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Commentary

"Landscape of Phase 2 Trials in Alzheimer's Disease": Perspective on Adaptive Trials

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Abstract. Better means of conducting more efficient clinical trials for the development of Alzheimer's disease (AD) therapeutics are required. Adaptive clinical trial designs have many advantages based on the ability to make changes in the trial conduct depending on the ongoing experience in the trial. In their report in the *Journal of Alzheimer's Disease*, Lee and colleagues show that in the past 25 years only 2.5% of AD clinical trials have used adaptive designs. The report calls attention to the opportunity to use adaptive designs more often in Phase 2 clinical trials to improve trial efficiency and accelerate treatment development.

Keywords: Adaptive design, ADCOMS, Alzheimer's disease, clinical trial, lecanemab, parallel group

Alzheimer's disease (AD) drug development is complex and expensive, and frequently has negative outcomes with no drug-placebo differences demonstrated. Means for increasing the efficiency of randomized clinical trials (RCTs) may decease the cost, increase the success rate, and accelerate the progress of drugs urgently needed by patients with AD or those at risk. RCT designs that contribute to study efficiency are those that require the fewest participants and least infrastructure resources to obtain a scientifically rigorous answer to the question posed for the trial [1]. Adaptive designs represent one means of achieving greater study efficiency. Lee and colleagues have explored the frequency of use of adaptive trials as identified on clinicaltrials.gov to determine their role in the current AD drug development landscape [2].

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The US Food and Drug Administration (FDA) defines the adaptive approach as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on accumulating data collected from participants in the trial [3]. The adaptive design contrasts with the more commonly used randomized, parallel group design in which few modifications are made during the course of the trial and the drug-placebo differences assessed in the trial are based on the original sample size, eligibility criteria, and outcome measures. Adjustments can be made to parallel group designs using protocol amendments; these are not pre-specified and do not represent adaptive trial methodologies. Adaptive designs can be used to address several types of development question including early termination for efficacy or futility, adaptive dose-finding, sample size adaptation, adjustments of the population including adaptive enrichment, adaptation in patient allocation (e.g., discontinuing one dose arm for toxicity or lack of efficacy), or rarely, adaptions in the endpoints [2, 3].

In their guidance, the FDA notes several potential advantages of adaptive designs including improved statistical efficiency with greater power or smaller required sample sizes than non-adaptive trials (FDA, 2019). Ethically, the ability to stop a trial early if futile can reduce the number of participants exposed to risks of adverse events associated with an ineffective investigational treatment. Participants exiting a futile trial may be candidates for a more promising therapeutic. A broader range of scientific questions can sometimes be answered with adaptive compared to non-adaptive designs. It may be possible to demonstrate effectiveness in a subgroup of the trial population, where a non-adaptive alternative might require much larger sample sizes. Designs with adaptive dose selection may provide better estimates of the dose-response relationship, supporting efficacy, and facilitating planning of subsequent trials. Adaptive designs may be more acceptable to stakeholders than a comparable non-adaptive design. For example, dose-adaptive trials increase the probability that participants will be assigned to the more effective treatment or dose making this attractive to potential participants [3].

Adaptive designs have challenges not associated with parallel group designs. An important disadvantage of adaptive trials is that adaptive design modifications must be preplanned, requiring more time and effort at the design stage. Thus, lead times between planning and starting the trial may be increased. Adaptive design methods are complex and may require trial simulations for the detailed prespecifications involved. Expertise in adaptive trials design techniques is not widely available and this may comprise a hurdle to use of the adaptive approach.

The BAN2401 (lecanemab; Leqembi®) Phase 2 trial is an example of a dose-adaptive design used successfully in AD research [4]. The trial had a sample size of 800 and began with 5 dose arms and a placebo arm. Following randomization of the first 196 subjects (56 on placebo; 28 in each active dose arm), response-adaptive randomization was implemented where dose allocation probabilities were updated at each prespecified blinded interim analysis—conducted each time 50 new participants were randomized—until the target population of 800 participants was reached. The Bayesian dose-adaptive design aimed to identify the most effective dose and to allocate more subjects to the most likely effective dose(s) at each interim analysis. The definition of effectiveness in the dose adaptive randomization process was based on the Alzheimer's Disease Composite Score (ADCOMS), a clinical measure consisting of elements of the Clinical Dementia Rating scale, the Mini- Mental State Examination, and the Alzheimer's Disease Assessment Scale-cognitive subscale [5]. Monitoring for futility was initiated at the first interim analysis and the trial would have been stopped early for futility if any of the initial interim analyses had shown a <5% probability that the most promising dose was less than 25% superior to placebo. This strategy showed that the two highest doses were most effective, and the single highest dose was advanced to the Phase 3 trial [6].

Lee and colleagues [2] interrogated clinicaltrials.gov to determine how often adaptive trial designs were used in Phase 2 AD trials over the past 25 years. They found that only 2.5% ($N = 12$) of registered trials used adaptive designs. A variety of adaptive strategies were observed in the trials including early stopping rules, adaptive dose-finding, adaptive treatment arm selection, and response adaptive randomization. They noted that adaptive designs were more often used when the trial sponsor was a biopharmaceutical company compared to other classes of sponsor; the small numbers prohibit firm conclusions about these relationships. They found no temporal trends in use of adaptive designs over the past 25 years when analyzed in 5-year epochs.

This study has limitations related to clinicaltrials.gov. Registration of all trials conducted in the US is required; most trials from other global regions are registered but the site is not inclusive of all global trials. Some aspects such as start date, primary completion date (known for completed trials, projected for ongoing trials), eligibility criteria, and primary and secondary outcomes are standardized and easily located on the website. The trial design, however, may vary in detail, and some trials with adaptive features may not have been detected. Lee and colleagues [2] searched for "Alzheimer's disease" in the registry but might not have detected "Alzheimer disease," "dementia of the Alzheimer type," "mild cognitive impairment due to Alzheimer's disease," and other variations that search programs must "learn" to make the search comprehensive. Expanding the search term vocabulary might have detected more trials. The key point of the study is that adaptive designs have not had a major role in AD drug development.

The low rate of success of AD clinical trials and the urgent need for new therapies across the AD continuum require that the drug development community continue to examine strategies and iden-

tify approaches that may improve trial efficiency. The study by Lee and colleagues [2] demonstrates that adaptive designs are infrequently used and that greater consideration of the role for adaptive designs in AD drug development may accelerate the identification of efficacious treatments and availability of new therapies.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

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