Optimizing scoring algorithms of the MDS-UPDRS Part 3 for clinical trials in early-stage Parkinson's disease

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Introduction

- As the focus of interventional trials in Parkinson's disease (PD) shifts from symptomatic treatment to disease-modifying therapies, the population of interest is moving earlier in the disease course.
- Existing measures, including the MDS-UPDRS, and common clinical trial endpoints were developed with the full spectrum of PD severity in mind and are not optimized for early-stage PD (Hoehn & Yahr ≤2; treatment naïve or on symptomatic treatment).
- To address these limitations, a multistakeholder pre-competitive collaboration was established with the sponsorship of The Michael J. Fox Foundation (MJFF) under the umbrella of Critical Path Institute's (C-Path's) Critical Path for Parkinson's (CPP), a pre-existing consortium with precedented regulatory strategies.
- A task force of clinical outcome assessment (COA) specialists drives the collaboration with input from broader CPP experts. The initiative relies on CPP members and experts contributing data and evidence to be synthesized across sources to identify patterns and inform recommendations regarding item retention, scoring, and endpoint construction.
- Quantitative methods were employed to investigate subsets of items and alternative scoring strategies that might improve MDS-UPDRS Part 3 measurement properties and responsiveness (sensitivity to change) in early PD.

Methods

Data & Inclusion Criteria

Data from the Critical Path for Parkinson's (CPP) database, across multiple studies.

- Hoehn & Yahr stage ≤2
- Not on symptomatic treatment or in the practically defined "off" medication state
- Identifiable more-affected side at baseline
- No item-level missingness (for a given timepoint)

Dimensionality & Responsiveness Analyses

Dimensionality: Fit confirmatory factor analysis (CFA) models to data at baseline & 12 months.

Responsiveness: Change on Part 2 used as an anchor to examine Part 3 responsiveness (5-pts of change; Pagano et al., 2025).

Type of Study	*Time*	*N*	*# Studies*
Interventional	Baseline	1137	6
	12 Mos.	791	5
Observational	Baseline	983	1
	12 Mos.	633	1

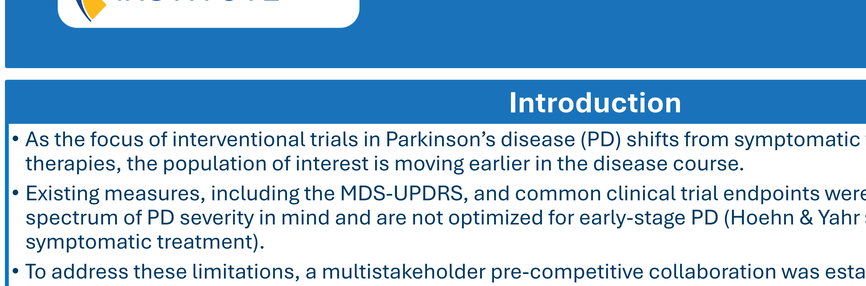
Power Analysis

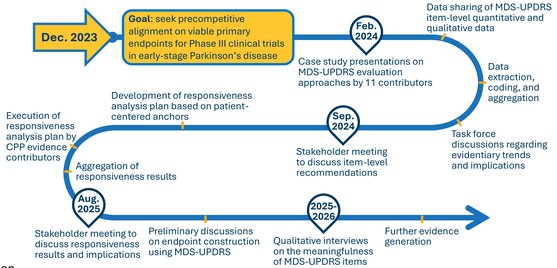
- To ensure analysis was agnostic to scoring algorithm, bootstrapped data across 500 replications.
- For observational data, fit a latent class growth mixture model (LCGMM) to identify participants who worsened vs remained stable over 12 months.

Type of Study	*Time*	*Placebo or Worsening N*	*Active or Stable N*
Interventional	Baseline	95	82
	6 Mos.	94	81
Observational	Baseline	861	103
	12 Mos.	861	103

Evidence Synthesis

- Data were extracted, coded, and aggregated across contributed qualitative and quantitative item-level MDS-UPDRS evidence.
- Iterative consultations with taskforce members, clinical experts, and representatives from FDA's Office of Neuroscience identified trends.
- Prioritized evidence that provided support for the meaningfulness of items to people with PD and the ability of items to detect changes over time.





