

# Clinical Trial Simulation

## Providing Insight and Interpretation for Alzheimer's Disease Trials

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### Introduction

The use of clinical trial simulation (CTS) in new drug development is increasingly being recognized by pharmaceutical companies and regulatory authorities as a cost-effective means to determine which trial designs will be most efficient in detecting therapeutic effect in new drugs.<sup>1</sup> One therapeutic area which may benefit from CTS is Alzheimer's disease (AD), in which the vast majority of clinical trials in recent years have been unsuccessful. An area of particular need is the increased understanding of trials of disease-modifying drugs for AD following several high-profile trial failures over the past year. In this article, we demonstrate the application of CTS in AD trial design using the AD ACE simulator, an analytic framework that places prediction of AD progression and treatment response within the context of a simulated trial design.

### An Opportunity to Reassess AD Trial Design with CTS

In the past year, several highly anticipated Phase III trials of disease-modifying drugs in mild to moderate AD, targeting either amyloid or tau pathology, have

either failed to meet their primary endpoint or been terminated early. Results from a 15-month trial of the first tau-targeted drug to reach late-stage testing (LMTM) did not show treatment benefits related to cognition and activities of daily living.<sup>2</sup> The EXPEDITION 3 trial found that an amyloid-targeting antibody, solanezumab, failed to meet the primary endpoint of a slowing in cognitive decline.<sup>3</sup> Following this announcement, EXPEDITION PRO, another Phase III study of solanezumab, in which the trial population included only people with prodromal AD, was ended by the sponsor.<sup>4</sup> Similarly, the EPOCH trial of verubecestat, another drug targeting amyloid pathology,

was terminated early based on recommendations from an external Data Monitoring Committee, which saw minimal chance of the trial meeting its primary endpoint.<sup>5</sup>

Despite these recent trial outcomes, there is still substantial support for the amyloid hypothesis, with one proposed explanation for the observed outcomes to be that the involvement of amyloid in AD progression may be more critical in the beginning stages of AD before symptoms occur.<sup>6</sup> According to this hypothesis, amyloid-targeted treatments must be tested in earlier stages of the disease, as is the case in ongoing trials of therapies targeting amyloid pathology in individuals who are healthy but at a genetically high risk of AD.<sup>6</sup> In order to explore this hypothesis, we simulated a trial similar to EXPEDITION 3 while testing several alternate trial designs that probe specific elements of the hypothesis, including sample size, mechanism of action, and population.

