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Embedding Patient Input in Outcome Measures for LongTerm DiseaseModifying Parkinson Disease Trials

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BRIEF REPORT

Embedding Patient Input in Outcome Measures for Long-Term Disease-Modifying Parkinson Disease Trials

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ABSTRACT: Background: Clinical trials of disease-modifying therapies in PD require valid and responsive primary outcome measures that are relevant to patients.

Objectives: The objective is to select a patient-centered primary outcome measure for disease-modification trials over three or more years.

Methods: Experts in Parkinson's disease (PD), statistics, and health economics and patient and public involvement and engagement (PPIE) representatives reviewed and discussed potential outcome measures. A larger PPIE group provided input on their key considerations for such an endpoint. Feasibility, clinimetric properties, and relevance to patients were assessed and synthesized.

Results: Although initial considerations favored the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III in Off, feasibility, PPIE input, and clinimetric properties supported the MDS-UPDRS Part II. However, PPIE input also highlighted the importance of nonmotor symptoms, especially in the longer term, leading to the selection of the MDS-UPDRS Parts I + II sum score.

Conclusions: The MDS-UPDRS Parts I + II sum score was chosen as the primary outcome for large 3-year disease-modification trials. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: clinical trials; disease modification; endpoints; outcome measures; Parkinson disease; Patient and Public Involvement and Engagament (PPIE)

A key issue for disease-modifying trials in Parkinson's disease (PD) is the choice of the best primary outcome measure (OM) to demonstrate disease modification. Increasingly, importance is being given to input from people with PD (PwP) in drug development, supported

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The full Consortium list can be found in Supplementary Material 1.

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by regulators progressively putting outcomes meaningful to patients at its center.[1]

This paper describes the central role of PwP in selecting the primary OM for a multi-arm, multi-stage (MAMS) platform trial of disease-modifying therapies in manifest PD, as part of the Edmond J. Safra Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) initiative. An inventory of possible OM for such trials and a framework for future adaptation are reported elsewhere.[2]

Patients and Methods

A group of experts in fields related to OM in PD, including three people with lived experience of PD, reviewed the literature studies on OM in PD and specifically those used in trials of potential disease-modifying agents, and met nine times to discuss the appropriate OM. In addition, a group of 11 patient and public involvement and engagement (PPIE) representatives provided further feedback, thus enhancing the consideration of PwP's views. Each group member reviewed the literature in their area of expertise regarding suitability of a MAMS trial for disease-modification in PD and contributed to the overall discussions.

Given the required duration of such disease-modifying trials (3 years or more) and the expected large participant numbers (around 400 per treatment arm), key criteria to select the primary OM were functional relevance, validity, sensitivity to change, feasibility (eg, remote deliverability), acceptability to PwP, and compliance with requirements by regulators.

To understand PwP's priorities, we reviewed previous publications gathering views on the most relevant aspects of PD in the long term from PwP. We also surveyed our PPIE group about a list of symptoms, specifically asking "How important is this to PwP less/more than 5 years from diagnosis?", from 0 (not important) to 10 (extremely important). Symptoms were ranked according to median scores. We also gathered their views on the utility of each Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) subsection.

Results

The literature review revealed that most identified phase 2 and 3 disease-modifying trials in PD included parts of the MDS-UPDRS, its previous version (UPDRS), or measures derived from these (eg, axial sub-score) as their primary OM. The MDS-UPDRS has well-established clinimetric properties and has been shown to be reliable, valid, and sensitive to change in numerous PD trials. In addition, the MDS-UPDRS and UPDRS have been classified as "core" OM in PD trials by the National Institute of Neurological Disorders and Stroke Common Data Elements (NINDS-CDE) initiative (http://www.commondataelements.ninds.nih.gov/).[3,4] It assesses the spectrum of disease in PD most comprehensively, including motor and nonmotor symptoms and complications, and is partly patient-reported and partly clinician-assessed.[5,6] Our selection process was therefore focused on these measures. Among them, Part III (motor examination) during the *off* period showed a significant difference at 1 year in a phase 2 randomized controlled trial (RCT) not seen in Parts I, II, or III in *on*.[7] However, another phase 2 RCT reported improvement in the Non-Motor Symptoms Scale (NMSS) and the MDS-UPDRS Part II but not the MDS-UPDRS Part III in *off* at 1 year.[8]

Based on the excellent and extensive data on validity and sensitivity to change of MDS-UPDRS Parts II and III particularly in *off* in symptomatic treatment trials, and initial data from disease-modifying trials, the MDS-UPDRS Part II and Part III in *off* were considered the main candidates. Due to our MAMS trial requiring large sample sizes, the potential for Part II to be administered remotely was considered particularly advantageous. Nevertheless, only limited data are available on performance of Parts II and III over two or more years in disease-modifying trials,[9,10] when nonmotor features may gain relevance.[11–13]

Feedback from the PPIE Group

PPIE representatives highlighted the need for measures that (1) are patient-completed, (2) address issues most relevant to patients, (3) assess motor and nonmotor symptoms, and (4) are not restricted to early disease.

