Re-Weighting MDS-UPDRS Parts II and III Items to Improve Assessment of Motor Decline in Untreated Parkinson's Disease

Sam Dickson[1], Basia Rogula[2], Jordan Dubow[3], Nick Kozauer[4*], Lauren Powell[2], Michele Potashman[4], Patrick O'Keefe[1], Ellen Korol[2], Madeleine Crabtree[2], Fernanda Nagase[2], Vlad Coric[4], Liana S. Rosenthal[5], Suzanne Hendrix[1], Gil L'Italien[4]

[1]Pentara Corporation, 2261 E 3300 S, Salt Lake City, UT, USA; [2]Broadstreet HEOR, 343 Railway St, Vancouver, BC, Canada; [3]Clintrex, 2 N Tamiami Trail #308, Sarasota, FL, USA; [4]Biohaven Pharmaceuticals, Inc, 215 Church St, New Haven, CT, USA; [5]Johns Hopkins Medicine, Department of Neurology, Baltimore, MD, USA

*At the time of study completion

CONCLUSIONS

1. Composite scales combining motor and activities of daily living items from the MDS-UPDRS scales were derived using two distinct data sources and were more responsive than the original scales.
2. The two PARCOMS-Motor scales were not entirely consistent, possibly due to slight differences in disease characteristics of patients enrolled in clinical trials versus natural history datasets and/or expectation bias.
3. Use of PARCOMS-Motor could increase trial efficiency and power to detect meaningful delay in disease progression with disease modifying therapies (DMTs).

References:

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PPMI: https://ppmi-info.org

CPP: data was downloaded on September 13, 2023

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INTRODUCTION

- There is considerable interest in improving the sensitivity of Parkinson's disease (PD) measures to adequately capture the effect of DMTs.
- Composite scales are increasingly being recognized as useful tools for transforming clinically validated tools that assess a broad range of disease signs and symptoms into targeted scales appropriate for measuring disease progression.[1,2,3]
- Composite scales can be particularly helpful in trials of early stages of PD when progression is slow, and trial follow-up may not be sufficient to capture delay in disease decline.
- Deriving composite scales relies on access to either robust natural history datasets or placebo arm data from clinical trials of DMTs.[3]

OBJECTIVE **To use two PD datasets to generate a composite scale, PARCOMS-Motor, from MDS-UPDRS-Parts II and III items optimized for sensitivity to detect motor decline over 1-year.**

METHODS

Study Participants and Data

- Data were obtained from the multicenter natural history cohort Parkinson's Progression Markers Initiative (PPMI) and the Critical Path for Parkinson's (CPP, data downloaded on September 13, 2023), a collaborative initiative to advance drug development in early PD.
- Data availability:
  - **PPMI:** Data from July 1, 2010 to July 1, 2023 for subjects in the PD cohort.
  - **CPP:** Data up to September 13, 2023 for subjects in the placebo group of three DMT trials.
- Subjects with confirmed PD, diagnosed within the previous two years, naïve to dopaminergic treatment, with baseline Hoehn and Yahr stage 1 and 2 from the both datasets were included in the analysis.
- These cohorts included data up to three years post baseline, although clinical trials for the CPP model were of shorter duration, ranging from one to three years.
- The MDS-UPDRS Parts II and III were selected to create a scale that would be responsive to motor changes (Part III) and impact of motor function on activities of daily living (Part II) in the target population.
- Items from Part II and III were mapped to clinical concepts in consultation with clinical experts.
- The PARCOMS-Motor scales derived from PPMI and CPP datasets were compared with each other and with the original MDS-UPDRS scale.

Statistical Analysis

- For each model, items were selected using partial least squares (PLS) regression applying a variable importance in projection (VIP) threshold of 0.5.
- The sum of selected items weighted by their model coefficients created the composite scale. Weights reflected the contribution of the item, with higher weights attributed to the more progressive items.
- PARCOMS-Motors' responsiveness to change was measured using a 1-year mean-to-standard-deviation ratio (MSDR), with higher values indicating better sensitivity.
- Baseline characteristics for the natural history and placebo arm cohorts were summarized and compared descriptively.
- The items retained and their weights were compared for the scales derived from natural history (PPMI) vs clinical trial placebo arms (CPP).

RESULTS

- Baseline demographic and disease characteristics are presented in **Table 1.** Subjects in the CPP and PPMI cohorts were comparable in age, sex, race, and time since diagnosis. Mean Part II and III scores at baseline were also similar between cohorts.
- The percent change from the original MSDR for PARCOMS-Motor derived in CPP was nearly twice that of the model derived with PPMI data (**Table 2**).
- In PARCOMS-Motor, 34 of the 46 items (74%) from the MDS-UPDRS Parts II and III were retained in either the CPP or PPMI derived composite scales (**Figure 1**).
  - There were 17 out of 34 (50%) items retained in both the PPMI and the CPP derived composite scales; six (18%) were retained only in the CPP composite scale, and 11 (32%) were retained only in the PPMI scale.
  - Fewer items were retained in the CPP derived PARCOMS-Motor (23 items) compared to the PPMI derived scale (28 items).
- Items retained in both PPMI and CPP derived scales predominantly measured irregular/involuntary movement. However, in CPP, there was relatively higher importance of activities of daily living and oral dysfunction compared to PPMI (**Figure 2**).

