Weighting MDS-UPDRS Part II items for optimal sensitivity to Parkinson's disease progression using Parkinson's Progression Markers Initiative natural history data

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

[1]Pentara Corporation, 2261 E 3300 S, Salt Lake City, UT, USA; 2Broadstreet 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

CONCLUSIONS

1. A weighted combination of Part II Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) items was shown to measure clinical decline with greater sensitivity than the original scale.
2. Each of the composite scales is optimized to detect clinical decline in the population from which it was derived, with different Part II items being more responsive to disease progression at different stages of Parkinson's disease (PD).
3. Scales that exhibit increased sensitivity to disease progression will allow for more efficient trial design when examining disease modifying therapies (DMTs).

References:

1. The Michael J Fox Foundation. Symptoms. n.d.; https://www.michaeljfox.org/symptoms.
2. Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology. 2017;89(24):2495-2502.;
3. Wang J, Logovinsky V, Hendrix SB, et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. J Neurol Neurosurg Psychiatry. 2016;87(9):993-999.

Data Acknowledgment:

PPMI: https://ppmi-info.org

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Alzheimer's and Parkinson's Disease Conference (AD/PD) • March 5-9, 2024 • Lisbon, Portugal & Virtual

INTRODUCTION

- Despite considerable interest, no (DMTs are available to PD patients.
- Progression of PD signs and symptoms occurs at different rates over the course of the disease and further can be related to background use of symptomatic therapy. This heterogeneity causes challenges in demonstrating the benefits of even highly effective DMTs in clinical trials.
- Clinical trials assessing outcomes in PD patients typically use scales designed to comprehensively measure a range of PD symptoms that occur across the spectrum of disease, of which the MDS-UPDRS is a cornerstone measure.
- To address this challenge, there is precedent for the development of composite scales optimized for sensitivity to clinical decline according to disease stage, treatment status, and symptom presentation.[1,2]

OBJECTIVE

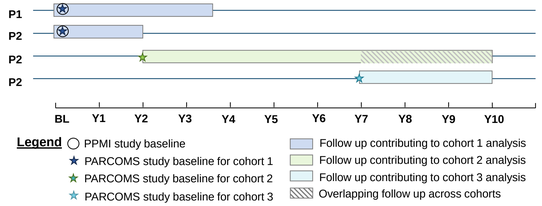
To demonstrate how a composite scale derived from the MDS-UPDRS Part II items can better detect meaningful changes in patients with PD as compared to the original scale

METHODS

Study Participants and Data

- Data were obtained from the PD cohort of the Parkinson's Progression Markers Initiative (PPMI), an ongoing, international, multicenter natural history cohort primarily funded by the Michael J. Fox Foundation. Data were available from July 1, 2010 to July 1, 2023.
- This analysis utilized data from the MDS-UPDRS scale (© 2008 International Parkinson and Movement Disorder Society) Part II (13 items assessing motor experience of daily living) in subjects with confirmed PD. The analytic dataset included patients who had baseline and ≥1 post-baseline visit with complete data on Part II within 3 years.
- Three cohorts were defined based on use of dopaminergic medications and presence of motor complications (≥25% time of waking day in OFF-state and/or dyskinesia assessed on MDS-UPDRS Part IV).
  - **Cohort 1:** Untreated, no dopaminergic mediation use
  - **Cohort 2:** Treated without (w/o) motor complications
  - **Cohort 3:** Treated with motor complications
- Patients were re-baselined once they met the criteria of another cohort (**Figure 1**).

Figure 1. Re-baseline of patients as cohort criteria are met over time



Patient 1: Example of patient who only ever fulfills criteria for cohort#1. Entire length of follow up contributes to model for cohort #1.

Patient 2: Example of patient who fulfills criteria for all three cohorts over the course of their follow up. When patient meets criteria for treated cohort #2, they are censored from the untreated analysis.

METHODS

Statistical Analysis

- 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.
- Composite scale responsiveness to change was assessed using a 2-year mean to standard deviation ratio (MSDR) for treated cohorts and a 1-year MSDR for the untreated cohort (due to data limitations).
- Sample sizes were calculated based off observed MSDRs, slowing of 30%, and power of 80% for an independent sample t-test. Changes in power were calculated using the initial N and the MSDR from the CS.

RESULTS

- Baseline disease characteristics varied across PD cohorts as expected (**Table 1**), with patients in the treated cohorts being more advanced than patients in the untreated cohort.
- The three most responsive items (with their combined weights) were: **cohort 1** - turning in bed, tremor, getting out of bed/car/chair, (45%); **cohort 2** - turning in bed, getting out of bed/car/chair, and speech (57%); **cohort 3** – turning in bed, speech, and handwriting (54%), respectively (**Table 2**).
- For the original vs optimized scales, the MSDRs increased from 0.5431 to 0.5652 (+4%), 0.4265 to 0.5004 (+17%), and 0.3128 to 0.3822 (+22%), for cohort 1, cohort 2, and cohort 3.
- The increase in scale sensitivity corresponded to sample size decreases of ~8%, 27%, and 33%, reflecting powering improvements of ~3, 11 and 13 percentage points at 80% initial power.

