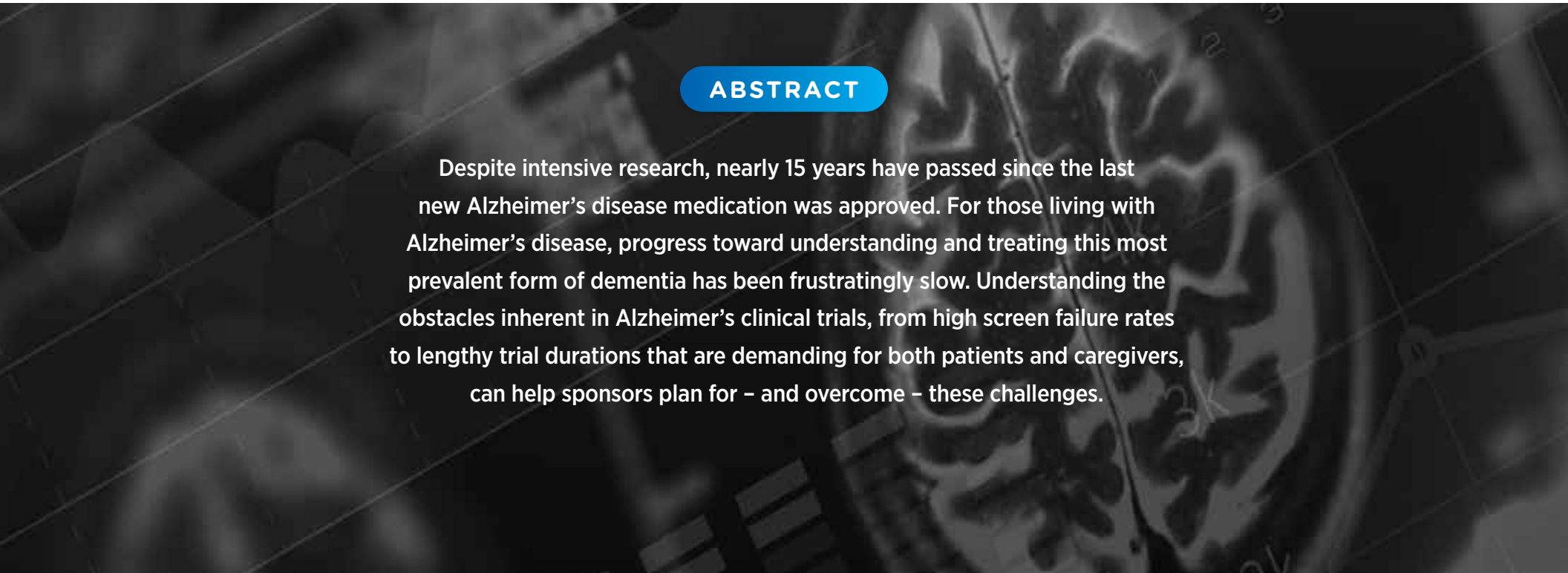
WHITE PAPER

premier research
IT'S WHAT WE DO. BEST.

NEUROSCIENCE

A Vast Unmet Need:
Challenges in Alzheimer's Disease Clinical Trials



ABSTRACT

Despite intensive research, nearly 15 years have passed since the last new Alzheimer's disease medication was approved. For those living with Alzheimer's disease, progress toward understanding and treating this most prevalent form of dementia has been frustratingly slow. Understanding the obstacles inherent in Alzheimer's clinical trials, from high screen failure rates to lengthy trial durations that are demanding for both patients and caregivers, can help sponsors plan for – and overcome – these challenges.

Among the leading causes of death, AD is the only condition that cannot be prevented, cured, or even significantly slowed, making it imperative that we develop new pharmacologic therapies.

Background

Dementia is a growing global epidemic, affecting nearly 50 million people worldwide.[1] That number is expected to approach 75 million by 2030, when the cost of patient care is forecast to reach $2 trillion.[2] And the trend will only accelerate: By 2050, it's estimated that 115 million people will suffer from some form of dementia. Alzheimer's disease (AD) is by far the most common of these afflictions occurring late in life. Among the leading causes of death, AD is the only condition that cannot be prevented, cured, or even significantly slowed, making it imperative that we develop new pharmacologic therapies.

