Design and Conduct of Trials in Alzheimer's Disease Following the Impending Approvals of Disease-Modifying Agents

Fortunately, after nearly two decades of negative studies, two amyloid-lowering drugs have recently received accelerated approval for Alzheimer's Disease (AD) by the FDA, and one of these drugs is likely to receive full approval by July of this year. Submissions have also been made to regulatory authorities in Asia and Europe, and it is possible there will be global approval by the end of 2023, or early 2024. Notably, these drugs go beyond symptom management and appear to directly affect the disease pathology. Given the long dearth of new approvals and the shift from symptomatic treatment to disease modification, the clinical trial landscape will need to undergo substantial change when one or more of these drugs receives full approval. To aid sponsors and other stakeholders to navigate this new potential environment with success, several concepts and considerations are reviewed here.

Recruitment & Retention

While the regulatory authorities deliberate on the disease modifying therapies (DMT) in consideration for approval, research sites continue to try to recruit patients to ongoing AD clinical trials. Recruitment into study protocols in the more severe stages of the disease is less likely to be affected by these approvals, although the expected large influx of enquiries for treatment with one of the DMTs is bound to result in a resource issue at many trial sites, in terms of staffing. The real challenge for research sites will be the continued recruitment into DMT protocols in the Early AD (eAD) space. In the US, patients and families might prefer to wait for full approval by the FDA, rather than commit themselves to a long-duration, placebo-controlled trial with no guarantee of success, or an unknown safety profile. The Centers for Medicare and Medicaid Services (CMS) have intimated that if a monoclonal antibody directed against amyloid for the treatment of Alzheimer's disease subsequently receives traditional FDA approval, CMS will provide broader coverage of reimbursement. Theoretically, at least in the US, this would mean that those patients with appropriate health insurance coverage would have their costs for treatment partially or fully reimbursed, although this of course needs to be confirmed. It is less clear, at this moment in time, whether the national or private health systems of countries outside the US will allow the reimbursement of the DMT upon approval from the applicable health/drug authorities.

Assuming that at least one DMT receives full approval, and CMS (or the corresponding national health system in other countries) agrees on a reimbursement package, typical eAD patients and caregivers will infer that approval confirms efficacy and a reasonable safety profile, while providers understand that all investigational compounds come with uncertainty on both fronts. Sponsors will need to give significant thought to educational programs and materials to equip site personnel to understand differences between the proposed investigational compound and approved treatments in the same space. This knowledge is critical for two reasons: 1) to speak to potential reasons to consider an investigational compound over an approved treatment, and 2) to ensure that site staff form educated opinions on the relative merits of treatment options for their patients.

Cost-benefit analysis of pursuing approved treatments will play significantly different roles in patient/caregiver decision-making outside the US. The US Centers for Medicare and Medicaid Services (CMS) and private insurers may come to different conclusions regarding the predicted cost of care for patients at different stages of disease, and therefore the appropriateness to reimburse for newly approved treatments. By contrast, patients in most other countries where approved treatments are available may have relatively fewer financial factors influencing decision-making when pursuing treatment via approved drug or a clinical trial. As a result, recruitment rates might be more significantly adversely impacted in the US in the short term and less so in the long term, as compared to other countries.

Sponsors should ask sites to have candid and practical conversations with patients about their realistic potential to receive approved treatments, particularly in cases where patients might be at risk of soon declining beyond the boundary of eligibility for clinical trials.

Retention of patients in clinical trials may also become more problematic. Some patients may enter a trial such that all diagnostic investigations are conducted free of charge, and then withdraw consent when the opportunity arises to receive an approved treatment. The setting of expectations with patients is paramount to predictable realisation of screened to enrolled subjects, and therefore to recruitment.

Study Design

Any approval of a DMT in Early AD, reimbursed either via health insurance or state, may also have an impact on study design. Once a treatment becomes a standard of care, it is imperative to consider both placebo-controlled studies and those with an active control, using an approved DMT. Several important issues must be considered, including:

- **Different rates of decline:** Early AD trials inevitably include patients with either mild cognitive impairment (MCI) due to AD or patients with Mild AD. There is a need to examine the differential rates of decline of these two populations of patients to determine whether the intuitive notion that MCI due to AD patients may take longer to show a deterioration is indeed correct. Current psychometric tests used for efficacy measures may not be adequate to detect decline in this very early group of patients, and alternatives are needed to enable the reduction of treatment time currently used in such trials. Eighteen months on placebo may not be a palatable option for many patients, but a shorter period may be more acceptable and therefore more likely to encourage participation.

