Accelerating evidence on beneficial or harmful effects of aducanumab by randomizing the site sequence of medication rollout

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Abstract

The US Food and Drug Administration recently provided accelerated approval for aducanumab to treat Alzheimer's disease (AD). Substantial uncertainty remains about whether the medication improves cognition or functioning of individuals with AD. The FDA mandated a confirmatory randomized controlled trial evaluating the benefits of the medication. This trial is unlikely to be completed for at least a decade, potentially exposing millions of patients to an ineffective or harmful therapy before final trial results are available. Conversely, millions of patients who might benefit may choose not to use the medication because the only currently documented clinical effects of aducanumab are adverse events. There is no need to operate in an evidence vacuum as we await the confirmatory trial: several expedited study designs could be implemented almost immediately and would deliver valuable evidence of clinical benefits and harms within two years. These designs are inspired by the fact that aducanumab rollout will by necessity be staggered because of manufacturing pipelines. Structuring the inevitable delays in access due to manufacturing so they are randomly staggered by site of delivery would create a convincing quasi-randomized trial. The quasi-randomized study is not as rigorous as the phase-4 randomized controlled trial mandated by the FDA, but several design features – including a pre-treatment waitlist, longitudinal neuroimaging or biomarker assessments -- could move the quality of evidence very close to such a trial. A lottery-based staggered rollout has additional advantages with respect to equity and clinical care. The lottery-based rollout could be implemented by any of several actors, including the Centers for Medicare & Medicaid Services (CMS) via a national coverage with evidence development (CED) determination. Large provider systems with multiple sites of care and longitudinal data on their patient base or collaborative networks of treatment centers could also implement a randomly staggered rollout. In this paper, I describe potential design features, beginning with the simplest, core components of the design involving no individual data collection, and adding study design features such as individual data collection, which would make the study increasingly rigorous and informative. I review the importance of expediting evidence development on aducanumab's harms and benefits, rather than waiting a decade for the confirmatory trial. A lottery-based rollout is feasible and fair and would enable millions of people affected by AD to make informed treatment decisions.

The US FDA provided accelerated approval to Biogen's medication aducanumab in June, 2021[1]. Accelerated approval allows Biogen to sell the medication to patients until a confirmatory randomized controlled trial (RCT) has been completed. The FDA specified that Biogen must report results of that RCT by February 2030. Approval was based entirely on the effect of aducanumab on removing brain amyloid, despite documented adverse effects of treatment and substantial debate about whether such amyloid reduction will translate to improved cognition or functional outcomes[2,3].Trials of aducanumab to date have included almost no Black, Indigenous, or Latino participants, so there is no data on potential adverse effects of treatment on these groups. A decade-long delay in evidence while patients are being treated with an unproven and potentially harmful therapy is unacceptable and could be substantially shortened with a pragmatic quasi-experimental approach.

Below I review the design features of such potential studies. I first consider the minimum necessary design to deliver useful evidence, a design which would not require any additional patient burden or individual level data collection. I next consider enhancements on this core design that increase the quality and breadth of evidence but are more difficult to implement and require individual level data collection. I end by discussing the urgent need for such a design and the potential actors who could implement the design, including the Centers for Medicare and Medicaid Services (CMS), health care organizations, collaborative networks of clinical care centers, or the manufacturer.

Simplest possible expedited, pragmatic study design based on site sequence randomization with administrative data linkage

Because Biogen must undertake a large production and distribution process, a staggered rollout of aducanumab is inevitable. There is not enough medication available to immediately meet likely demand. Biogen has stated that there are currently 900 sites in the United States with appropriate equipment and qualifications to safely deliver the medication and monitor patients for progress and safety. A staggered rollout based on randomized sequence of sites would stage the release of aducanumab across the U.S., introducing medication availability in waves at sites in a randomly selected order. Data from this design mirror a stepped wedge study design, considered a rigorous approach to evaluating new interventions in applied settings[4].