More than three decades ago, the cholinergic hypothesis proposed that degeneration of cholinergic neurons in the basal forebrain — and the associated loss of cholinergic neurotransmission in the cerebral cortex, hippocampus, and other areas — contributed significantly to cognitive deterioration in Alzheimer's disease. That hypothesis led to the development and FDA approval of the first Alzheimer's drug, tacrine, in 1993.

Despite clinical trials of numerous agents over a wide range of mechanisms that include neurotransmitter modulation and disease-modifying therapy targeting amyloid and tau, the last new Alzheimer's medication, memantine, was approved in 2003. To address this unmet need, the National Alzheimer's Project Act in the U.S. mandated the formulation of a national plan to address AD and, in 2012, that plan articulated the goal of preventing and effectively treating AD by 2025.

Unfortunately, Alzheimer's drug development is costly, time-consuming, and inefficient. Site functions, trial design, and patient recruitment all require improvement. At 99.6 percent, the trial failure rate is the highest of any therapeutic area. Innovation is critical to shortening the development cycle of new therapies and identifying drugs that have limited or no therapeutic potential.

In this white paper, we will review the current global pipeline of Alzheimer's trials and their geographic locations, describe innovations in trial design, and discuss considerations of optimal clinical trial processes, including preclinical patient populations, clinical assessments sensitive to the earliest disease-related changes, and biomarkers as outcomes of clinical trials.

The development of both full and partial agonists of the M1 muscarinic receptor has been limited to adverse events. However, agents targeting sigma1 and muscarinic receptors are currently under development and investigation.

The path to 2025: past failures and future opportunities

Treatments for Alzheimer's disease can be classified according to two broad categories:

1. Symptomatic therapies
2. Disease-modifying therapies and therapies for behavioral disturbances

Symptomatic therapies[3]

The well-known cholinesterase inhibitors donepezil, rivastigmine, and galantamine are approved symptomatic therapies for AD. Although several other molecules from this group have been investigated, they were ultimately unsuccessful due to lack of efficacy, intolerable side effects, or impractical or ineffective dosing. Approval of new formulations and new dosing of existing medication has occurred, but there have been no novel drugs.

Thus far, there has been little success with nicotine receptor agonists. The development of both full and partial agonists of the M1 muscarinic receptor has been limited to adverse events. However, agents targeting sigma1 and muscarinic receptors are currently under development and investigation. Despite the approval of memantine, other glutamate-NMDA receptor and glutamate-AMPA receptor modulators have not shown efficacy to date.

A number of serotonin receptors have been postulated to be potential therapeutic targets for the cognitive, behavioral, and affective symptoms of AD, but have not shown evidence of significant efficacy in clinical trials. The h3 histamine receptor antagonists and numerous other agents targeting various neurotransmitter systems, including GABA(B) receptor antagonists and phosphodiesterase-4 (PDE4) inhibitors, have also been investigated without success. Due to the alterations in cerebral glucose metabolism observed in AD, insulin has also been tested in AD. There are currently studies where intranasal insulin, peroxisome proliferator-activated receptor gamma agonists, and glucagon-like peptide 1 agonist are being tested on various stages of AD.

Figure 1a. Compounds and therapies that have been studied in AD

SYMPTOMATIC THERAPIES
Cholinesterase inhibitors*
Nicotine receptor agonists
Muscarinic agonists
Glutamate-NMDA receptor modulators*
Glutamate-AMPA receptor modulators
Serotonin receptor agonists and antagonists
Histamine receptor agonists
Other neurotransmitters
Antidiabetic agents
Miscellaneous, including deep brain stimulation, transcranial magnetic brain stimulation, curcumin, estrogen replacement, acetyl-l-carnitine, ginkgo biloba, omega-3 fatty acid, etc.

