DEFINING OPTIMAL TIME-TO-EVENT ENDPOINTS FOR PARKINSON'S DISEASE CLINICAL TRIALS

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1 Summary

- Time-to-event (TTE) endpoints are used in Parkinson's disease (PD) trials. Event(s) are defined based on Minimal Clinically Meaningful changes from baseline Thresholds (MCMT) on MDS-UPDRS scores (Part II, III, Total). Clinical trial simulation was used to assess whether MCMTs are optimal for detecting treatment effects. Initial results suggest that TTE endpoints based on MCMTs may not be optimal.

2 Methods

- **Assumed study design**: 18-month, double-blind, randomized, placebo controlled, two-arm (Placebo/Active Treatment) study with 1 to 1 randomization.
- **Data**: Parkinson's Progressive Markers Initiative (PPMI[4]) data (Version 2023-06-12) used to generate two virtual populations: (i) idiopathic PD subjects (n=1135); (ii) idiopathic PD subjects on stable Levodopa equivalent daily dose (LEDD) between 100 and 500 mg for at least 20 months (n=351).
- **Simulation**: power to detect treatment effects on TTE endpoints across MDS-UPDRS score changes from baseline (CBL) thresholds and sample sizes estimated by clinical trial simulation using PPMI data
  - Generate virtual placebo and active treatment population TTE responses
    - Treatment effect modelled as 30% reduction of CBL scores
  - Generate 10,000 virtual clinical trial TTE outcome instances by random sampling from virtual populations
  - Compare active and placebo arm TTE responses for all outcome instances using a log-rank test and estimate power.

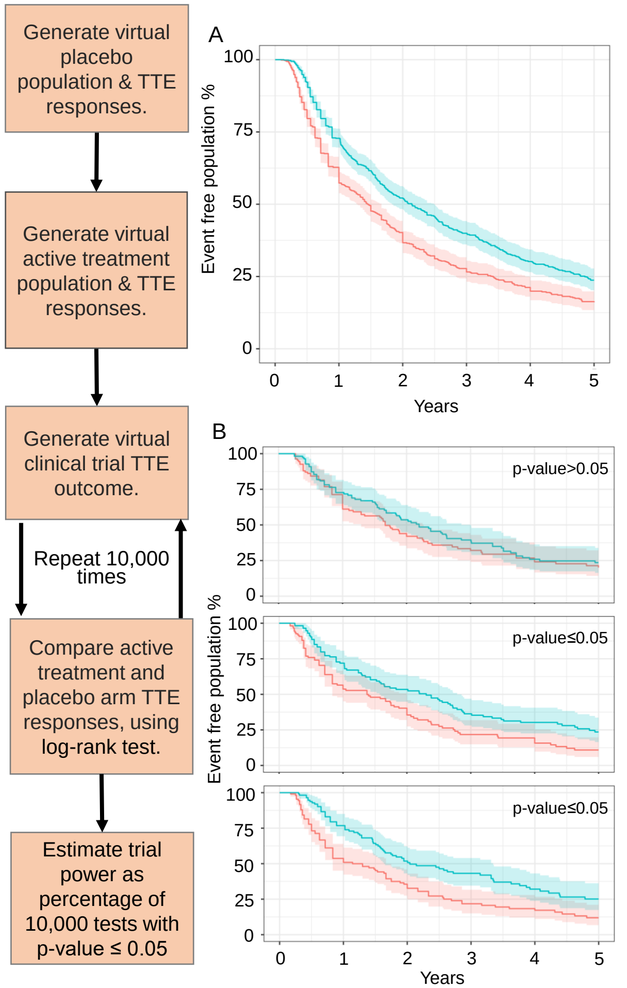

***Figure 1**: Left: Schematic overview of clinical trial simulation methodology. Right: A: Simulated TTE response for Idiopathic PD population with 5-point CBL threshold for MDS-UPDRS III score. Placebo response in red and active treatment response in blue. B: Example of three virtual clinical trial TTE outcomes assuming 125 subjects per study arm with corresponding log-rank test p-values.*