The two essential features for the rollout to be informative are (1) randomization of the sequence in which sites begin aducanumab treatments; and (2) linkage to a data source that can be used to identify both the site at which patients would be expected to receive care and subsequent outcomes for those patients. The staggered rollout could be implemented by listing all potentially eligible sites

and assigning each site a random number ranging from 1 to the number of eligible sites. As aducanumab becomes available, it is delivered in sequential order to each site. It is important that once a site's sequence number is reached, medication is not subsequently interrupted for the patients who initiate treatment at that site. Demand at each site should be fully met before expanding access to the next site in the randomly assigned sequence. There need never be intentional delay in distribution of aducanumab, but the distribution must be in order of randomly assigned sequence of sites. The anticipated manufacturing pipeline from Biogen is approximately 12 to 18 months. Given the dose-ramp up of the medication, this delay is likely sufficient time to demonstrate a benefit of the treatment using a site-randomized rollout.

Medicare records could provide a minimum data source. This would not involve any new data collection beyond that passively accrued by Medicare in the normal course of care reimbursement. Relying on Medicare limits outcomes to new diagnoses and utilization measures. Because of this, the "eligible" population at each site would be defined as individuals with mild cognitive impairment (MCI) receiving care (prior to the release of aducanumab) at that site. At each site, eligible patients are defined as Medicare beneficiaries with documented MCI who have received the majority of their care at that site during the previous 24 months. Further restrictions on the eligible population could be made based on information recorded prior to the first aducanumab treatments (e.g., utilization data). Identifying individuals at high risk of incident dementia who are highly likely to pursue aducanumab treatment at the site would improve statistical power and therefore precision of effect estimates.

Outcomes would be measured for the 21 months following the date when the first site initiates treatment. Because this quasi-experiment could have sample sizes many-fold larger than the phase 3 RCTs, small early benefits could be detectable. Relevant outcomes might include: cumulative incidence of dementia as well as potential adverse effects of the medication, including mortality, delirium, stroke, and hospitalization. Secondary outcomes such as costs could be evaluated even if not-prespecified, provided they are available in the Medicare records.

The analysis of outcomes would respect the intent-to-treat principle embedded in randomization of the sequence of rollout, but correct for the varying doses received by the average patient at different sites. Analysis would proceed in two stages, first calculating the cumulative dose an individual treated at each site has on average received within the 21 months of follow-up, and then using that dose (which varies between patients only due to differences in randomly assigned rollout timing) to predict cumulative risk of dementia among eligible patients. Average cumulative dose is calculated by

summing each week's recommended dose for patients on treatment across all weeks since the site's lottery number was reached, and the site began treating patients. For example, at 21 months, the first sites randomized to treat patients would have delivered an average dose of 170 mg/kg (with patients at full dose of medication for 15 months), whereas a site randomized to begin treatment at 12 months would have delivered an average dose of only 60 mg/kg (with patients at full dose of medication for only 4 months). This calculation is illustrated in **Table 1**. To correct for the fact that not all eligible patients at any site will choose to receive aducanumab, this cumulative site dose is multiplied by the percentage of eligible patients at the site who initiated aducanumab at the site.

The model using the above cumulative dose calculation is premised on the assumption that the key determinant of effect of treatment is the cumulative dose of aducanumab. A slightly more biologically plausible alternative is that aducanumab has effects that depend on both the cumulative dose and duration of treatment. To accommodate this possibility, a secondary analysis could be based on cumulative site-specific dose-months. This would be calculated by summing the dose delivered in each month times the months between administration of that dose and outcome assessment. For the earliest initiating sites, this cumulative dose months in the above example would be 1550 mg/kg months (1mg/kg*21 months+1mg/kg*20 months+3mg/kg*19 months+…10 mg/kg*1 month); patients receiving treatment sites randomized to begin treatment at 12 months would have been exposed to only 230 mg/kg months of treatment (15% as many dose-months as patients at the earliest initiating sites). Just as for the cumulative dose calculation, this number would be corrected by the percentage of eligible patients at each site who actually initiated treatment.