*approved therapy

Figure 1b. Compounds and therapies that have been studied in AD

DISEASE-MODIFYING THERAPIES AND THERAPIES FOR BEHAVIORAL DISTURBANCES
y-secretase inhibitors
Modulators of y-secretase
Anti-aggregants
Active and passive immunotherapy
Anti-tau agents, including immunotherapy, phosphokinase inhibitors, tau aggregation inhibitors and microtubule stabilizers
Antioxidant and anti-inflammatory agents

Disease-modifying therapies and therapies for behavioral disturbances[3]

There are two dominant pathways of disease-modifying therapies: anti-amyloid agents and tau-targeted therapies. The amyloid therapy hypothesis has been the main target for disease modification therapies for over 20 years, and the goal of these therapies is to decrease production, prevent aggregation, or increase removal of beta-amyloid derived from amyloid precursor protein (APP) via sequential proteolytic cleavage by β- and y-secretase.

Unfortunately, the challenge with y-secretase inhibitors is poor selectivity as these compounds also target Notch. Given the safety issues in previous trials, there are concerns regarding y-secretase inhibitors. Modulators of y-secretase have been similarly unsuccessful.

Agents targeting beta-site APP cleaving enzyme (BACE) are much more promising. There are currently a number of clinical trials testing drugs targeting inhibition of BACE. Notably, in February 2017, Merck announced termination of the EPOCH study, a Phase II/III study evaluating verubecestat, an investigational small molecule inhibitor of BACE1, for lack of efficacy.[4]

Another group of candidate compounds is comprised of molecules for binding the soluble forms of amyloid beta, with the aim of preventing further aggregation.

Active and passive immunotherapy is designed to clear amyloid beta and reduce its toxic effect. However, given the declining immune system response of elderly patients to vaccination, active immunotherapy may be best implemented in a younger population or as part of a prevention strategy. Passive immunotherapy has potential advantages over active immunotherapy due to its ability to target specific domains of amyloid and its lower risk of irreversible autoimmune complications. Unfortunately, one of the biggest disappointments of the last 12 months was the failure of solanezumab, a monoclonal antibody which failed to slow cognitive decline in patients with mild AD.[5]

This failure, along with other failures of anti-amyloid agents to reach primary clinical endpoints, has shifted focus to other approaches such as tau-targeted therapies. There is currently in development an immunotherapy agent stimulating the immune system to produce antibodies against phosphorylated tau protein. Phosphokinase inhibitors, tau aggregation inhibitors, and microtubule stabilizers molecules are also being investigated.

As part of the pathogenesis of AD is micro-inflammation, numerous antioxidant, anti-inflammatory, cholesterol-lowering agents; homocysteine-lowering agents; and neuro-protectants have been studied, but have not been found to be effective. Potential new agents for the behavioral disturbances associated with AD, such as depression, agitation, or aggressiveness, have also been investigated.

Development pipeline

Approximately 70 percent of compounds currently in Phase II or III trials are aiming to alter the underlying pathophysiology of AD, while the remaining 30 percent are aiming to lessen the behavioral symptoms often associated with the disease. A pipeline analysis presented at the Alzheimer's Association International Conference in London in July 2017 showed that there are 92 compounds in Phase II trials (see Figure 2). According to this analysis, twenty-seven drugs in Phase III clinical trials and eight drugs in Phase II trials may launch in the next five years.[6]

Based on this same analysis, the development timeline for disease-modifying therapies after pre-clinical development and initial characterization is approximately 13 months for Phase I, 28 months for Phase II, and 51 months for Phase III, followed by a regulatory review period of 18 months. As a result, the total development timeline for an AD drug, including pre-clinical development, may be more than nine years.

Beyond the shift from anti-amyloid treatments to tau-targeted therapies, another factor that has changed over the last few years is the stage of AD targeted by putative therapeutic agents. With advances in our understanding of the underlying anatomical and pathophysiologic changes in AD which begin many years before the onset of clinical symptoms, research and development have shifted to the earlier, pre-dementia stages of AD known as mild cognitive impairment (MCI) or prodromal AD.