Table 1. Demographic and baseline characteristics of the PPMI cohorts

	Cohort 1 (n=428)	Cohort 2 (n=424)	Cohort 3 (n=536)
Age in years, mean (SD)	62.8 (9.1)	65.0 (9.8)	64.5 (10.1)
Sex, n (%)			
Male	294 (69)	260 (61)	320 (60)
Female	134 (31)	164 (39)	216 (40)
Age at diagnosis (years), mean (SD)	61.7 (9.1)	61.3 (10.2)	59.1 (9.9)
Race			
White	398 (93)	396 (93)	510 (95)
Multiracial	10 (2)	12 (3)	12 (2)
Black/African American	8 (2)	6 (1)	6 (1)
Asian	5 (1)	5 (1)	6 (1)
Native American	1 (0)	1 (0)	1 (0)
Not specified	6 (1)	4 (1)	1 (0)
Time since diagnosis (years), mean (SD)	0.6 (0.5)	3.2 (2.0)	5.0 (2.4)
Hoehn and Yahr stage, n (%)			
1	160 (37)	104 (25)	82 (17)
2	268 (63)	320 (75)	355 (75)
3	NA	NA	35 (7)
4	NA	NA	2 (0)
MDS-UPDRS Part II Score, mean (SD)	5.2 (4.0)	7.2 (4.8)	9.7 (6.3)

MDS-UPDRS, movement disorder society unified Parkinson's disease rating scale; SD, standard deviation.

DISCUSSION

- MDS-UPDRS Part II is a patient centric measure of the impact that PD has on activities of daily living. This study used robust PPMI natural history data to identify the aspects of daily living which decline at the different stages of PD.
- Identifying key MDS-UPDRS Part II items and weighting selected items increase focus on the items that are most responsive to disease progression for each stage of PD, the sensitivity of the overall scale was increased.
- This may have significant implications for clinical trial design in PD (e.g., reduced sample size and follow-up time), whereby DMTs can reach patients more efficiently.

Table 2. VIP scores and corresponding PLS coefficients for the MDS-UPDRS Part II PPMI composite scales, VIP cut-off 0.5, stratified by cohort

Item	MSDR at 1 year	VIP	PLS weight	% contribution
Cohort 1				
2.9 Turning in bed	0.3663	1.001	0.8551	18.7
2.10 Tremor	0.2387	1.031	0.5962	13.0
2.11 Getting out of bed, a car, or a deep chair	0.2190	1.138	0.5910	12.9
2.7 Handwriting	0.2554	1.410	0.5029	11.0
2.12 Walking and balance	0.2846	0.778	0.4544	9.9
2.4 Eating tasks	0.2976	0.840	0.4052	8.8
2.1 Speech	0.2318	0.774	0.3499	7.6
2.5 Dressing	0.3217	0.875	0.3030	6.6
2.2 Saliva and drooling	0.2062	1.112	0.2583	5.6
2.8 Doing hobbies and other activities	0.2143	1.203	0.1496	3.3
2.6 Hygiene	0.2145	0.542	0.1183	2.6
Overall MSDR	**0.5652**			0 30
Cohort 2				
2.9 Turning in bed	0.3723	1.286	0.9400	26.5
2.11 Getting out of bed, a car, or a deep chair	0.2960	1.213	0.5761	16.3
2.1 Speech	0.2496	1.020	0.4937	13.9
2.12 Walking and balance	0.2850	0.935	0.3452	9.7
2.13 Freezing	0.1648	0.560	0.3347	9.5
2.5 Dressing	0.2382	0.962	0.2355	6.7
2.8 Doing hobbies and other activities	0.3573	1.250	0.2278	6.4
2.2 Saliva and drooling	0.1546	0.873	0.2033	5.7
2.7 Handwriting	0.1630	1.031	0.0997	2.8
2.6 Hygiene	0.2289	0.577	0.0848	2.4
Overall MSDR	**0.5004**			0 30
Cohort 3				
2.9 Turning in bed	0.2550	1.220	0.5608	21.4
2.1 Speech	0.3049	1.109	0.4587	17.5
2.7 Handwriting	0.2288	1.303	0.3968	15.2
2.13 Freezing	0.1664	0.902	0.3826	14.6
2.12 Walking and balance	0.2691	0.966	0.2520	9.6
2.3 Chewing and swallowing	0.0980	0.546	0.2469	9.4
2.2 Saliva and drooling	0.0940	0.583	0.1365	5.2
2.8 Doing hobbies and other activities	0.1760	1.239	0.0951	3.6
2.5 Dressing	0.1782	0.817	0.0896	3.4
Overall MSDR	**0.3822**			0 30

MDS-UPDRS, movement disorder society unified Parkinson's disease rating scale; MSDR, mean to standard deviation ratio; PLS, partial least squares; SD, standard deviation; VIP, variable importance in projection.