Site-specific average cumulative dose (or dose-months) is then used to predict cumulative outcomes at 21 months, typically in a simple logistic regression model (alternative regression specifications would be appropriate for non-binary outcomes, e.g., continuous utilization measures). Given important questions about heterogeneity of effects, we would also evaluate interactions with sex, race/ethnicity, and baseline comorbidities such as hypertension or stroke history. For evaluating effects of aducanumab dose on outcomes among a specific subgroup of people (e.g., men), the site-specific cumulative dose must be multiplied by the percentage of eligible patients in that subgroup who were treated at that site. Otherwise, the analysis is the same.

This study design would provide patients and providers with vastly better information than currently available. It is incredibly simple and requires no new data collection or monitoring. The best quality data would be afforded if implemented by CMS under a CED designation because this would reduce

crossover, increase sample size and therefore precision of estimates, and maximize generalizability. Other parties could act if CMS does not, however, for example large networks of providers could implement such a study design.

There are however a handful of important limitations with this design. First, because dementia diagnoses include a subjective element of self- or caregiver reported functioning, the outcome may be vulnerable to placebo effects if patients believe the medication is helping. This would lean towards apparent benefit of aducanumab. There is no perfect solution, but the bias could be evaluated by (1) assessing outcomes that are not vulnerable to placebo effects, such as hospitalization and mortality; and (2) assessing the timing of apparent benefits of initiating treatment. Patients and caregivers are likely to experience a placebo effect immediately upon initiating treatment, whereas there is little biological plausibility for a benefit during the first few months of treatment.

A second potential concern is patient crossover, if patients seek aducanumab at a different site than the location where they were receiving treatment prior to aducanumab rollout. Conceptually, this is like non-adherence in an RCT. Provided no more than half of patients seek care outside of their 'assigned' site and those who seek treatment elsewhere are not differentially likely to respond to aducanumab, the model is robust to such non-adherence. Although nonadherence attenuates apparent effects in an ITT analysis, by using the average , but the analytic approach above corrects for this, just as an instrumental variables (IV) analysis would correct for non-adherence in an RCT without violating the ITT principle[5–7]. Related to this is the possibility that sites change their diagnostic practices upon learning of aducanumab or becoming eligible to provide aducanumab. Potential biases from this are addressed by defining each site's eligible population as MCI patients diagnosed at that site prior to the approval of aducanumab.

Medicare data has intrinsic limitations, for example diagnostic information for individuals enrolled in Medicare Advantage plans. This is a problem only insofar as the effect of aducanumab differs for Medicare Advantage enrollees compared to other individuals or if people switch from fee for service plans to Medicare Advantage during the study follow-up. Differential effects on outcomes other than utilization seem unlikely. Plan-switching will occur but is unlikely to be large or differential. If this study design were implemented by provider networks, such as health care membership organizations or collaborations of the Alzheimer's disease research centers, the electronic health record data would obviate this concern.

A pragmatic design augmenting site-sequence randomization with individual level data collection

The extremely simple design described above did not involve collecting any new individual level data, but used only passively accrued data such as Medicare records. A more informative but still feasible design would leverage site-sequence randomization of aducanumab rollout and combine this with a patient wait-list or registry. This approach also mirrors a stepped wedge study design. As with the simplest possible rollout described above, this design would ensure equity in access, accelerate evidence on the benefits and harms of aducanumab, and be feasible to implement, for example under Medicare's CED pathway. By including individual level data collection, more detailed information on the effects of aducanumab could be detected, including subtler changes in cognition and functional outcomes. This design would ameliorate some of the potential biases in the design using only linkage to administrative records and could answer important additional questions – such as the timing of first benefits of treatment and the validity of amyloid as a surrogate outcome. Given the value of individual level data collection, this design might be best implemented at a smaller number of sites, chosen to be able to collect high quality data.

