MELODEM statement on aducanumab: treatment rollout should be structured to deliver clear and timely evidence on efficacy.

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In June 2021, the US Food and Drug Administration (FDA) provided accelerated approval for aducanumab (trade name Aduhelm) to treat Alzheimer's disease (AD), despite the absence of convincing evidence of clinical benefit of the medication. The FDA's approval cited the effect of aducanumab on reducing brain amyloid and argued amyloid reduction was reasonably likely to predict clinical benefit in AD. In its approval letter, FDA mandated a randomized controlled trial (RCT) to verify efficacy of aducanumab to be reported by the year 2030.

As methodologists focused on rigorous analytic approaches in dementia research, the Methods for Longitudinal Studies in Dementia (MELODEM) leadership team considers the plan and RCT design mandated by FDA needlessly slow. If the massive marketing campaign Biogen has launched succeeds in convincing patients or providers that aducanumab is desirable care, the mandated post-approval RCT will face major impediments to enrollment. If the medication is harmful, millions may be harmed before evidence from an RCT is available.

Urgent concerns with respect to aducanumab must be resolved much sooner than 2030, including overall efficacy, potential adverse effects, generalizability to real-world patients, and whether amyloid reduction is an appropriate surrogate for clinical improvement in AD. We strongly recommend the implementation of pragmatic study designs that will provide rigorous evidence years earlier than FDA's timeline. These study designs leverage quasi-experimental rollout of aducanumab treatment. Numerous possible design options could be immediately implemented across the clinical care landscape: by providers, insurers, or AD researchers.

Need for more evidence on adverse effects of aducanumab: The benefits of aducanumab are uncertain, but some adverse effects are established. Treatment causes delirium and confusion in a small fraction of people. Amyloid-related imaging abnormalities (ARIA) -- related to vasogenic edema or microhemorrhages -- are experienced by approximately 35% of treated individuals. This frequency of adverse events occurred in trials that excluded people at highest risk of these events, exclusions not reflected on the prescription label for aducanumab.

Need for more evidence on generalizability to real-world patient populations: As the recent appropriate use guidelines for aducanumab note, the level and severity of adverse events in the broader population is unknown. Populations at highest risk of dementia were severely underrepresented in late-stage trials, raising further questions about generalizing already-shaky treatment efficacy to real-world settings. Medications commonly used by older adults, such as anticoagulants, may increase vulnerability to side effects. Some patients may seek to end anticoagulant treatment to be eligible for aducanumab. Even a small uptick in stroke due to reduced anticoagulation could outweigh any plausible cognitive benefit of aducanumab.

Need for more evidence on possible clinical benefits of amyloid reduction: The aducanumab approval was premised on the assumption that amyloid reduction is a biomarker reasonably likely to predict clinical benefit. However, no study, observational or randomized, has yet demonstrated that amyloid reduction leads to clinical improvements or slows disease progression in the context of AD. If amyloid reduction is a valid surrogate, it could dramatically expedite research. If it is not, we risk approving many clinically useless medications. Already, two additional medications have been placed in the pipeline for approval based on established impact on amyloid, despite ambiguous evidence for clinical benefit.

Benefits of RCT alternatives to determine aducanumab efficacy: The individually randomized, double-blind, placebo-controlled RCT is a gold standard for evidence on treatment effects, but pragmatic modifications to this ideal study design can provide very convincing evidence on the safety and efficacy of aducanumab in a fraction of the time. There are only two essential features of a rigorous study design: (1) there must be a data source to define a population eligible to receive treatment and monitor outcomes for those individuals; (2) the reason that some people receive treatment while others do not must be random or "fair", i.e., unrelated to their likelihood of subsequent cognitive or functional outcomes.

