions will provide key information to federal agencies, national advocacy and local community-based organizations, trial sponsors, diagnostic companies, health care providers and provider organizations, health insurers, the research community and the public. Above all, the critical barriers facing AD clinical trials today can be overcome when stakeholders from academia, industry, philanthropy, government and volunteers work together to address this immense public health challenge and find novel ways to expedite the development of therapies for AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to Dr. Heather M. Snyder at the Alzheimer's Association and Dr. Laurie Ryan at the National Institute on Aging for their participation and scientific guidance on this project.

Funding

Financial support for this study was provided by the USC Schaeffer Center for Health Policy & Economics and by Gates Ventures.

Disclosures

Jessica B. Langbaum reports grants from National Institutes of Health (NIH) and consulting fees from Alector, Biogen and Provoc. Julie Zissimopoulos has received grants from National Institute on Aging (NIA) and is an advisory board member of Center for Aging and Policy Studies at Syracuse University and Demography of Aging Center at University of Texas, Austin. Rhoda Au has received grants from NIH/NIA, Alzheimer's Drug Discovery Fund, American Heart Association and Gates Ventures and consulting fees from Signant Health, Biogen, Eisai, GSK and Davos Alzheimer's Collaborative. Niranjan Bose is a board member of Alzheimer's Disease Data Initiative, Early Detection of Neurodegenerative Diseases Initiative (EDoN) and Global Health Labs. Chris

J. Edgar is an employee of Cogstate Ltd and is a board member of CHDI Foundation. Evan Ehrenberg is a co-founder and CEO of Clara Health, holds stock in Clara Health and is a board member of Xperii Corp. d/b/a Clara Health. Howard Fillit reports grant from NIA, royalties from Icahn School of Medicine at Mount Sinai, consulting fees from Alector, Biogen, LifeWorx, Otsuka and Samus Therapeutics, pending patent for Alzheimer's disease treatment and is the chair of Independent Data Management Committee for Alector. Carl V. Hill reports grants from NIH/NIA, CDC and Genentech. Michael Irizarry is an employee of Eisai and the industry co-chair of Critical Path in Alzheimer's Disease Consortium. Sarah Kremen is an advisory member of Medical and Scientific Committee for Alzheimer's Los Angeles and reports grants from State of California for UCLA California Alzheimer's Disease Research Center and royalties from UpToDate; has not received honoraria or consulting fees from pharmaceutical companies, but has been a site principal investigator for studies sponsored by Biogen, Eisai, Eli Lilly, Suven Life Sciences, Merck and Roche. Darius Lakdawalla has received grants from NIH and research support, speaker fees, travel assistance or consulting income from Amgen, Biogen, Genentech, Gilead, GRAIL, Edwards Lifesciences, Mylan, Novartis, Otsuka, Perrigo and Pfizer; owns equity in Precision Medicine Group and previously served as a consultant for them. Nancy Lynn is an employee of BrightFocus Foundation which receives educational grants from