Essential elements of the stepped wedge design with individual data collection are described in **Table 2**. The design and advantages of specific features are provided in more detail below. An approximate timeline for patient contact is in **Figure 1**.

Step 1: At each site, create a waitlist for people eligible and interested in receiving treatment with aducanumab. This waitlist registration would, at a minimum, include eligibility information and cognitive assessments. Because blinding treatment is impossible with this study design, it is important to select outcome assessments that would be least influenced by placebo effects, e.g., due to a patient or caregivers' optimism about receiving a medication. The NIH Toolbox cognition battery, augmented with the Toolbox version of the Face-Name test can be administered on an iPad in around 30 minutes[8,9]. Assessing the CDR-SB (the primary outcome of the phase 3 EMERGE and ENGAGE trials considered by the FDA in the aducanumab approval filing) would facilitate direct comparisons with previous evidence on aducanumab. Potential adverse effects of aducanumab should be monitored. Additional questions on patient demographics could improve statistical power. For example, education is a strong predictor of cognitive test scores, so being able to account for education will provide more precise estimates in a faster time frame. Knowing demographics will also enable us to evaluate whether aducanumab has similar benefits or harms for individuals regardless of demographic profiles. This is a major concern given the limited racial/ethnic diversity in the prior trials.

Additional neuroimaging and assessment of blood-based biomarkers would permit assessment of important ancillary questions. Amyloid burden at baseline may modify benefits of the medication. Although the FDA identified reductions in amyloid as a surrogate outcome for aducanumab, there is currently no clinical evidence to support the premise that reductions in amyloid will slow cognitive decline. To the contrary, the available evidence suggests this is not the case[2,3]. Incorporating additional neuroimaging and blood biomarkers will help address this evidence gap. This is relevant not only for aducanumab but for any other future amyloid-targeting therapies that may seek FDA approval based on amyloid as a surrogate outcome. Because blood-based biomarkers are lower cost and less invasive, adopting and validating such biomarkers is likely to enhance diversity of study participation and expedite trials.

Step 2: As supplies of aducanumab become available, use a lottery to determine the order in which sites receive supplies. This is identical to the site-sequence lottery used in the administrative-data only study design. The lottery should be at the site level, not at the individual level. Once a site has been selected, they should be kept regularly supplied to meet demand at that site. Sites selected for delayed receipt of the medication should re-contact waitlist members every 3 months to confirm continued interest and collect cognitive assessments. A stratified lottery prioritizing sites serving communities of color would be preferable given the particular paucity of data on efficacy of the medications for individuals who identify as Black, Latino, Asian, or Indigenous. The caveat to this advantage is that sites located in communities of color do not necessarily have patient panels representative of community residents.

Step 3: As sites receive aducanumab, patients on the waitlist are recalled to receive treatment. Each patient repeats cognitive assessments prior to initiating treatment and after 18 months of treatment. Only baseline and end of follow-up cognitive assessment are essential, but repeated assessments improve the capacity to address practice and placebo effects, mitigate bias from mortality or loss-to-follow-up, and identify the precise timing when cognitive improvements emerge during treatment. Additional cognitive assessments would also modestly improve statistical power. Additional information on amyloid Neuroimaging and additional biomarkers would, as discussed above, be valuable for validation of surrogate outcomes such as amyloid PET. Any other biomarker assessments, e.g., plasma amyloid or tau, could also be checked for future evidence as surrogate markers. All patients undergoing treatment must receive an MRI to assess for safety prior to their 7th and 12th doses of aducanumab. These would be natural time points for amyloid assessments as well.

Step 4. Data will be pooled and monitored by a data coordinating center. Monitoring for adverse events will be ongoing. All waitlisted participants will be linked to Medicare records to monitor changes in diagnosis or vital status. An interim analysis can begin at month 16, when the earliest treated individuals will have been on full dose for 6 months. The primary analysis can begin in month 21, approximately 18 months after the first sites begin treating patients. Primary analyses use all available data from all sites, including for individuals who have only recently begun treatment.