Of 143 Alzheimer's trials active as of July 2017, fifty-one are targeting healthy, healthy at-risk, or MCI to mild AD patients, including 21 studies focused on completely asymptomatic patients. In February 2013, the FDA issued draft guidance for the industry regarding development of drugs for the treatment of early-stage AD. This guidance addresses potential adaptation of the current approach to drug development for the treatment of dementia-stage AD to make it more appropriate for clinical trials in early stages of the disease.[7]

Figure 2. Ongoing clinical trials by mechanism of action

		2017	2018	2019	2020	2021	2022
Phase II	Neurotransmission	8	6	1	1		
	Inflamation	0	0	1	0		
	Insulin/glucose	3	1	1	0		
	Amyloid	4	3	2	1		
	Neuronal/synaptic growth	1	2	2	0		
	Tau	1	2	4	0		
	Other	3	2	4	0		
Phase III	Neuro transmission	4	4	0	3	1	0
	Inflammation	0	0	1	0	0	0
	Insulin/glucose	0	1	2	0	0	0
	Amyloid	0	2	3	2	2	3
	Neuronal/synaptic growth	0	0	2	0	0	0
	Tau	2	0	1	0	0	0
	Other	0	0	5	0	1	0

Strategies for increasing clinical trial success rate

While the high level of research activity in AD provides hope for the future, the many failures in the history of AD clinical trials suggests that either the hypothesis of underlying AD pathophysiology or the design of clinical trials must be revised.

Figure 3. Active Alzheimer's trials around the world

Incorporating international trial sites

Sponsors of AD trials can leverage a number of strategies to help increase the success rate of their clinical trials. One option is to accelerate enrollment by adding ex-U.S. countries to the geographic distribution of the study. In the U.S., approximately 85 to 90 percent of AD trials experience delayed recruitment.

Of currently active Alzheimer's trials, seventy-one percent are being conducted in the United States. While the U.S. has the most trial sites of any single country, the majority of sites are in other countries. Understanding the startup timelines – as well as the competitive clinical trial landscape and local regulatory environment – in each country under consideration is critical for successful enrollment. Sponsors may want to consider emerging countries, such as China, where the population is large and there is access to treatment-naïve patients, which may be difficult to find elsewhere.

There are compelling reasons to consider incorporating international sites in AD trials. However, there are also key aspects and nuances that must be considered when planning a global AD trial, including:[8]

- **Education levels.** Level of education can vary significantly from country to country, and it is known that individuals with lower levels of education tend to progress more slowly in the course of AD
- **Exercise levels.** Level of exercise is also country-dependent, and individuals with higher levels of exercise have lower levels of amyloid deposition in the brain
- **Factors influencing drug pharmacokinetics.** For example, differences in body size are expected to contribute to differences in brain exposure levels when similar doses of drug are given. In addition, obesity, which is more common in Western populations, may affect drug metabolism and distribution.

- **Genetic diversity.** Polymorphism may influence drug metabolism, central nervous system drug exposure, and drug response across ethnic groups. Genetic diversity also creates differences in the biology of AD. For example, apolipoprotein E4 varies between ethnicities and geographic regions.
- **Differences in perception of AD symptoms.** These differences may lead to late diagnosis of AD. For example, Asian countries place less emphasis on the importance of memory in aging, and AD is less likely to be perceived as an abnormality in those countries. Rates of apathy are also lower in Asian populations, compared to the U.S. population, possibly due to differences in expectations of activity levels.

  In addition, the role of caregiver may be more straightforward in Western countries than in many developing nations where patients tend to live at home in extended families with multiple caregivers. This can be a challenge because the presence of a reliable caregiver is essential for AD trials, where protocols typically define a reliable caregiver as someone who spends at least 10 hours per week with a patient.
- **Use of clinical trial instruments and equipment.** Nearly all widely-used clinical instruments for AD were developed in North America. As a result, the data collected from different countries may be affected by cultural and national influences. Further, the biomarker capacity, access to radioactive tracers, and willingness to adopt new technology may vary widely between regions as well. Sites may require additional technical expertise to ensure quality. Centralized reading of brain imaging can help to minimize site-to-site variability in image interpretation.
- **Experience in conducting AD trials.** Raters with little or no experience may contribute to greater score variability and more difficulty demonstrating a drug-placebo difference. Providing standardized training for raters and implementing in-study rater surveillance programs can help in optimizing data quality.
- **Regulatory and legal factors.** Strategies and requirements differ from country to country. Sample collection and handling may pose challenges as well. For example, if a country places restrictions on DNA and plasma export, this may require identification and standardization of a reference lab within that country.

