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Evaluating Digital Twins for Alzheimer's Disease using Data from a Completed Phase 2 Clinical Trial

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Theme: Drug Development

Abstract

Background: Complex Alzheimer's Disease (AD) clinical trials that require a large number of subjects leads to long trial timelines and significant costs. Our novel methods can accelerate randomized clinical trials (RCT) by reducing the required number of subjects using a combination of deep learning-based predictive models and statistical methods while meeting regulatory requirements. Our method leverages historical control clinical data in a way that allows for faster trials without sacrificing the reliability of traditional RCT analyses. A Phase 2 study on crenezumab (the ABBY study, NCT01343966) in mild-to-moderate AD was used to retrospectively assess the validity of this approach for AD clinical trials and the potential impact on future studies.

Method: A probabilistic deep learning model of AD progression was used to predict longitudinal outcomes using baseline data for 184 subjects from the placebo arm of the ABBY study. These clinical predictions are called Digital Twins, and are comprehensive outputs across several outcomes, including the 12-component Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog12), the Clinical Dementia Rating Sum-of-Boxes (CDR-SB), labs, and vitals. After Digital Twins were created blind to subject outcomes, they were compared to observed outcomes across visits and statistical metrics were computed to evaluate the utility of predictions in accelerating this Phase 2 clinical trial. The Pearson correlation coefficient defines the extent to which Digital Twins can provide a reduction in subjects in a clinical trial.

Result: Using the 18-month outcomes for the change in ADAS-Cog12 and CDR-SB scores from baseline, the Digital Twin predictions had a correlation of 0.46 (ADAS-Cog12) and 0.37 (CDR-SB) with the observed values from subjects that took placebo. These values suggest that in similarly designed studies, this approach can yield 21% (ADAS-Cog12) or 14% (CDR-SB) smaller studies when maintaining randomization, or 35% (ADAS-Cog12) and 24% (CDR-SB) smaller control arms when maintaining treatment arm size.

Endpoint	Correlation between subject outcomes and digital twins for the score change from baseline at 18 months	Prospective sample size reduction (maintaining a 1:1 randomization ratio)	Prospective control arm size reduction (starting from a 1:1 randomization ratio)
ADAS-Cog12	0.46	21%	35%
CDR-SB	0.37	14%	24%

Table 1. The correlation between observed outcomes and the Digital Twin predictions for the ADAS-Cog12 and CDR-SB change from baseline at 18 months, as well as the resulting prospective sample size or control arm reductions from 1:1 randomized study.

Conclusion: When used with appropriate statistical analysis methods, Digital Twins offer the ability to accelerate RCTs by requiring fewer subjects to achieve a desired power. Because these methods follow regulatory guidance, they can be applied in large pivotal studies to reduce trial timelines, costs, and potentially bring effective therapies to market faster.