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Applying prognostic scoring adjustments to enhance clinical trial efficiency in neurodegenerative diseases

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Harry completed his PhD in Biostatistical Oncology in 2023 at the Institute of Cancer Research (ICR), London, UK, specialising in medical statistics and clinical prediction modelling. His research focuses on developing dynamic prediction models for prostate cancer prognosis, leveraging advanced statistical methods to enhance treatment outcomes and patient care, which has been published in high-impact journals, including European Urology and BMC Medical Research Methodology. Since then, he has transitioned into industry, joining GSK's Statistics & Data Sciences Innovation Hub (SDS-IH), within the predictive modelling pillar. In this role, he applies his expertise to develop novel statistical methodologies across a broad range of therapeutic areas, driving innovation and improving health outcomes on a global scale.

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Background

Alzheimer’s Disease (AD) is a complex neurodegenerative disorder with substantial heterogeneity in its clinical presentation and progression, impacting both trial timing and subsequent analyses. Recently, there has been a growing interest in leveraging machine learning (ML) techniques and external data to better understand this heterogeneity, aiming for more efficient AD trials. Here, we introduce a novel methodology that showcases statistical efficiency gains and explores extensions into a repeated-measures framework.

Methods

We train an ensemble of ML models to construct prognostic scores (PS) and quantify power improvements. Synthetic data is generated, motivated from real Alzheimer’s disease

studies using mixed model of repeated measures (MMRM). The endpoint is a change of cognitive decline from baseline. We stress-test our assumptions under varying scenarios, including nonlinearity between PS and outcome, heterogeneous treatment effects, and population shifts, to quantify robustness.

Results

Applying PS within MMRM demonstrates power improvements. Simulations show that incorporating PS is robust often improving precision of our treatment effect without worsening bias and improves power by an additional 5%+ from intended 80%.

Conclusions

By leveraging observational data and using ML techniques, we can effectively capture the nonlinear, heterogeneous, and temporal dynamics between known covariates and outcomes, improving trial efficiency, precision, and maximising power. With these expected improvements under plausible assumptions, incorporating such methods into AD trials' statistical analysis plans should become standard practice. This approach offers reduced sample sizes, improves probability of success, and hence accelerated development of urgently needed treatments for AD patients.