the biopharmaceutical industry and reports consulting fees from PCH Films. Tetsuyuki Maruyama is a board member of Brain Protection Co., ProteKt Therapeutics and Structural Genomics Consortium, reports consulting fees from Cerevance Therapeutics and FutuRx Inc. and stock in Takeda Pharmaceuticals, Brain Protection Co., Cerevance Therapeutics and ProteKt Therapeutics. Holly A. Massett reports consulting fees from AB InBev. Eric M. Reiman reports grants from NIH, State of Arizona, Banner Alzheimer's Foundation, NOMIS Foundation, Alzheimer's Association, GHR Foundation, FBRI and Gates Ventures, contracts with Eli Lilly/AVID, Roche/Genentech, and Novartis/Amgen, consulting fees or travel assistance from Alkahest, Alzheon, Aural Analytics, Denali, Green Valley, Retromer Therapeutics, Roche, Roche Diagnostics and Vaxxinity, patent for methods to accelerate the evaluation of Alzheimer's disease prevention therapies and pending patent for Alzheimer's disease treatment and prevention, is a board member of Flinn Foundation and National Advisory Council on Aging and is a co-founder and shareholder of ALZPath, a company that seeks to help advance the role of blood-based biomarkers in research, treatment development, and clinical care. Carol Routledge is a scientific advisor for EDoN, on the scientific advisory board of Cognetivity and on the board of directors of Alzinova; reports consulting fees from EDoN and Exeter University Entrepreneur in Residence and stock options in Cognetivity. Michael W. Weiner reports research support from NIH, US Department of Defense, Patient-Centered Outcomes Research Institute (PCORI), California Department of Public Health, University of Michigan, Siemens, Biogen, Hillblom Foundation, Alzheimer's Association, State of California, Johnson & Johnson, Kevin and Connie Shanahan, General Electric, Vanderbilt University Medical Center, Australian Catholic University, Stroke Foundation, and Veterans Administration; stock options in Alzheon, Alzeca, and Anven; has served on advisory boards for Acumen Pharmaceuticals, Alzheimer's Disease Neuroimaging Initiative, Alzheon, Brain Health Registry, Eli Lilly, Cerecin, Dolby Family Ventures, Merck, Nestle/Nestec, NIA, PCORI/PPRN, Roche, Sharp & Dohme Corp., T3D Therapeutics, University of Southern California (USC) and UCSF Committee for Human Research; has received consulting fees, speaker fees or travel assistance from Cerecin, Bioclinica, Nestle/Nestec, Roche, Genentech, NIH, Buck Institute for Research on Aging, Fujifilm Toyama Chemical, Garfield Weston, Baird Equity Capital, USC, Cytox, Japanese Organization for Medical Device Development and T3D Therapeutics. Stacie Weninger is employed by FBRI LLC, a subsidiary of FMR LLC which along with its affiliates invests broadly in many companies, including life sciences and pharmaceutical companies. Paul S. Aisen has received grants from NIA, Alzheimer's Association, Eisai, Eli Lilly, Foundation for the National Institutes of Health, Janssen, and consulting fees from AbbVie, Axon, Biogen, ImmunoBrain Checkpoint, Merck, Roche, Rainbow Medical, and Shionogi Inc. Lynne Hughes, Kristina Malzbender, Deep Patel, Desi Peneva and Klaus Romero report no conflicts of interest.