### Clinical Trial Simulation with the AD ACE

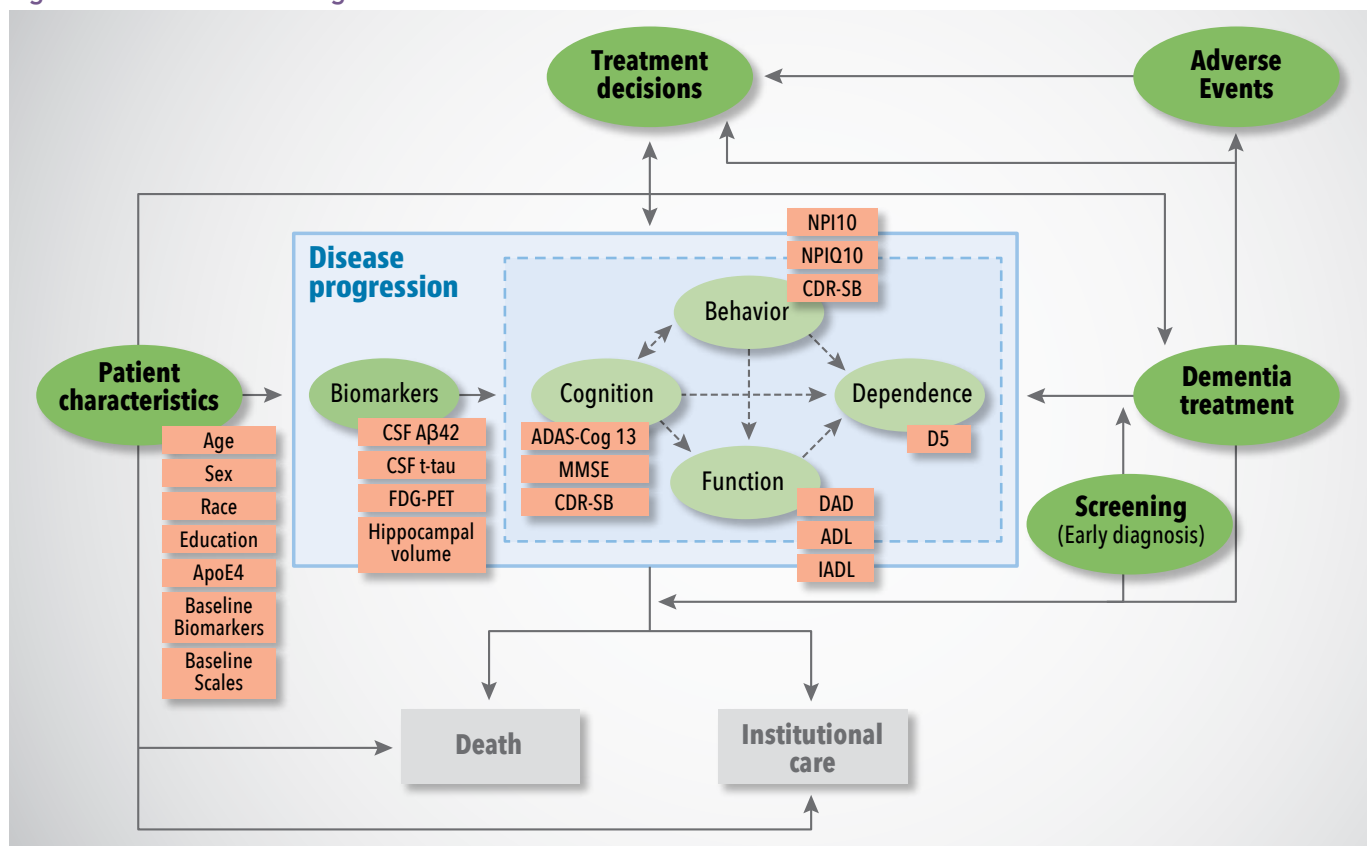
The AD ACE is a discretely integrated condition event (DICE) simulation of AD developed at Evidera.<sup>7</sup> The simulator incorporates measures of the underlying pathophysiology of AD, including measures of amyloid (CSF A $\beta$ 42) and tau (CSF t-tau) levels and their connections to clinical presentation of AD, including

**“The AD ACE simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity.”**

cognition and behavioral scales (Figure 1). The relationship between changes in these measures over time are quantified using predictive equations derived from long-term observational data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) to predict natural history of individuals with normal cognition through to severe AD. This design enables the simulation to evaluate the impact of disease-modifying treatments (DMTs) and symptomatic treatments on both the clinical and economic consequences of AD. The AD ACE simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity.

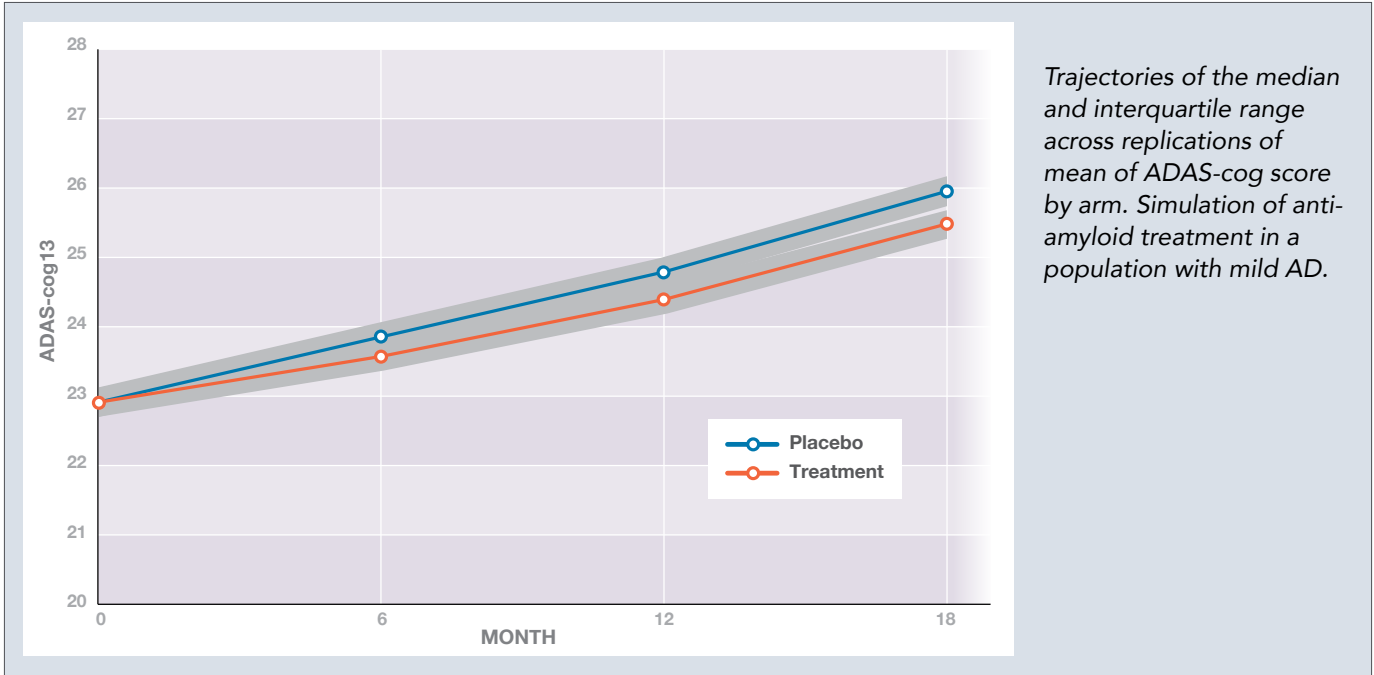
CTS draws from the trajectories for patients with and without treatment predicted by the AD ACE. Patients are included in a simulated trial based on inclusion/exclusion criteria at baseline, and CTS then follows the trajectories