Possible data sources: Leveraging existing, ongoing data collection platforms will expedite the research. Possible data sources include existing observational studies, which would take advantage of prior investments in recruitment, data collection, neuroimaging, and already planned ongoing monitoring of participants. Ideal ongoing cohorts would have a large, diverse, pools of participants with MCI or AD, at least some of whom might wish to pursue aducanumab treatment, if offered. Among other cohorts, the [New IDEAS](#) study, a project to evaluate the impact of amyloid PET imaging, is appealing because of its focus on racial/ethnic diversity. Pragmatic study designs often require large sample sizes, preferencing passive follow-up data sources that can quickly accrue large samples, *e.g.*,medical records in large care networks or Medicare records. The specific outcomes assessed would depend on already routinely recorded data elements, but nearly any such data source would also support adverse effects surveillance.

Creating pragmatic quasi-experiments via lottery-based distribution or timing: Under normal circumstances, the most motivated or privileged patients would likely access aducanumab first. This is especially likely to be the case given the cost Biogen set for the medication. This distribution scheme is both unfair and will preclude learning about effects of the medication. A lottery based system that influences the timing of when individuals have the opportunity to begin aducanumab treatment could provide rigorous evidence on safety and efficacy. Many versions of such a lottery are feasible, ranging from individual level randomization as in an RCT, to randomized timing of when clinics or sites first offer treatment, randomly assigning the date for active outreach to patients to assess their interest in the medication, or even sequence based on any truly random characteristic of patients, such as the day of their birth (e.g., odd versus even days). These lotteries could be informative whether fielded nationally (e.g., by CMS) or within a large health care network. Given the timing of medication effects, the lottery would need to assign individuals to roughly a 0 to 12 month delay.

Leveraging discontinuity designs as a source of random variation in chance of treatment: Arbitrary thresholds or discontinuities are another straightforward-to-implement pragmatic study design. Health care systems may take advantage of sharp thresholds for treatment initiation, such as an MMSE score below 26, or diagnosis of mild cognitive impairment (MCI) prior to August 1, 2020, creating an arbitrary discontinuity in the likelihood of receiving treatment. That threshold can be used to estimate the effect of treatment on longer-term outcomes. For example, if aducanumab is offered as soon as available to people diagnosed with MCI on July 31, 2020, but not offered to someone diagnosed on August 1 until about a year after the earliest treatments, is it expected that -- within about 18 months of aducanumab's availability -- a difference would emerge in outcomes for people diagnosed on either side of that that arbitrarily chosen threshold date. Treatment sites or care provider networks may implement this based on organizational needs if providers do not have resources to immediately treat all interested patients and need to delay treatment for some individuals. As long as the sequence in which patients are offered treatment is random, i.e., not related to likely cognitive progression of patients, this would allow rigorous evidence on the effects of treatment.

Leveraging pragmatic designs to address the utility of amyloid burden reduction: Aducanumab safety and efficacy is a priority for post-approval research, but the validity of amyloid reduction as an appropriate outcome in the context of AD is also vital. Pragmatic designs can be structured or enhanced to incorporate amyloid measurements alongside cognitive assessments, establishing that reductions in amyloid reliably translate into improved, meaningful cognitive outcomes. Building pragmatic studies onto existing longitudinal cohort studies that include amyloid measures already would facilitate evaluation of amyloid reduction as a surrogate.

Tailoring the study designs: None of these designs are perfect and each will need to be tailored to the context, the data source, the operational considerations, and the priorities of patients and clinicians. All designs entail limitations, such as lack of blinding and potential provider-shopping, which will be specific to the design and setting. Planning must build in design elements to ameliorate potential biases. However, the proposed pragmatic designs could deliver convincing evidence within two years, irrespective of whether trials are coordinated by CMS, provider networks, care systems, or even research networks.

Given the goals of FDA's [accelerated approval](#) pipeline, a phase IV confirmatory trial likewise deserves rapid implementation and analysis. The Phase IV confirmatory RCT should be complemented by pragmatic study designs which provide the best balance of research rigor, safety, and timeliness in determining the efficacy of aducanumab. Millions of families grappling with AD hang in the balance, and they deserve answers before the end of the decade.

About MELODEM

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