References

1. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2021;17(3):327–406. [PubMed: 33756057]
2. Zissimopoulos J, Crimmins E, St. Clair P. The value of delaying Alzheimer's disease onset. fhep. 2015;18(1):25–39.
3. Brookmeyer R, Kawas CH, Abdallah N, Paganini-Hill A, Kim RC, Corrada MM. Impact of interventions to reduce Alzheimer's disease pathology on the prevalence of dementia in the oldest-old. Alzheimers Dement. 2016;12(3):225–232. [PubMed: 26900132]
4. Goldman DP, Fillit H, Neumann P. Accelerating Alzheimer's disease drug innovations from the research pipeline to patients. Alzheimers Dement. 2018;14(6):833–836. [PubMed: 29680407]
5. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. Alzheimers Dement: Transl Res Clin Interv. 2021;7(1):e12179.
6. Malzbender K, Lavin-Mena L, Hughes L, Bose N, Goldman D, Patel D. Key barriers to clinical trials for Alzheimer's disease. USC Schaeffer Center for Health Policy

and Economics. https://healthpolicy.usc.edu/research/key-barriers-for-clinical-trials-for-alzheimers-disease/. Published 2020. Accessed Feb 25, 2021.

7. Watson JL, Ryan L, Silverberg N, Cahan V, Bernard MA. Obstacles and opportunities in Alzheimer's clinical trial recruitment. Health Aff. 2014;33(4):574–579.
8. Fargo KN, Carrillo MC, Weiner MW, Potter WZ, Khachaturian Z. The crisis in recruitment for clinical trials in Alzheimer's and dementia: An action plan for solutions. Alzheimers Dement. 2016;12(11):1113–1115. [PubMed: 27836052]
9. Indorewalla KK, O'Connor MK, Budson AE, Jackson J. Modifiable barriers for recruitment and retention of older adults participants from underrepresented minorities in Alzheimer's disease research. J Alzheimers Dis. 2021;80(3):927–940. [PubMed: 33612540]
10. Grill JD, Galvin JE. Facilitating Alzheimer's disease research recruitment. Alzheimer Dis Assoc Disord. 2014;28(1):1–8. [PubMed: 24322484]
11. Alzheimer's Disease International. World Alzheimer Report 2021: Journey through the diagnosis of dementia. https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf. Published 2021. Accessed Dec 28, 2021.
12. Galvin JE, Meuser TM, Boise L, Connell CM. Predictors of physician referral for patient recruitment to Alzheimer disease clinical trials. Alzheimer Dis Assoc Disord. 2009;23(4):352–356. [PubMed: 19561438]
13. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019;15(3):321–387.
14. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD™ test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 2021;519:267–275. [PubMed: 34015303]
15. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: Findings from a multi cohort validity analysis. Mol Neurodegener. 2021;16(30):1–12. [PubMed: 33413517]
16. Teunissen CE, Verberk IM, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: Towards clinical implementation. Lancet Neurol. 2021;S1474–4422(21)00361–6.
17. Young CB, Mormino EC. Prevalence rates of amyloid positivity—updates and relevance. JAMA Neurol. 2022.
18. Jones RW, Andrieu S, Knox S, Mackell J. Physicians and caregivers: Ready and waiting for increased participation in clinical research. J Nutr Health Aging. 2010;14(7):563–568. [PubMed: 20818472]
19. Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged≥ 65 years. Alzheimers Dement. 2019;15(1):17–24. [PubMed: 30243772]
20. Centers for Disease Control and Prevention. U.S. burden of Alzheimer's disease, related dementias to double by 2060. https://www.cdc.gov/media/releases/2018/p0920-alzheimers-burden-double-2060.html. Published 2018. Accessed Mar 1, 2021.
21. Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. Alzheimers Dement. 2019;15(2):292–312. [PubMed: 30555031]
22. Ballard EL, Gwyther LP, Edmonds HL. Challenges and opportunities: Recruitment and retention of African Americans for Alzheimer's disease research: Lessons learned. Alzheimer Dis Assoc Disord. 2010;24(0):S19–23. [PubMed: 20711060]
23. Gilmore-Bykovskyi AL, Jin Y, Gleason C, et al. Recruitment and retention of underrepresented populations in Alzheimer's disease research: A systematic review. Alzheimers Dement: Transl Res Clin Interv. 2019;5:751–770.
24. Zhou Y, Elashoff D, Kremen S, Teng E, Karlawish J, Grill JD. African Americans are less likely to enroll in preclinical Alzheimer's disease clinical trials. Alzheimers Dement: Transl Res Clin Interv. 2017;3(1):57–64.
25. Canevelli M, Bruno G, Grande G, et al. Race reporting and disparities in clinical trials on Alzheimer's disease: A systematic review. Neurosci Biobehav Rev. 2019;101:122–128. [PubMed: 30946856]