- **Delayed administration of trial medication:** In DMT-controlled studies, there is a need to ensure that the short-term commonly reported side effects have run their course before adding a trial medication. This may require that patients spend at least 3–6 months on an approved DMT before initiating treatment with the new study drug being tested, incurring obvious cost and clinical implications.

- **DMT control costs:** Assuming a DMT-controlled, 18-month study, there is a need to establish whether payment for the DMT will be covered by insurance or state funding. Given the likely cost of these drugs, it is highly unlikely that any small biotech and pharma companies will have the resources to pay for initiation and 18 months treatment of the approved drug.

- **Lengthy period requiring availability of DMT control:** Clearly if a trial is of minimally 18 months' duration, the approved DMT must be made available for the full study period. In other words, the terms of reimbursement of the drug cannot be limited, or potentially based on treatment success.

- **Practical challenges to global reimbursement:** Although approved, reimbursement of DMTs will remain a significant challenge, primarily in the US but potentially in other countries later. Consequently, studies beginning in 2023 and 2024 may suffer from restrictions on which countries can be included due to differing approval timelines, outcomes, and levels of reimbursement.

- **Global differences in clinical meaningfulness:** Recent work discussing clinical meaningfulness in randomized controlled trials lays the foundation for critical next steps in demonstrating benefit to patients and therefore adequate impact for regulator consideration.[1] While globally applicable, this discussion is somewhat US-centric. If international regulatory authorities utilize different criteria, then the ability to use approved DMT drugs may be compromised. More specifically, consideration should be given to the potential for labels to restrict treatment to patients with milder disease. As DMT drug developers have come to understand the likely mechanisms of most study drugs – namely, to slow or stop decline – the focus has been plainly put on identifying mechanisms of action with effect at earlier stages of disease progression. Were evidence to demonstrate, in regulators' eyes, that a given DMT is not suitable for more severely impaired patients, trial recruitment might be accordingly impacted. Further, if long-term treatment objectives are focused on patients with

MCI or pre-symptomatic AD, sponsors may be faced with the significant challenge that approved treatments compete directly for the same subpopulation sought for clinical trials.

- **Likelihood of segregation of trial- and treatment-focused sites in the US and associated knock-on effects:** Perhaps uniquely to the United States, many clinical trial sites do not serve as dedicated treatment centers. As a result, patients might receive an approved DMT from one physician and practice while seeking concomitant treatment in a clinical trial conducted at another provider's facility. Potential impacts may include: 1) reduced data quality/completeness, 2) diminished safety monitoring, 3) inconsistent dosing or treatment cessation practices in the event of approved-DMT-related AEs, and more.

Equity, Diversity & Inclusion

Finally, reimbursement and cost of care paradigms in the US will likely have different implications for people of different races, ethnicities, cultures, and socioeconomic statuses. Well documented differences in diagnoses and care rates among under-served people of different races and ethnicities[2] are microcosms of the potential factors at play in over- and underrepresentation of subpopulations of patients globally. As each trial and context will differ, sponsors should conduct a rigorous review of study design, mechanism of action, and AD subpopulation to be treated as factors impacting the potential demographic composition of the eventually enrolled population of subjects. For example, any ethnic, racial, and socioeconomic differences might impact the likelihood of reimbursement by managed care companies in the US. The representation of American people of colour might be unduly impacted in clinical trials due to mistrust and stigma associated with medical care,[3,4] as patients from these backgrounds might more readily choose approved DMTs over a treatment offered via clinical trial.

In the context of potentially poorly representative clinical trial populations, it is important to consider not only the implications for study acceptance by regulators – in light of recommendations (and likely requirements) to achieve reasonably diverse study populations[5] – but also to possibly impact signal. Racial and ethnic differences in AD biomarker studies have been widely observed in recent years,[6,7] significantly calling into question whether AD treatments act similarly across these populations. If clinical trial population diversity is abjectly affected by the availability of approved DMTs, stakeholders must be prepared to mitigate these imbalances during study design, site selection, and recruitment stages to help ensure adequate study of investigational compounds across all populations intended to be treated.

Summary

Given the strong possibility of regulatory full approval being granted to at least one DMT later this year, serious thought needs to be given to the likely impact on both ongoing RCTs in AD and future clinical studies. Both recruitment and retention may be more challenging, and clinical trialists may need to adapt trial design and conduct to reflect the new standard of care that will arise.

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