As with the simplest possible staggered rollout design leveraging administrative data, the model specification when individual level data are available would include two stages. The first step of the analysis is to calculate the cumulative dose an individual enrolled at each site has on average received up to each week of the study. This analysis could use either the cumulative dose calculation or the cumulative dose-months calculation, but unlike in the administrative data structure, the dose would vary across the 21-month follow-up period, and represent the cumulative dose to date at that site. In the discussion below, we assume cumulative site-specific dose to date (instead of dose-months to date) is used.

Longitudinal data on each individual will enable specification of a mixed model, evaluating change in functioning based on dose of aducanumab delivered on average by that individual's site up to that date. This model again preserves ITT principles but uses an IV correction to account for imperfect medication adherence and estimate the effect of cumulative dose of aducanumab on outcomes. Implicitly, the statistical model matches a separate-sample two stage least squares analysis, in which the site-specific cumulative dose calculation is the first stage. The mixed model can incorporate random coefficients to accommodate heterogeneity in level of functioning and age-related slope of change for each individual participant. The primary coefficient of interest tests whether cognition is predicted by variations in the dose of aducanumab received to date, considering only variations in dose due to the site sequence randomization. Adjusting for an indicator of whether this is the first cognitive assessment the individual has taken will help ameliorate practice effects[10].

As with the administrative data study design, interactions with sex, race/ethnicity, and baseline cognitive function could be evaluated. A patient-level random coefficient for site-dose might also be useful to indicate heterogeneity in treatment effect due to unknown patient characteristics. A simple sensitivity analysis for possible placebo effects is to evaluate sudden "bumps" at treatment initiation, when dose is too low to plausibly have cognitive benefits. A second sensitivity analysis is to compare

changes for outcomes that incorporate a subjective report of functioning by the patient or care partner. Placebo effects should be larger for subjective reports than objective cognitive assessments.

If longitudinal amyloid measures are available, the primary analyses can be complemented by a model evaluating mediation of treatment initiation effects by amyloid changes[11]. The mediation results could strengthen the credibility of amyloid or any other biomarker as a surrogate outcome. Valid surrogates should largely or fully mediate effects of treatment on patient-oriented outcomes (i.e., cognition or functioning). Changes in the hypothesized surrogate should reliably predict improvements in patient-oriented outcomes.

A registry of aducanumab users has been proposed. A registry alone, however, will not be sufficient to evaluate harms and benefits of aducanumab, because there will not be any source of comparison. The key to making a registry useful is to also adopt a site-sequence randomization plan.

Why an expedited, pragmatic study design is needed

Why is it so important to adopt a pragmatic study design immediately? Aducanumab was approved based on convincing evidence that the drug removes brain amyloid. Unfortunately, many prior studies have also removed brain amyloid and not shown any clinical benefit to patient cognition or functioning. One trial of aducanumab showed slightly better cognition in individuals randomized to the highest dose arm of the trial, but the sister trial found no such benefit at any dosage level. Based on this, FDA advisory committee unequivocally indicated that clinical benefit had not been shown and the FDA accelerated approval required an additional trial to document clinical benefit.

The FDA mandated confirmatory trial is to be reported by 2030, a devastatingly long time to wait for evidence on the benefits and harms of a treatment with no documented clinical benefit. Final trial results may not be available even by 2030. Medications on the accelerated approval pathway are frequently granted extensions if the confirmatory trials cannot be completed on time[12]. If CMS provides coverage for the cost of aducanumab, the confirmatory trial is likely to be severely delayed: individuals willing to take the documented risks of adverse effects of aducanumab are not likely to be amenable to being randomized to no treatment. Further, Biogen marketing of the medication is likely to directly compete with the RCT, pulling potential trial participants into the paying customer base. From a financial perspective, Biogen currently has no incentive to expedite the trial. The pragmatic study would likely deliver valuable evidence eight or more years before the trial. Making a CMS CED coverage determination with a restricted number of sites included determination may expedite

enrollment in Biogen's confirmatory trial, as pathway to medication access for patients not receiving care at a site included in the CED study.

