Towards FDA and EMA Endorsement of Clinical Trial Simulation Tools to Increase Efficiency of Drug Development in Mild Cognitive Impairment and Early Parkinson Disease

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Background
- Drug development in Alzheimer (AD) and Parkinson disease (PD) is focusing on earlier disease stages.
- Challenges in early AD and PD clinical trials include: (a) uncertainty for adequate patient selection, (b) interindividual heterogeneity, and (c) slow rate of change in clinical outcomes.
- An understanding of the rate of change and its predictors, for registration endpoints, is critical for optimal trial design.

Objectives
The goal herein was to develop disease progression model-based clinical trial simulation (CTS) tools to inform design of trials in subjects with amnestic mild cognitive impairment (aMCI) and early motor PD (ePD) with CDR-SB and MDS-UPDRS Part III, respectively, as endpoints.

Methods and Results
- Subject-level data from the PPMI + PRECEPT (N = 672) for ePD, and the ADNI-I+2 (N = 702) studies for aMCI were used.
- Relevant predictors of disease progression rate were: ePD: presence/absence of dopaminergic deficit, age; aMCI: sex, APOE genotype, baseline hippocampal volume, MMSE and age.
- The disease progression models* were used to develop web-based CTS in aMCI and ePD (see Figures). FDA and EMA endorsements are being pursued.

Conclusion
These interfaces can increase adoption of CTS to optimize aMCI and ePD trial design. Expansion of the dataset with additional clinical trials will contribute to refine and further validate the CTS.

DAT Neuroimaging-Informed Early PD Clinical Trial Simulator - Version 1.0
Simulate clinical trials on patients with early-stage Parkinson disease

Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator
Simulate clinical trials on patients with amnestic mild cognitive impairment

Notes:
- Only few simulations were performed for illustration purpose. Acronyms: APOE = Apolipoprotein E, CDR-SB = Clinical Dementia Rating-Sum of Boxes, ICU-NV = Intracranial volume-adjusted hippocampal volume, LDA® = Learning Embeddings Atlas Propagation, MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, SWEDD = Subjects with Scans Without Evidence of Dopaminergic Deficiency

*Details on the ePD disease progression model can be found at Conrado et al. Clin Transl Sci. 2018 Jan; 11(1): 63-70, and on the aMCI disease progression can be found at Conrado et al. Transl Sci. 2018 May; 5(3): 346-52

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