Figure 1. AD ACE Model Diagram



Predictive longitudinal equations that determine trajectories of cognitive decline derived from ADNI and AHEAD (Assessment of Health Economics in Alzheimer’s Disease)

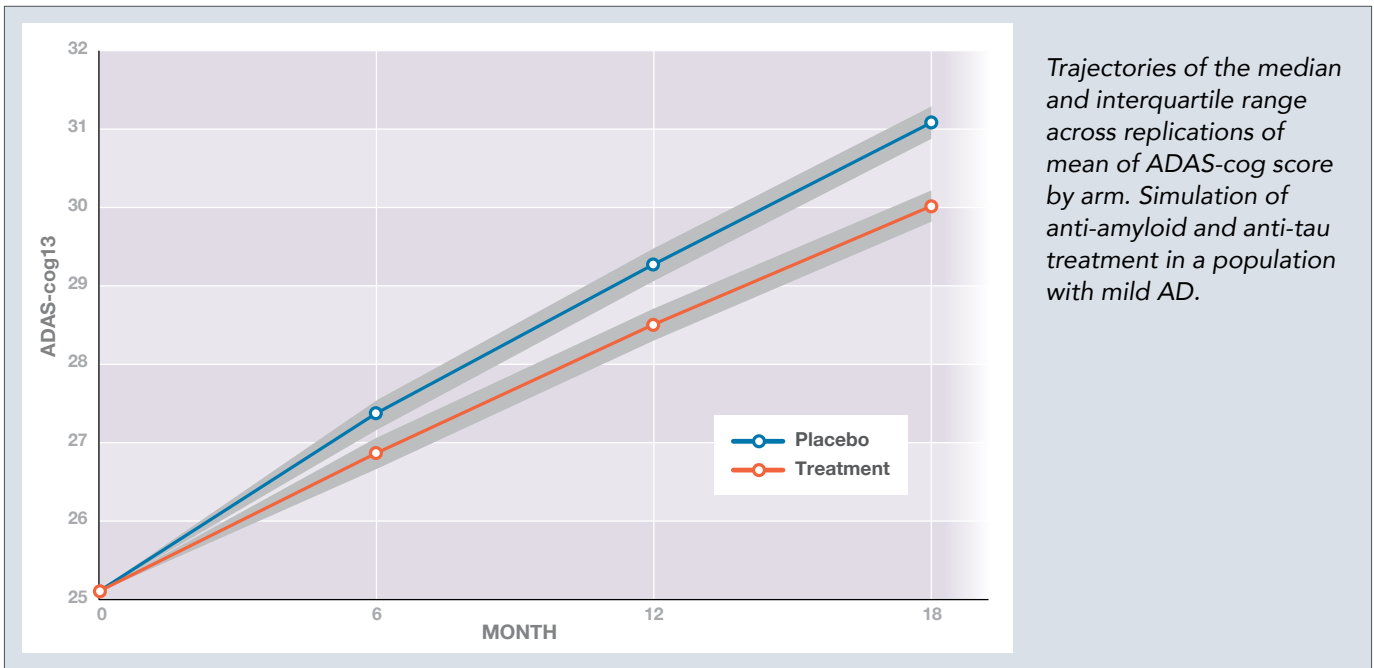
Figure 2. Trajectories of ADAS-Cog from Simulation Based on EXPEDITION 3 Protocol



