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-1+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

Click here for more information on this application.

Number of Subjects per Arm: 200

Duration of Subjects Follow-up (Months): 1 – 24

Assessment Interval (Months): 1 – 3 – 12

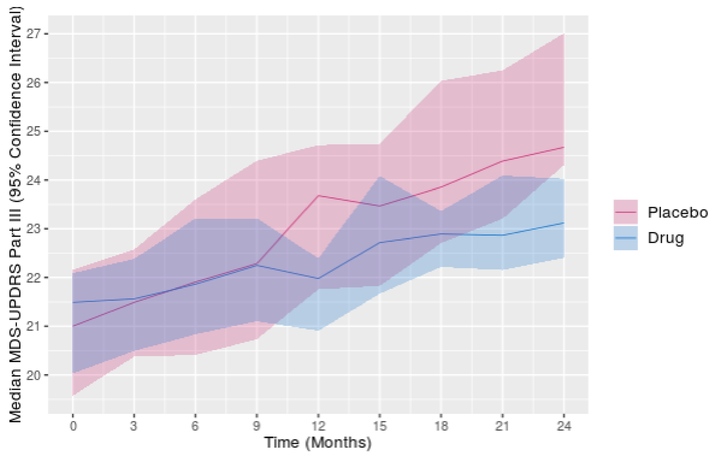
Proportion of Subjects with SWEDD (%): 0 – 14 – 28

Effect of Drug on Rate of Disease Progression (% Reduction): 0 – 50 – 100

Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction): 0 – 99

Number of Simulations: 10

Simulate



Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction)	0
Proportion of SWEDD (%)	14
Proportion of Female (%)	34
Median age (95% Confidence Interval) (Years)	62 (61, 63)
Number of Simulations	10
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	12.6
Statistical Power (%, 95% Confidence Interval)	80 (44.4, 97.5)

By Daniela Conrado (Model and App Developer) and Jackson Burton (App Developer) on behalf of the Critical Path for Parkinson's (CPP) consortium. E-mail DConrado@c-path.org with questions or comments.

Only few simulations were performed for illustration purpose. Acronyms: APOE = Apolipoprotein E, CDR-SB = Clinical Dementia Rating-Sum of Boxes, ICV-HV = Intracranial volume-adjusted hippocampal volume, LEAP™ = 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.

Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

Simulate clinical trials on patients with amnestic mild cognitive impairment

Number of Subjects per Arm: 200

Trial Duration (Months): 3 – 24 – 48

Assessment Interval (Months): 1 – 3 – 24

Proportion of Females (%): 35 – 40 – 60

Range of MMSE Scores at Baseline: 24 – 30

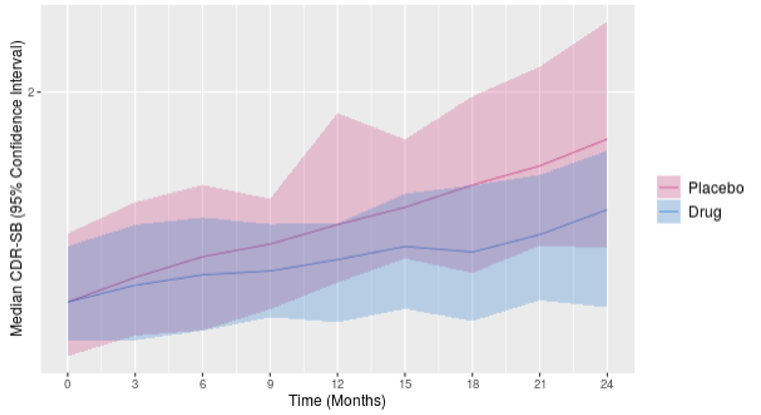
Proportion of APOE-e4 Noncarriers (%): 0 – 50 – 70

Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (LEAP, cm3): 3 – 8.5

Effect of Drug on Rate of Disease Progression (% Reduction): 0 – 50 – 100

Number of Simulations: 50

Simulate



Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Proportion of Female (%)	40
Range of MMSE Scores at Baseline	[24, 30]
Proportion of APOE-e4 Noncarrier (%)	50
Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3)	[3, 8.5]
Median Age at Baseline (95% Confidence Interval) (Years)	73 (72, 74)
Median MMSE Score at Baseline (95% Confidence Interval) (Points)	28 (27, 28)
Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3)	5.2 (5.1, 5.3)
Number of Simulations	50
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	6.9
Statistical Power (%, 95% Confidence Interval)	62 (47.2, 75.3)

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*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:

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