Retain	*Carry Forward and Test*	*Exclude*
Speech (3.01)	Arising from chair (3.09)	Facial expression (3.02)
Rigidity (3.03)	Global bradykinesia (3.14)	Freezing of gait (3.11)
Finger tapping (3.04)	Postural tremor (3.15)	
Hand movements (3.05)	Kinetic tremor (3.16)	
Pronation supination (3.06)	Resting tremor amplitude (3.17)	
Toe tapping (3.07)	Constancy of resting tremor (3.18)	
Leg agility (3.08)		
Gait (3.10)		
Postural stability (3.12)		
Posture (3.13)		

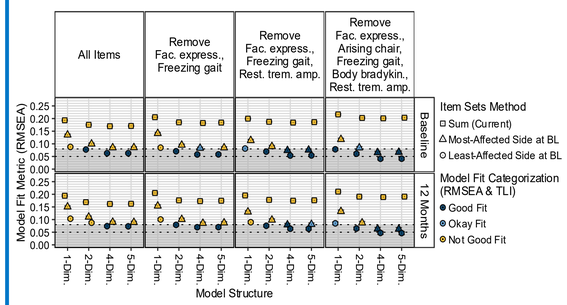
- Qualitative evidence was obtained from 9 interview and literature sources (e.g., concept elicitation, cognitive debriefing of MDS-UPDRS items), and quantitative psychometric evidence was obtained from 15 randomized control trial and observational sources (e.g., item response theory, regression).
- Based on the trends observed across these evidence sources, we identified 16 Part 3 items for further consideration in an optimized use of MDS-UPDRS in early PD.
- A consensus analysis plan was developed by the task force to be independently conducted by members with available clinical trial data.
- The analysis plan focused on responsiveness and use of patient-centered anchors.

Responsiveness Results

Items with Highest Responsiveness Values	*Evidence Synthesis Categorization*
Speech (3.01)	Retain
Rigidity (3.03) [*both sides*]	Retain
Hand movements (3.05) [*both sides*]	Retain
Pronation supination (3.06) [*least-affected side*]	Retain
Toe tapping (3.07) [*least-affected side*]	Retain
Leg agility (3.08) [*least-affected side*]	Retain
Arising from chair (3.09)	Carry forward & test
Postural stability (3.12)	Retain
Global bradykinesia (3.14)	Carry forward & test

Independently conducted responsiveness results broadly agreed with those conducted using the CPP database

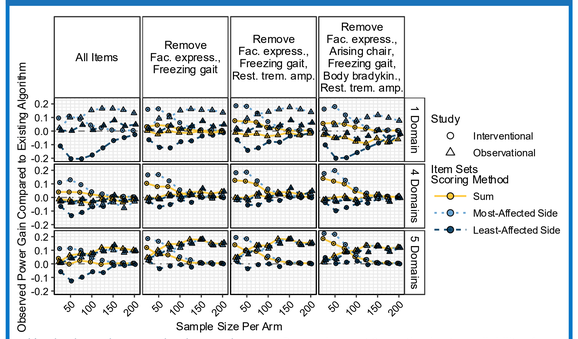
Dimensionality Results



"Good Fit"	TLI ≥ 0.90 *and* RMSEA ≤ 0.08
"Okay Fit"	TLI ≥ 0.90 *and* RMSEA CI encompasses 0.08
"Not Good Fit"	TLI < 0.90 *or* RMSEA CI > 0.08

CI = Confidence Interval

Power Results



Y-axis shows increase in observed power over the existing scoring algorithm

Power shown at 6 months due to availability of interventional trial data; similar results at 12 months

Conclusions

- These results highlight the importance of tailoring chosen clinical outcome assessment-based endpoints to the population of interest.
  - Suitable endpoints for earlier stages of a condition are likely not the same as those developed to assess meaningful benefit of novel treatments in later stages of the same condition.
  - We note the importance of clear operational definitions of target population although there is a lack of consensus in the field. Differences in population definitions across studies is a limitation of these analyses.
- They also demonstrate the effectiveness of using patient-focused qualitative and quantitative data to guide decisions.
- Alignment with regulators is key in advancing patient-focused drug development strategies.

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