26. Olson NL, Albensi BC. Race-and Sex-Based Disparities in Alzheimer's Disease Clinical Trial Enrollment in the United States and Canada: An Indigenous Perspective. J Alzheimers Dis Rep. 2020;4(1):325–344. [PubMed: 33024940]
27. Faison WE, Schultz SK, Aerssens J, et al. Potential ethnic modifiers in the assessment and treatment of Alzheimer's disease: Challenges for the future. Int Psychogeriatr. 2007;19(3):539–558. [PubMed: 17451614]
28. National Academies of Sciences Engineering and Medicine (NASEM). Implications for behavioral and social research of preclinical markers of Alzheimer's disease and related dementias: Proceedings of a workshop–in brief. https://www.nia.nih.gov/sites/default/files/2021-08/final-report-bsr-biomarkers-preclinical-diagnostics-of-ad-adrd.pdf. Published 2021. Accessed Jan 7, 2022.
29. Alzheimer's Association. Race, ethnicity, and Alzheimer's fact sheet. https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf. Published 2020. Accessed Mar 2, 2021.
30. Banzi R, Camaioni P, Tettamanti M, Lucca U. Older patients are still under-represented in clinical trials of Alzheimer's disease. Alzheimers Res Ther. 2016;8(32):1–10. [PubMed: 26776763]
31. Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimers Res Ther. 2010;2(34):1–11. [PubMed: 20122289]
32. Largent EA, Karlawish J, Grill JD. Study partners: Essential collaborators in discovering treatments for Alzheimer's disease. Alzheimers Res Ther. 2018;10(1):1–7. [PubMed: 29370870]
33. Grill JD, Monsell S, Karlawish J. Are patients whose study partners are spouses more likely to be eligible for Alzheimer's disease clinical trials. Dementia and Geriatric Cognitive Disorders. 2012;33(5):334–340. [PubMed: 22759982]
34. Cary MS, Rubright JD, Grill JD, Karlawish J. Why are spousal caregivers more prevalent than nonspousal caregivers as study partners in AD dementia clinical trials? Alzheimer Dis Assoc Disord. 2015;29(1):70–74. [PubMed: 24805971]
35. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. Alzheimers Dement. 2018;14(3):367–429.
36. Peavy GM, Jenkins CW, Little EA, et al. Community memory screening as a strategy for recruiting older adults into Alzheimer's disease research. Alzheimers Res Ther. 2020;12(1):1–12.
37. Rodríguez-Gómez O, Rodrigo A, Iradier F, et al. The MOPEAD project: Advancing patient engagement for the detection of "hidden" undiagnosed cases of Alzheimer's disease in the community. Alzheimers Dement. 2019;15(6):828–839. [PubMed: 31076376]
38. Winblad B, Jessen F, Kramberger MG, et al. The IMI-EU H2020 project MOPEAD: Outcome of different screening methods to identify MCI/early AD. Alzheimers Dement. 2020;16(6):e044524.
39. Walter S, Clanton T, Langford O, et al. Recruitment into the Alzheimer Prevention Trials (APT) Webstudy for a Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease (TRC-PAD). J Prev Alzheimers Dis. 2020;7(4):219–225. [PubMed: 32920623]
40. Langbaum JB, High N, Nichols J, Kettenhoven C, Reiman EM, Tariot PN. The Alzheimer's Prevention Registry: A large internet-based participant recruitment registry to accelerate referrals to Alzheimer's-focused studies. J Prev Alzheimers Dis. 2020;7(4):242–250. [PubMed: 32920626]
41. Weiner MW, Nosheny R, Camacho M, et al. The Brain Health Registry: An internet-based platform for recruitment, assessment, and longitudinal monitoring of participants for neuroscience studies. Alzheimers Dement. 2018;14(8):1063–1076. [PubMed: 29754989]
42. Larsen ME, Curry L, Mastellos N, Robb C, Car J, Middleton LT. Development of the CHARIOT research register for the prevention of Alzheimer's dementia and other late onset neurodegenerative diseases. PLoS One. 2015;10(11):e0141806.
43. Georgia Memory Net. https://gamemorynet.org/. Accessed Apr 20, 2021.
44. Jacobson M, Thunell J, Zissimopoulos J. Cognitive assessment at Medicare's annual wellness visit in fee-for-service and Medicare Advantage plans. Health Aff. 2020;39(11):1935–1942.
45. Owens DK, Davidson KW, Krist AH, et al. Screening for cognitive impairment in older adults: US Preventive Services Task Force recommendation statement. JAMA. 2020;323(8):757–763. [PubMed: 32096858]