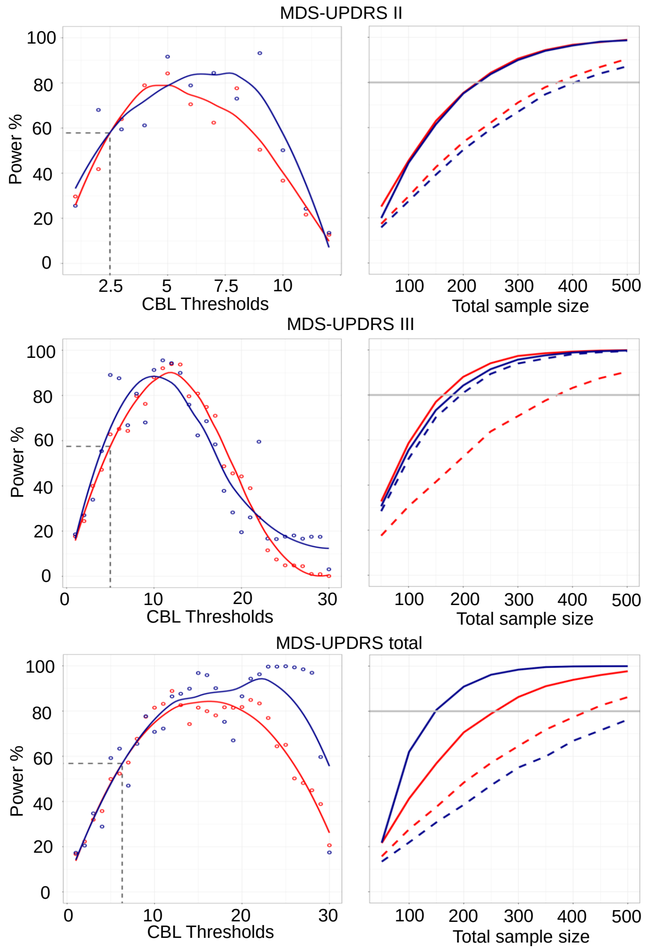

***Figure 2**: Left Panel: Study Power with 250 subjects versus TTE CBL threshold curves. Dots denote simulated power estimates. Curves denote LOESS fits to power estimates. Vertical dashed lines denote MCMT and horizontal dashed lines denote corresponding power. Right Panel: Study Power versus sample sizes curves. Dotted lines denote curves for TTE endpoints based on MCMTs whilst solid lines denote curves based on estimated optimal thresholds. The horizontal line denotes 80% power. For all curves: red denotes Idiopathic PD population; blue denotes stable LEDD population with power estimated for a 30% treatment effect.*

***Table 1**: Estimated power to detect 30% treatment effect for 250 subjects by MSD-UPDRS score, population, MCMT and estimated optimal CBL threshold. Power for optimal TTE CBL thresholds estimated from the power versus CBL threshold curves.*

MDS-UPDRS:	Part II:	Part III:	Total score:
MCMT (power): Idiopathic PD population	2.5[1] (58%)	5[2] (57%)	6.3[3] (57%)
Optimal CBL threshold range (optimal power): Idiopathic PD population	4.2-5.3 (79%)	10.4-13.3 (90%)	14.8-17.7 (84%)
MCMT (power): Stable LEDD population	2.5[1] (58%)	5[2] (66%)	6.3[3] (57%)
Optimal CBL threshold range (optimal power): Stable LEDD population	6.2-7.9 (84%)	8.6-11.5 (88%)	20.6-23.6 (94%)

3 Results

- Simulated power versus threshold curves initially increase, reach a peak and then decline (*Fig 2, left*). This was observed for all curves, with the curve profile sensitive to population and score used.
- Power for optimal thresholds consistently larger by an average of 28% relative to MCMT (*Table 1*).
- Need approximately 150 subjects less to achieve 80% power when using optimal thresholds as compared to MCMT (*Fig 2, right*).

4 Conclusion

- MCMT based TTE endpoints may not be optimal, as larger thresholds were estimated to have higher power for detection of treatment effects
- Larger optimal thresholds are clinically meaningful since they are larger than corresponding MCMT
- Recommend inclusion of TTE endpoints across a wider range of thresholds as exploratory endpoints in future PD clinical trials

[1]Krisztina Horváth et al (2017). Minimal clinically important differences for the experiences of daily living parts of movement disorder society– sponsored unified Parkinson's disease rating scale. Movement Disorders, Volume 32 (Issue 5), p.789-793: [2] Zanigni, S. (2022). ESTIMATING THE MEANINGFUL WITHIN-PATIENT WORSENING THRESHOLD FOR THE MDS-UPDRS PART III [Poster presentation], ADPD 2022 Conference: [3] N. Kovács, A. Juhász, Z. Aschermann. Are the MDS-UPDRS-based composite scores clinically applicable? [abstract]. Mov Disord. 2018; 33 (suppl 2). https://www.mdsabstracts.org/abstract/are-the-mds-updrs-based-composite-scores-clinically-applicable/. Accessed January 28, 2025:

[4] PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including 4D Pharma, Abbvie, AcureX, Allergan, Amathus Therapeutics, Aligning Science Across Parkinson's, AskBio, Avid Radiopharmaceuticals, BIAL, BioArctic, Biogen, Biohaven, BioLegend, BlueRock Therapeutics, Bristol-Myers Squibb, Calico Labs, Capsida Biotherapeutics, Celgene, Cerevel Therapeutics, Coave Therapeutics, DaCapo Brainscience, Denali, Edmond J. Safra Foundation, Eli Lilly, Gain Therapeutics, GE HealthCare, Genentech, GSK, Golub Capital, Handl Therapeutics, Insitro, Jazz Pharmaceuticals, Johnson & Johnson Innovative Medicine, Lundbeck, Merck, Meso Scale Discovery, Mission Therapeutics, Neurocrine Biosciences, Neuron23, Neuropore, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi, Servier, Sun Pharma Advanced Research Company, Takeda, Teva, UCB, Vanqua Bio, Verily, Voyager v. 25MAR2024 Therapeutics, the Weston Family Foundation and Yumanity Therapeutics. Accessible at https://www.ppmi-info.org.

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