Aducanumab treatment entails potential harms: 35% of patients who used the medication in trials experienced amyloid related imaging abnormalities (ARIA) related to vasogenic edema (ARIA-E); 19% experienced ARIA related to intracerebral microhemorrhage (ARIA-H); 15% ARIA-H with superficial siderosis; and 8% experienced confusion, delirium, or altered mental state[1]. The vast majority of participants in trials of aducanumab have identified as non-Latino White -- approximately 1% of patients included in trials to date identified as Black -- so there is no evidence on whether adverse effects may vary by race/ethnicity[13]. ARIA was more common among trial participants who carried the APOE-e4 allele, which is far more prevalent among individuals with African ancestry than European ancestry[14]. There is thus reason to worry that the adverse effects of aducanumab are more common among individuals with African ancestry.

Receipt of the medication requires monthly infusions, and ongoing safety monitoring. Because the medication is not curative, these treatments would continue indefinitely. The currently announced price for a year of medication is $56,000, over twice the median income for individuals age 65 or older in the US[15]. Treating all 5.8 million people in the United States who are thought to have AD -- thus eligible under the original FDA labeling -- would cost around $325 billion. Costs would be higher when accounting for screening and safety monitoring and would double or more if people with brain amyloid but no clinical symptoms were also treated[16]. In early July, the FDA revised the labeling for aducanumab as indicated for people "mild cognitive impairment or mild dementia stage of disease."[17] This population is estimated to be about 1.5 million people, reducing the anticipated costs of providing the medication to a mere $84 billion per year. The CMS has not yet made a decision about coverage for aducanumab. CMS cannot negotiate the price of medication[18], but may make a CED determination[19]. Under CED, the medication is covered only when provided as part of a study to establish benefits for patients.

For countless individuals living with AD, evidence from a pragmatic study could help them make an informed choice about pursuing treatment. This could help avoid the tragedy of treating potentially millions of patients over the coming decade with a drug that turns out to be unhelpful or even harmful. Such medical reversals are common when medications or procedures are widely adopted without RCT based evidence of improved clinical outcomes[20]. For example, use of post-menopausal hormone therapy to reduce cardiovascular risk was strongly supported by observational evidence and

biological plausibility; it was widely in use for years before rigorous RCTs showed that it had no such benefit and on net long-term use was clearly harmful[21,22]. Oncology medications with major side effects have been given accelerated approval only to find they offer no survival benefit.

For researchers and pharmaceutical companies evaluating the most promising therapeutic strategies, this evidence could help vindicate amyloid targeting therapies or redirect resources to other targets. One hope for aducanumab approval was the possibility that it would stimulate additional research on AD treatments, possibly combining aducanumab with other medications for larger benefit. However, this strategy is only useful if we can confirm that aducanumab has some clinical benefit.

A staggered rollout could also help address the concern that access to aducanumab will not be equitable, with socioeconomically advantaged patients accessing the medication before disadvantaged patients. If the demographic profile of patients who acquire earliest access to aducanumab mirrors the demographics of patients who participate in typical AD biomarker research[23,24], we should expect that White, highly educated individuals will be substantially overrepresented compared to the burden of AD in this population. Aducanumab studies to date have egregiously underrepresented racial/ethnic minorities, and the company has pledged its commitment to enhancing equity moving forward. The staggered rollout design could ameliorate such inequities, by assigning access based on site rather than individuals. The design could make even more of an impact on equity by adopting stratified randomization such that providers with a high non-white patient base were prioritized.

Finally, a staggered rollout may help ameliorate the dilemma faced by clinicians whose patients may be eligible for aducanumab. Many patients will likely assume that FDA approval indicates that aducanumab is an effective treatment. Some clinicians may feel that prescribing a drug with no documented clinical benefit and some potential harm is unethical. With the staggered rollout design, every treated patient is contributing much needed evidence on the value of the drug.