Table 1. Demographic and baseline characteristics of the CPP and PPMI cohorts

	CPP cohort (n=183)	PPMI cohort (n=430)
Age in years, mean (SD)	63.1 (9.4)	62.8 (9.1)
Sex, n (%)		
Male	114 (62)	295 (69)
Female	69 (38)	135 (31)
Age at diagnosis (years), mean (SD)	62.9 (9.6)	61.7 (9.1)
Race, n (%)		
White	169 (92)	400 (93)
Multiracial	2 (1)	10 (2)
Black/African American	2 (1)	8 (2)
Asian	1 (1)	5 (1)
Native American	1 (1)	1 (0)
Not specified	8 (4)	6 (1)
Time since diagnosis (years), mean (SD)	0.6 (0.5)	0.6 (0.5)
Hoehn and Yahr stage, n (%)		
1	60 (33)	161 (37)
2	123 (67)	269 (63)
MDS-UPDRS Part II Score, mean (SD)	5.0 (4.1)	5.3 (4.0)
MDS-UPDRS Part III Score*, mean (SD)	21.4 (8.7)	20.8 (8.9)

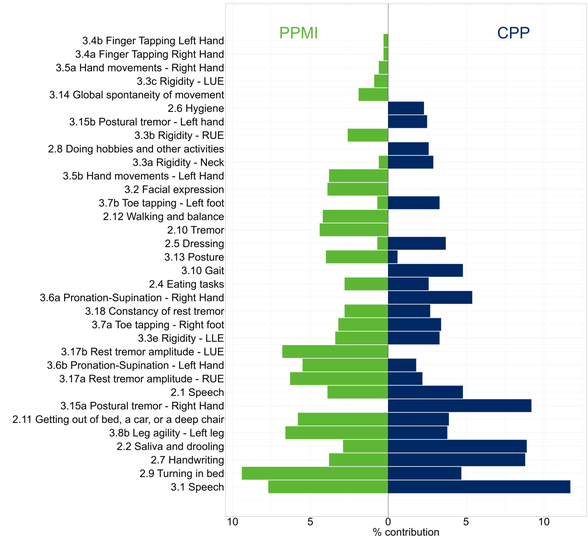
*MDS-UPDRS Part III score measured in blank or ON state
Abbreviations: CPP, Critical Path for Parkinson's; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease rating scale; PPMI, Parkinson's Progression Markers Initiative; SD, standard deviation.

Table 2. Changes in MSDRs for PARCOMS-motor from the CPP and PPMI models

Model	MSDR of original scale	MSDR of composite	% Change from original
CPP model	0.6922	0.8826	27.5
PPMI model	0.7615	0.8612	13.1

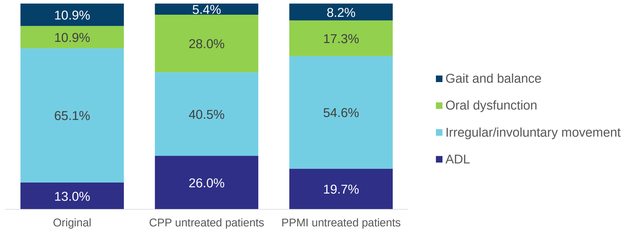
Abbreviations: CPP, Critical Path for Parkinson's; MSDR, mean-to-standard-deviation ratio; PPMI, Parkinson's Progression Markers Initiative.

Figure 1. Percent contributions (weighting) of items in PARCOMS-Motor in CPP and PPMI cohorts (MDS-UPDRS Parts II and III)



Abbreviations: ADL, Activities of daily living; CPP, Critical Path for Parkinson's; LLE, left lower extremity; LUE, left upper extremity; MDS-UPDRS Movement Disorder Society Unified Parkinson's Disease rating scale; PPMI, Parkinson's Progression Markers Initiative; RUE, right upper extremity.

Figure 2. Impact of re-weighting MDS-UPDRS Parts II and III items based on PARCOMS-motor PLS regression results by clinical concepts



Abbreviations: ADL, Activities of daily living; CPP, Critical Path for Parkinson's; MDS-UPDRS Movement Disorder Society Unified Parkinson's Disease rating scale; PLS – Partial least square; PPMI; Parkinson's Progression Markers Initiative.

DISCUSSION

- The PARCOMS-Motor scale resulted in a 13-26% increase in responsiveness, as measured by MSDR, with a 50% reduction in the number of items from the original component scales.
- In both CPP and PPMI derived PARCOMS-Motor scales, activities of daily living and oral dysfunction items were weighted higher than in the original MDS-UPDRS scales.
- Differences in item retention across the CPP and PPMI derived scales may speak to impacts from the expectation bias and/or placebo effects hypothesized to occur in PD clinical trials. The CPP derived PARCOMS-Motor retained fewer items than the PPMI scale, indicating more stability of items in the clinical trial population.
- The use of composite scores optimizes current validated measures by improving the sensitivity of the original scales to progression. This, in turn, decreases the number of patients required to detect statistically significant change in clinical trials, thus improving their efficiency.