of those patients as they proceed through the trial protocol. In order to understand the range of potential trial outcomes, CTS simulates many replications of the specified trial design. For each replication, the endpoints of the trial are assessed using appropriate statistical tests. In this study, we considered Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) change from baseline as the primary endpoint. A successful trial replication was defined to be one in which the primary

endpoint showed a difference between the treatment and placebo arms that met statistical significance at the  $p < 0.05$  threshold. In order to assess the likelihood of success of a given design, we report the fraction of replications in which the trial was successful. The mean trajectory of ADAS-cog in each arm is also reported for the median replications along with those at the 25<sup>th</sup> and 75<sup>th</sup> percentile.

Figure 3. Impact of Greater Therapeutic Effect on Trajectories of ADAS-Cog



## Case Study: CTS Based on EXPEDITION 3 Protocol

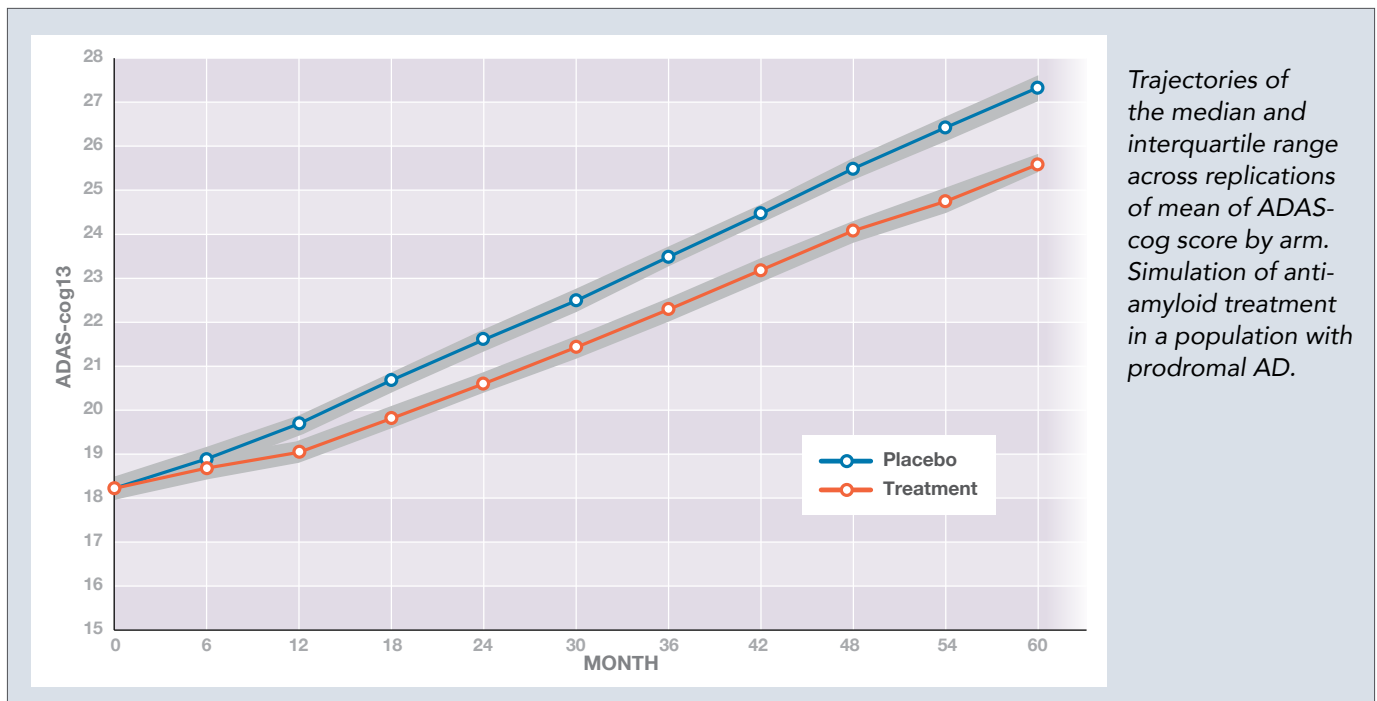
In replicating the EXPEDITION 3 protocol, simulated patients were selected according to the eligibility criteria of the trial: patients between the ages of 55 and 90 who were diagnosed with AD and had a Mini-Mental State Examination (MMSE) score of 20 through 26. The trial sample size was 1,000 patients per treatment arm. To mimic the challenges of real clinical data, an annual dropout rate of 10% was applied along with 3% of data missing at random. We assumed complete normalization of amyloid-beta pathology in the simulation, which is likely a substantial overestimate of the true effect of any purely anti-amyloid treatment.<sup>8</sup> The model estimated the likelihood of a successful trial based on the observed difference in ADAS-cog between a treatment which normalized amyloid pathology and placebo at the end of the 18-month trial period. The results suggested a low probability of success (about 10%) for this protocol. We found this was not an issue of sample size, as doubling sample size to 2,000 patients per arm only minimally increased the probability of a statistically significant difference in ADAS-cog to 15% (Figure 2).

