Machine learning generated digital twins as an external control in non-randomized trials

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Methodological Issue Being Addressed We propose a digital twin based methodology to generate an external control (EC) for non-randomized trials. Compared to propensity score matching (PSM), digital twins use predicted progression of trial participants under standard of care generated from a machine learning model while PSM attempts to match historical progressions to trial participants.

Introduction Non-randomized trials are a frequent component of clinical development for investigational drugs in neurodegenerative diseases. Early-phase studies often focus on safety and pharmacokinetics but typically assess preliminary efficacy signals as well. In proof-of-concept and pivotal trials, open-label extensions are also widely used to provide confirmatory or long-term efficacy evidence. However, without a concurrent control group, interpreting efficacy in non-randomized settings is challenging. External controls are therefore commonly employed, with methods such as PSM used to adjust for population differences between current and historical trials. Here, we propose an alternative approach using machine learning generated digital twins.

Methods Digital twins are individualized longitudinal predictions of control outcomes generated from a pre-trained machine learning model. For treated participants, digital twins represent expected disease progression under standard of care—measured by clinical scales and biomarkers—conditional on each individual's baseline profile. We trained separate models for ALS and HD using extensive historical clinical trial and natural history datasets. The ALS model used data from more than 14,000 participants across PRO-ACT, PRO-ACE, APST, and other sources; the HD model used data from over 13,000 participants across trials from CHDI.

In non-randomized studies, digital twins can serve as ECs by providing the counterfactual outcome for each participant. Treatment effects can then be estimated using a direct plug-in estimator that compares observed outcomes to each participant's predicted trajectory. Since this approach requires the underlying model to be unbiased, we also evaluated an Augmented Inverse Propensity Weighting (AIPW) estimator, which extends the plug-in method by correcting for model bias.

We generated digital twins for participants in two trials—one ALS and one HD—using their baseline data. For each trial, we estimated treatment effects using three approaches: PSM, digital-twin plug-in, and digital-twin AIPW. Analyses were conducted across multiple clinical endpoints. We

additionally demonstrate that digital-twin analyses are straightforward to implement and can be pre-specified in statistical analysis plans.

Results Digital twin based estimators reduced standardized bias in the treatment effect estimates by up to 50% across an average of 4 endpoints in the 2Care study in HD compared to PSM. In the celecoxib study in ALS, digital twins reduced standardized bias 45% across an average of 2 endpoints. Digital twin estimators were also more efficient and reduced the variability of the treatment effect estimate, resulting in a more powerful analysis compared to PSM. In both the HD and ALS trials, average variance reduction across endpoints was up to 50% compared to PSM.

Conclusion Digital twins used as external controls may serve as robust comparators in non-randomized trials. When combined with PSM, digital-twin methodology can provide complementary evidence for efficacy signals. Recent FDA guidance on risk-credibility assessments for artificial intelligence offers a clear pathway for incorporating digital-twin approaches into clinical trial designs.

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