46. Borson S, Frank L, Bayley PJ, et al. Improving dementia care: The role of screening and detection of cognitive impairment. Alzheimers Dement. 2013;9(2):151–159. [PubMed: 23375564]
47. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in a primary care setting. Alzheimers Dement. 2013;9(2):141–150. [PubMed: 23265826]
48. California Alzheimer's Disease Centers. Assessment of cognitive complaints toolkit for Alzheimer's disease: Instruction manual. https://mph.ucdavis.edu/alzheimers/Patient_Care/ACCT-AD_Manual.pdf. Published 2018. Accessed Mar 31, 2021.
49. Go Annual. https://goannualga.com/. Accessed Apr 20, 2021.
50. Alzheimer's Association. Cognitive assessment and care planning services: Alzheimer's Association Expert Task Force recommendations and tools for implementation. https://www.alz.org/careplanning/downloads/cms-consensus.pdf. Accessed Mar 31, 2021.
51. Lees Haggerty K, Epstein-Lubow G, Spragens LH, et al. Recommendations to improve payment policies for comprehensive dementia care. J Am Geriatr Soc. 2020;68(11):2478–2485. [PubMed: 32975812]
52. Boustani M, Alder CA, Solid CA, Reuben D. An alternative payment model to support widespread use of collaborative dementia care models. Health Aff. 2019;38(1):54–59.
53. Sinsky CA, Dugdale DC. Medicare payment for cognitive vs procedural care: Minding the gap. JAMA Intern Med. 2013;173(18):1733–1737. [PubMed: 23939411]
54. Alzheimer's Drug Discovery Foundation Diagnostics Accelerator. Advancing cutting-edge Alzheimer's biomarkers and novel diagnostic technologies. https://www.alzdiscovery.org/uploads/media/ADD12_DxA_Report2020_r10_081121.pdf. Published 2021. Accessed Aug 12, 2021.
55. Hampel H, O'Bryant SE, Molinuevo JL, et al. Blood-based biomarkers for Alzheimer disease: Mapping the road to the clinic. Nat Rev Neurol. 2018;14(11):639–652. [PubMed: 30297701]
56. Henriksen K, O'Bryant SE, Hampel H, et al. The future of blood-based biomarkers for Alzheimer's disease. Alzheimers Dement. 2014;10(1):115–131. [PubMed: 23850333]
57. Alzheimer's Disease Data Initiative (ADDI). https://www.alzheimersdata.org/. Accessed Apr 20, 2021.
58. Global Alzheimer's Association Interactive Network (GAAIN). http://gaain.org/. Accessed Apr 20, 2021.
59. Smith AG, Rodrigo K, Lowe P, et al. Utilizing a mobile clinical trials unit: Lessons learned from the first three years: Clinical trial design and implementation. Alzheimers Dement. 2020;16(S9):e037099.
60. Smith AG, Smith JS, Morgan D. Utilizing a mobile clinical trial unit to enhance recruitment in prevention trials for Alzheimer's disease. Alzheimers Dement. 2018;14(7S):P1075.
61. Petersen RC, Nixon RA, Thies W, Taylor A, Geiger AT, Cordell C. Alzheimer's Association® TrialMatch™: A next-generation resource for matching patients to clinical trials in Alzheimer's disease and related disorders. Neurodegener Dis Manag. 2012;2(1):107–115.
62. Gold M, Amatniek J, Carrillo MC, et al. Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials. Alzheimers Dement: Transl Res Clin Interv. 2018;4:234–242.
63. Dorsey ER, McConnell MV, Shaw SY, Trister AD, Friend SH. The use of smartphones for health research. Acad Med. 2017;92(2):157–160. [PubMed: 27119325]
64. Apostolaros M, Babaian D, Corneli A, et al. Legal, regulatory, and practical issues to consider when adopting decentralized clinical trials: Recommendations from the clinical trials transformation initiative. Ther Innov Regul Sci. 2020;54(4):779–787. [PubMed: 32557302]
65. Ali Z, Zibert JR, Thomsen SF. Virtual clinical trials: perspectives in dermatology. Dermatology. 2020;236(4):375–382. [PubMed: 32126560]
66. Stergiopoulos S, Eustace C, Stem K, Getz KA. Mobile nurse services in clinical trials: Usage and industry perceptions. Ther Innov Regul Sci. 2016;50(4):442–449. [PubMed: 30227020]
67. Hawking M. Home nursing replacing site visits. In: Innovation in clinical trial methodologies. Elsevier; 2021:55–60.