Improving protocol design

Most of the common protocol designs for AD clinical trials were created in the development programs for cholinesterase inhibitors and memantine. These were double-blind, placebo-controlled, parallel group studies with a dual outcome including a cognitive measure and a global impression or activities of daily living outcome. In these designs, patients were randomized to drug or placebo, and the change from baseline in the placebo group was compared to the change in baseline in the treatment group after a specific number of weeks or months. In most cases, the investigational agent was an add-on treatment to the standard of care.

Clinical trials in AD often struggle to find ways to separate out symptomatic effects of potential agents from disease-modifying effects. Clinical trial designs have been developed to try to adjust for symptomatic effects and allow clinical rating scales to be used as endpoints. For example:[9]

- **Wash-in analysis.** This design compares the change between groups in clinical outcome measures over the first few weeks or months of a study. If a greater improvement is seen with the investigational agent, this could potentially indicate an early symptomatic effect because a true disease-modifying effect would not be seen so soon. This design is often combined with other design strategies.
- **Wash-out analysis/staggered withdrawal.** In this analysis, treatment is withdrawn from both the active agent- and placebo-treated groups at the end of the study. The active agent is assumed to have disease-modifying properties if patients treated with the agent show slower disease progression throughout the double-blind treatment period and less severe deterioration when treatment is withdrawn.
- **Randomized staggered start/delayed-start.** In this design, one group of patients is randomized to receive the investigational agent from the start of the study, while the second group is randomized to receive placebo for an initial period before being given the investigational agent. If the putative agent has a purely symptomatic effect, then the progression curves for the two groups should meet when the second group receives the drug. If the compound has a purely disease-modifying effect, then the progression curves of the second group will never catch up with those of the first group.
- **Futility.** This type of study compares the outcome of a single treated group against a pre-determined threshold value reflective of a clinically meaningful change. Futility studies may use a placebo control arm, but often use historical controls to establish the threshold for clinical meaningfulness. The advantage of this type of study is that fewer patients are observed for a shorter period of time in Phase II to facilitate decisions about which agents should be prioritized for further development.
- **Long-term follow-up.** Long-term follow-up trials where disease modification is inferred from sustained divergence in outcome measures between groups over time may be the best current trial design. However, these studies are time-consuming and expensive, and it is not yet clear how long follow-up studies should be.
- **Adaptive design.** These designs can help minimize the overall sample size and duration of a study by stopping recruitment early in response to strong signals of success or futility based on interim analysis. One challenge of this design is the difficulty of assessing the outcome measure early enough so that modification of randomization occurs well before recruitment is complete. This challenge can be addressed by using a Bayesian design, which requires extensive planning and a rapid flow of data from sites to a database to enable real-time interim analysis.
- **Emerging designs for treatments of behavioral disturbances.** These include withdrawal design, delay to onset design, and parallel sequential comparative design.

Sponsors should be aware that each of these study designs has limitations which may make it difficult to draw conclusions about an agent's disease-modifying properties.

Handling missing data

Approximately 25 percent of AD trial participants fail to complete the double-blind treatment period. Consequently, study results may be confounded by missing data, which can unbalance treatment arms over time, introduce bias, and reduce the overall efficacy of the study.

There are a variety of methods for dealing with missing data, including:

- Complete-case analysis
- Last observation carried forward (LOCF)
- Mixed modeling
- Data imputation

Clinical outcome rating scales

There is a broad array of instruments used to measure clinical endpoints in AD trials (see Figure 4). Clinicians and trial sites vary widely in their experience administering assessment instruments, leading to unintentional variability of data. To overcome this challenge, many sponsors and CROs implement standardized training for raters, as well as robust and ongoing rater monitoring and quality assurance programs, to ensure data quality.