Conclusion

The randomized site-sequence staggered rollout would not on average introduce any delay in when patients received medication and would be relatively low cost. Most importantly, a staggered rollout could rapidly provide evidence on whether aducanumab improves outcomes that matter to people living with AD. With this study design, convincing evidence may be reported up to eight years earlier

than the formal phase 4 RCT findings are available. CMS can implement this design efficiently using a CED designation. Support from the National Institutes of Health to augment study design elements would enhance the value of the study, but the minimum necessary elements of the study design are very simple. In the absence of action from CMS, provider networks could also implement the design. Many other possible quasi-experiments could be built into the aducanumab rollout. For example, discontinuities could be created by defining a sharp threshold for eligibility for aducanumab treatment. Such a threshold might be based on date of MCI diagnosis or patient age for example. Sharp thresholds demarcating likelihood of receiving aducanumab treatment would then support a regression discontinuity study design. Some pragmatic study designs could even be implemented by highly influential advocacy organizations with strong ties to a large number of people living with AD or incipient AD. The randomized site-sequence staggered rollout with individual data collection seems the strongest of the pragmatic approaches, but nearly any formal pragmatic study would be preferable to the default situation defined by the FDA mandate. Numerous pragmatic options could provide better information years before the FDA mandated RCT will be available. Leadership is necessary to implement any of these designs, however. People affected by AD deserve the best efforts of advocates, clinicians, and researchers to overcome bureaucratic barriers and pursue such studies.

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Table 1: Cumulative site-specific dose and dose-months across 21 months following Aduhelm label-recommended dosing schedule, comparing early to late start sites.

	Early Start Sites			Late Start Sites		
Month	**Dose (mg/kg)**	**Months Receiving Dose By Study End**	**Contribution to Cumulative Dose-Months (mg/kg months)**	**Dose (mg/kg)**	**Months Receiving Dose By Study End**	**Contribution to Cumulative Dose-Months (mg/kg months)**
1	1	21	21		21	0
2	1	20	20		20	0
3	3	19	57		19	0
4	3	18	54		18	0
5	6	17	102		17	0
6	6	16	96		16	0
7	10	15	150		15	0
8	10	14	140		14	0
9	10	13	130		13	0
10	10	12	120		12	0
11	10	11	110		11	0
12	10	10	100	1	10	10
13	10	9	90	1	9	9
14	10	8	80	3	8	24
15	10	7	70	3	7	21
16	10	6	60	6	6	36
17	10	5	50	6	5	30
18	10	4	40	10	4	40
19	10	3	30	10	3	30
20	10	2	20	10	2	20
21	10	1	10	10	1	10
Cumulative	**170**		**1550**	**60**		**230**

Table 2. Elements of a staggered rollout pragmatic trial of aducanumab efficacy with patient level data collection

Essential elements	Possible enhancements	Advantage of enhancements
1. Patients interested in receiving aducanumab enroll in a waitlist and complete cognitive assessments	a. Additional data on demographics b. Baseline biomarker assessments including amyloid-PET neuroimaging and blood-based markers of amyloid, tau, and neurofilament light	a. Evaluate heterogeneity in treatment effects; prioritize sites with more diverse patient base; improve statistical power of the study b. Evaluate relevance of aducanumab's hypothesized mechanism of action; evaluate heterogeneity of treatment effects; potentially support mediation modeling to demonstrate that amyloid reduction is an appropriate surrogate.
2. Randomly order the sequence in which sites receive aducanumab; ensure that a site, once selected, is continuously supplied with medication for patients on its waitlist	a. Stratify the site randomization based on sites with underserved populations	a. This would hasten evidence for groups who were not adequately represented in the pre-approval trials
3. All patients receiving aducanumab again participate in cognitive assessments immediately prior to receiving medication and at 12- and 18-month follow-ups	a. Additional amyloid-PET imaging b. MRI measures of ARIA c. Other biomarker assessments (plasma amyloid) d. More frequent cognitive assessments	a. By tracking changes in amyloid-PET alongside changes in cognition, we could evaluate the validity of amyloid-PET as a surrogate outcome and understand the time delay between amyloid reduction and cognitive benefit b. Understand whether ARIA has subtle consequences for cognitive outcomes or predicts treatment response c. Aim to identify other surrogate outcomes that are less costly d. Improve statistical power and demonstrate timing of benefit
4. Data from all sites on patient cognition across time and date of initiation of aducanumab must be pooled for analyses. Analyses are based on ITT principles using the timing of site-eligibility as a source of randomization	a. Mediation modeling evaluating whether aducanumab-induced reductions in amyloid translate to cognitive benefits	a. Confirm the validity of amyloid as a surrogate outcome