Table 1

Panel's proposed solutions to accelerate Alzheimer's clinical trials

Category	Solution
Cognitive screening and early detection	Assess innovative community-engaging prescreening strategies such as virtual engagement outreach and digital assessment tools to facilitate early diagnosis, trial recruitment, and trial retention
	Encourage CMS to (i) incentivize primary care physicians to execute annual wellness visits with cognitive screening; and (ii) reimburse diagnostics, such as amyloid PET scans for individuals with symptomatic cognitive impairment, to increase trial enrollment
	Develop communication streams with primary care physicians around training and resources to keep them informed about ongoing clinical research
	Partner with the U.S. Health Resources & Services Administration Geriatric Workforce Enhancement Program to encourage training on early screening and diagnosis in local primary care networks
	Increase medical, nursing, and social work school training about AD early screening and clinical research
Blood-based biomarker testing	Develop accurate, accessible, and affordable blood-based biomarker tests to support trial enrollment; address the practical issues related to their integration in clinical practice
	Provide a shared resource of (i) blood samples to support the comparison and neuropathological validation of different blood-based biomarker assays for AD; and (ii) blood and CSF samples and imaging data in underrepresented groups to establish the generalizability of blood tests across heterogeneous populations
	Build a centralized data-sharing platform with data collected on biomarker types, imaging, autopsy, co-pathology, and socio-economic status to facilitate the identification and analysis of phenotypes across heterogeneous populations
	Initiate public education campaigns on the benefits of blood-based biomarker tests targeting the community as well as healthcare providers
Public awareness and outreach	Initiate brain health awareness campaigns targeting diverse communities to promote the benefits of early screening and diagnosis, and activate asymptomatic individuals to participate in AD registries and clinical trials
	Develop awareness campaigns to promote uptake of cognitive screening at annual wellness visits, targeting both communities and primary care physicians
	Initiate awareness campaigns targeting healthcare providers to promote early screening and diagnosis, assessment tools, and referrals to AD clinical trials
Clinical trial architecture in the community	Facilitate clinical trial architecture in the community: leverage network's satellite sites to take trials to the community, utilize mobile trial units, community diagnostic clinics
	Work with local community leaders in faith- or culturally-based organizations to build trust and provide information about AD clinical trials
Screen-fail registry and digital engagement	Build a screen-fail registry to collect and share basic participant data during trial prequalification as well as after screen failure to improve trial matching and referrals
	Build a digital engagement strategy and platform to enroll self-identified individuals into multiple AD clinical trials simultaneously
	Create opportunities to provide trial participants with their information to maintain engagement and increase positive trial experiences
Virtual clinical trials	Leverage integrated, home-based computerized cognitive assessments and video conferencing to reduce burden on participants and study partners
	Increase use of virtual procedures for safety monitoring and remote assessment of cognition and function
	Increase number of remote nurses to visit participants at home to perform key lab tests and physical exams, administer therapy, and ensure the integrity of data collected remotely
Clinical trial design optimization through quantitative modeling	Utilize quantitative modeling and simulation tools, that leverage open patient-level data from AD clinical trials integrated into regulatory-grade standardized database, to develop clinical trial simulators with three basic components: disease progression, drug effects, and trial features such as placebo effect and dropouts

Category	Solution
	Submit such simulators through formal regulatory pathways for their review and potential endorsement (for example, FDA's Fit for Purpose Initiative, EMA's Qualification of Novel Methodologies in Drug Development)
Other potential solutions	Increase use of electronic health record (EHR) technologies to target specific groups, and integrate digital diagnostic tests with EHR data
	Leverage data from participant handoff points in the enrollment process to study where, why, and which populations drop off during trial enrollment
	Conduct focus groups and interviews with diverse populations to identify participation barriers such as lack of employer support, transportation, site hours, compensation
	Redesign the informed consent process, focusing on both participants and study partners, including eConsent, timing of disclosures, training of research staff
	Redesign study protocols to incorporate flexible screening procedures and review strict exclusion criteria including study partner requirements
	Utilize multifunctional digital tools to study numerous digital endpoints simultaneously to build algorithms to detect early disease