Given this low probability of success in the simulations, we sought to explore some of the hypotheses that have been suggested as explanations for the EXPEDITION 3 outcomes. We began by testing whether patients with mild AD might benefit from a larger therapeutic effect

on the underlying pathology of AD. To do so, we ran the same CTS of the EXPEDITION 3 protocol with the larger trial population size, while broadening the treatment effect by normalizing both amyloid-beta and tau pathologies. This may reflect either a treatment with a direct effect on both proteins or an interaction between amyloid and tau pathologies beyond that captured in the AD ACE disease model. Under this condition, the simulations yield an increased probability of 84% of observing a statistically significant difference in ADAS-cog after 18 months (Figure 3).

We also evaluate the hypothesis that amyloid-targeting therapies may be effective in asymptomatic stages of AD, exploring a trial population with prodromal AD. Patients were diagnosed with late mild cognitive impairment (LMCI) or early MCI (EMCI) and between the ages of 55 and 90 years. Patients were included only with CSF A $\beta$ 42 less than 192 ng/L, which has been shown to correlate with the presence of amyloid plaques in the brain. Again, each treatment arm had 2,000 patients. Treatment had a direct effect only on amyloid pathology. In keeping with the design of ongoing trials in subjects with prodromal AD, we extended the maximum follow-up simulated to five years. Even by two years, however, the probability of showing a statistically significant difference in ADAS-cog was 71% (Figure 4). The improvement in ADAS-cog increased as follow-up continued up to five years as did the predicted probability of observing a statistically significant difference.

Figure 4. Trajectories of ADAS-Cog When Targeting Amyloid in Prodromal AD





## Discussion

CTS can provide valuable insights when designing and interpreting AD trials. A disease model makes explicit the relationships between components of the disease and the quantitative data that underpins those relationships. In the analysis presented here, CTS was used to evaluate a trial protocol similar to that of EXPEDITION 3 and to explore the implications of different hypotheses of the disease pathology that have emerged from that and related trial results. The simulation predictions were consistent with the observed trial results, suggesting it was unlikely to show a statistically significant difference in ADAS-cog in a population with mild AD. This prediction reflected both the specific treatment effect assumed and the patient population treated. When a more potent treatment effect was hypothesized, affecting both amyloid and tau pathology, the predicted likelihood of success rose dramatically. Similarly, consistent with current thinking that amyloid targeting therapies may be more effective in earlier stages of the disease, the model estimated a high likelihood of success in a trial of people

with prodromal AD, particularly over longer treatment periods.

Overall, CTS provides a means to quickly and affordably explore AD trial design options using limited clinical information before drug testing. CTS can provide quantitative context for decisions regarding trial parameters, such as inclusion and exclusion criteria, subpopulations, and primary and secondary endpoints. At the completion of a trial, CTS can also offer insight into the consistency of specific biological hypotheses with the trial results and the implications of those hypotheses for future decision making. With advances in disease simulation and clinical trial simulation, CTS is beginning to reach the promise identified by the U.S. Food and Drug Administration (FDA) in the 2006 Critical Path Opportunities Report, that CTS “could reduce the risk and cost of human testing by helping product sponsors make more informed decisions on how to proceed with product testing and when to remove a product from further development.”<sup>1,9</sup> ■

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