Figure 1. Timeline for a Stepped Wedge Equity/Efficacy Trial of Aducanumab

Randomly Assigned Site Sequence	Months 1-3	Months 4-6	Months 7-9	Months 10-12	Months 13-15	Months 16-18	Months 19-21	Months 22-24
1,2	**Cog 0** Waitlist Signup	**Cog 1** Eligibility determination: amyloid PET Additional biomarkers Treatment Initiation	**Cog 2** Treatment continues, dose increased	**Cog 3** Treatment continues, full dose begins amyloid PET and additional biomarkers	**Cog 4** Treatment continues, full dose	**Cog 5** Treatment continues, full dose	**Cog6** Treatment continues, full dose	**Cog7** Treatment continues, full dose amyloid PET and additional biomarkers
3,4	**Cog 0** Waitlist Signup	**Cog 1** Recontact for cognitive assessment	**Cog 2** Eligibility determination: amyloid PET Additional biomarkers Treatment Initiation	**Cog 3** Treatment continues, dose increased	**Cog 4** Treatment continues, full dose begins amyloid PET and additional biomarkers	**Cog 5** Treatment continues, full dose	**Cog 6** Treatment continues, full dose	**Cog 7** Treatment continues, full dose amyloid PET and additional biomarkers
5,6	**Cog 0** Waitlist Signup	**Cog 1** Recontact for cognitive assessment	**Cog 2** Recontact for cognitive assessment	**Cog 3** Eligibility determination: amyloid PET Additional biomarkers Treatment Initiation	**Cog 4** Treatment continues, dose increased	**Cog 5** Treatment continues, full dose begins	**Cog 6** Treatment continues, full dose amyloid PET and additional biomarkers	**Cog 7** Treatment continues, full dose amyloid PET and additional biomarkers
7,8	**Cog 0** Waitlist Signup	**Cog 1** Recontact for cognitive assessment	**Cog 2** Recontact for cognitive assessment	**Cog 3** Recontact for cognitive assessment	**Cog 4** Eligibility determination: amyloid PET Additional biomarkers Treatment Initiation	**Cog 5** Treatment continues, dose increased	**Cog 6** Treatment continues, full dose begins amyloid PET and additional biomarkers	**Cog 7** Treatment continues, full dose amyloid PET and additional biomarkers
9,10	**Cog 0** Waitlist Signup	**Cog 1** Recontact for cognitive assessment	**Cog 2** Recontact for cognitive assessment	**Cog 3** Recontact for cognitive assessment	**Cog 4** Recontact for cognitive assessment	**Cog 5** Eligibility determination: amyloid PET Additional biomarkers Treatment Initiation	**Cog 6** Treatment continues, dose increased	**Cog 7** Treatment continues, full dose begins amyloid PET and additional biomarkers
Data Center	Data Pooling and cleaning	Link all waitlist members to Medicare records on vital status and dementia diagnoses (updated routinely through study end). Process measures of participation rates, treatment protocol deviations, and adverse event monitoring for sites with active treatment ongoing.				Interim analysis: 12 months of treatment; 6 months of full dose vs untreated	Data Pooling and cleaning	Data Pooling and cleaning; final analysis of treatment effect and validation of surrogates

Citations

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