Figure 4. Clinical rating scales for different domains of AD

An alternative approach could be using surrogate outcome biomarkers that objectively measure characteristics of the disease.

The shift toward studying earlier, even asymptomatic stages of AD requires instruments that are more sensitive and selective. Available instruments for evaluating early stage AD include:

- **Free and Cued Selective Recall Reminding Test (FCSRT).** This test identifies patients with MCI with high sensitivity and specificity
- **Clinical Dementia Rating Sum of Boxes (CDR-SOB).** This instrument assesses both cognitive and functional features of AD
- **Cognitive Function Instrument (CFI).** This test is intended to detect early changes in cognitive and functional abilities in individuals without clinical impairment
- **Composite Instruments**, such as the Integrated Alzheimer's Disease Rating Scale (iADRS), AD Composite Score (ADCOMS), and ADCS-Preclinical Alzheimer Cognitive Composite (ADSC-PACC)

Biomarkers

Clinical assessments are affected by symptomatic effects of therapies and, in the short term, cannot differentiate these effects from disease modification. An alternative approach could be using surrogate outcome biomarkers that objectively measure characteristics of the disease. The most commonly assessed biomarkers in AD trials include:

- **CSF biomarkers**, such as total tau (t-tau), phosphorylated tau (p-tau) 181 or 231, and the isoforms of amyloid beta. Of note, the primary changes in the core CSF biomarkers occur during the asymptomatic phase of AD.
- **Brain PET biomarkers**, using a variety of radioactive tracers including flouro-deoxyglucose (FDG), Pittsburgh compound B (PiB), florbetapir, and flortaucipir. The availability of these tracers in different countries must be considered in the planning of global AD trials.
- **Blood, plasma, and serum biomarkers**, ranging from amyloid beta precursors to C-reactive protein and insulin-like growth factor 1. Unfortunately, studies have failed to identify a robust and reproducible relationship between amyloid beta 42 levels in brain and blood, suggesting that blood might not reliably indicate disease.
- **Brain MRI biomarkers.** Currently, volumetric MRI measurement of different regions of the brain seems to be the most linked to cognitive decline
- **Ultrasound and Brain CT biomarkers.** These have been studied, but require further validation

Unfortunately, to date, there is no single accepted surrogate outcome biomarker for Alzheimer's disease.

Enrollment strategies

There is currently a crisis in recruitment for clinical trials in AD. Reasons why enrollment in AD trials is decreasing include:

- **Primary care physicians' lack of capacity and resources** to assess cognition and refer patients to research
- **Barriers to participation for under-represented communities**, such as lack of cultural sensitivity
- **The requirement for a study partner** (i.e., someone who can report on cognitive changes)
- **The use of invasive procedures**, such as lumbar punctures or brain imaging with an injected tracer agent. Lumbar puncture is especially unpopular in Asia and the radioactive tracers needed for PET scanning may not be available in all countries.
- **High screen failure rate**, with rates as high as 70 or 80 percent among patients suspected of having probable or prodromal AD
- **Shortage of sites** that are well-funded, well-trained, and fast-starting

Appealing to current participants of AD trials who have already demonstrated both eligibility and motivation to participate is one strategy for increasing enrollment. Another strategy is seeking referrals from memory care centers, which are increasing in number and many of which are not affiliated with medical schools or universities. Social media and community engagement is also becoming increasingly relevant for AD trials.

Registries represent a powerful source of potential study participants, for example:

- The Alzheimer's Prevention Registry
- The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), an expanded registry that aids in recruitment of individuals at risk of having a gene mutation that causes dominantly inherited AD to trials of potential DMTs
- The Brain Health Registry, a global online registry for anyone age 18 years and older interested in research of new treatments for AD, and other conditions that affect brain function
- The Global Alzheimer's Platform (GAP) initiative
- The Cleveland Clinic Healthy Brains Registry
- The Alzheimer's Disease Cooperative Study (ADCS), a federal-university collaboration that is also part of the Alzheimer Prevention Initiative
- The Join Dementia Research initiative in the UK

Even when recruitment is successful, retention remains an issue due to the lengthy duration of many Alzheimer's studies. This is a big commitment for generally elderly patients, who often have limited mobility and may also have transportation challenges. Thus, careful consideration and optimization of the clinical trial experience for participants is an essential component of study planning.

Conclusion

AD and other dementias may be one of the biggest global health crises of the 21st century. The world's aging population is fueling the demand to address this unmet need with therapies that can prevent or delay disease onset, slow progression, and improve the symptoms of AD.

As we look to the future, we expect to see trends that will re-engineer the overall approach to AD clinical trials, bridging the gap between research and clinical care. Already, the use of biomarker analyses to assess target engagement is increasingly employed in clinical trials of disease-modifying therapies. In addition, an increasing number of studies are targeting the earlier stages of disease. To maximize the likelihood of success, future clinical trial designs, including study duration, population size, and primary cognitive and functional endpoints, will need to be further optimized.

References

1. World Health Organization. Dementia – Fact Sheet, Updated December 2017. Available at http://www.who.int/mediacentre/factsheets/fs362/en/.
2. World Economic Forum. This is one of the biggest global health crises of the 21st Century, September 21, 2017. Available at https://www.weforum.org/agenda/2017/09/dementia-trillion-dollar-global-crisis/.
3. Yaari R, Hake A. Alzheimer's disease clinical trials: past failures and future opportunities. Clin Invest 2015;5(3):297-309.
4. Merck. Merck Announces EPOCH Study of Verubecestat for the Treatment of People with Mild to Moderate Alzheimer's Disease to Stop for Lack of Efficacy. Available at http://investors.merck.com/news/press-release-details/2017/Merck-Announces-EPOCH-Study-of-Verubecestat-for-the-Treatment-of-People-with-Mild-to-Moderate-Alzheimers-Disease-to-Stop-for-Lack-of-Efficacy/.
5. Lilly. Lilly Announces Top-Line Results of Solanezumab Phase 3 Clinical Trial. Available at https://www.prnewswire.com/news-releases/lilly-announces-top-line-results-of-solanezumab-phase-3-clinical-trial-300367976.html.
6. Us Against Alzheimers. Alzheimer's Drugs in Development Pipeline, released July 2017. Available at https://www.usagainstalzheimers.org/sites/default/files/alzheimers-drugs-development-pipeline-2017.pdf.
7. U.S. Food and Drug Administration. Guidance for Industry - Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease, Draft Guidance, February 2013. Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf.
8. Cummings J, Reynders R, Zhong K. Globalization of Alzheimer's disease clinical trials. Alzheimers Res Ther 2011;3(4):24.
9. McGhee DJM, et al. A review of clinical trial designs used to detect a disease-modifying effect of drug therapy in Alzheimer's disease and Parkinson's disease. BMC Neurol 2016;16:92.

premier research
IT'S WHAT WE DO. BEST.

Sebastian Turek, Ph.D. | Project Director

Dr. Sebastian Turek is a Project Director in Project Management with a focus on neuroscience. Previously, he worked in academia as well as various clinical research organization sectors, holding positions in Clinical Development and Project Management at a large CRO.

Dr. Turek has more than 10 years' experience in clinical research, managing clinical trials/program deliveries across North America, Latin America, Europe, the Middle East, Africa, and Asia Pacific from target Phase I pharmacokinetics and Phase II proof-of-concept studies as well as large, multivendor Phase III programs, predominantly in Alzheimer's Disease.

Dr. Turek received his doctorate degree in Pharmaceutical Sciences with the highest mention from the Faculty of Pharmacy of the Medical University of Wroclaw, Poland. He is certified by Barnett Good Clinical Practice.

About Premier Research

Premier Research is a leading clinical development service provider that helps highly innovative biotech, medical device, and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional, and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, dermatology, medical devices, neuroscience, oncology, pediatrics, and rare disease. Premier Research operates in 84 countries and employs 1,250 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.