The general feedback on MDS-UPDRS Part III was that, unlike Part II, it does not adequately capture symptoms relevant to patients' daily lives, such as fatigue, pain, or sleep problems. Concerns were also raised about the predominance of tremor items in Part III and its inter-rater variability. Regarding the requirement of face-to-face assessments to administer Part III fully, some members found this inconvenient, whereas others saw it as beneficial extra care.

The PPIE members also disliked *off-medication* assessments as they can have undesirable physical consequences (ie, worsening of motor symptoms), and a negative psychological impact, derived from witnessing the current stage of the condition. Data comparing *on* and *off* MDS-UPDRS motor assessments are insufficient, and although some evidence suggests greater sensitivity to change of Part III in *off*,[7,14] this has been recently questioned,[15] especially because the "practical *off*" state (eg, after overnight withdrawal) only allows for a partial washout of levodopa (L-dopa) effects.[14] This strategy is even less effective in the case of drugs with longer half-life, such as dopamine agonists.[16] *Off*-assessments

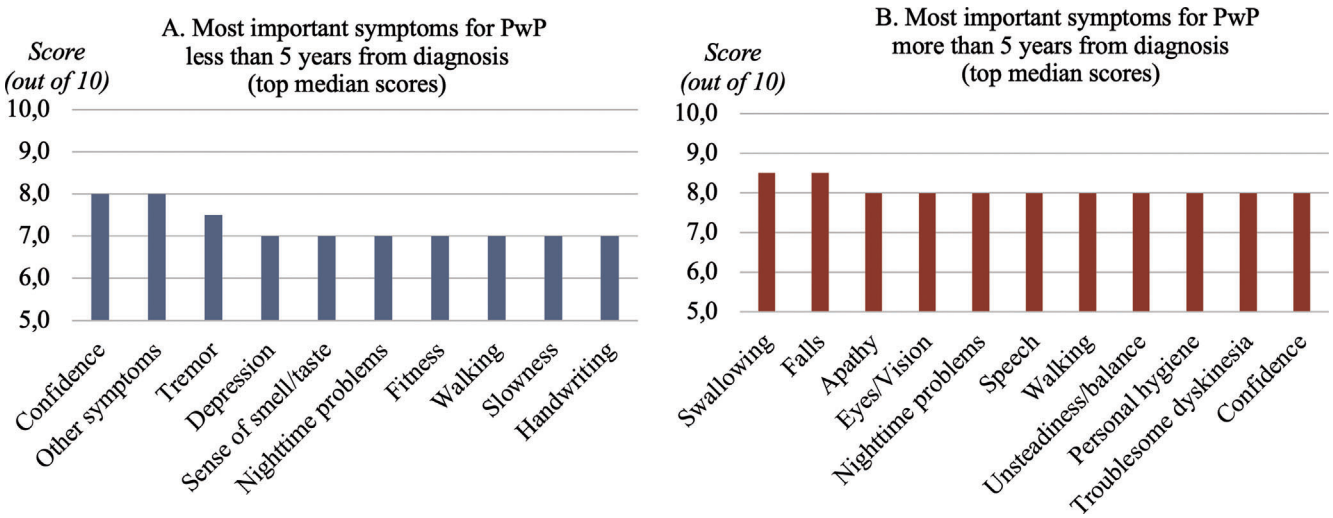

FIG 1. (**A, B**) Most important symptoms in our PPIE survey. Reported under "Other symptoms": "chronic nasal drip," "double vision," "hearing loss," "orthostatic hypotension leading to giddiness and fainting," "embarrassment of certain symptoms in public, such as tremors, drooling, etc." [Color figure can be viewed at wileyonlinelibrary.com]

reduce deliverability and are especially inconvenient for severely affected patients.[17] This all may impact retention, compromising its use as a primary OM.[18]

Consideration of the Most Relevant Symptoms According to PwP

In a Parkinson's UK 2020 survey of 790 PwP and care partners, nonmotor symptoms were present throughout the condition, with gait, speech, and medication-related problems gaining importance as PD progressed.[19] The top 10 most challenging symptoms in a 2018 EPDA/UCB survey among 2001 PwP and care partners were fatigue, sleep, gait, anxiety, depression, pain, bradykinesia, bladder/bowel function, thinking difficulties, and *wearing-off*.[20] A 2010 survey among 265 PwP divided into early (<6 years from symptom onset) and late (≥6 years) PD also revealed nonmotor symptoms and suboptimal response to medication to be the most troublesome aspects of PD as it progresses.[21] In our PPIE survey, the top 10 most important symptoms similarly were fatigue, pain, sleep, depression, apathy, gait/balance/falls, and speech/swallowing, with variation depending on disease duration. Figure 1 details the top-ranking symptoms. These results consistently show that nonmotor symptoms are rated among the most challenging, relevant, or a priority for improvement by PwP.

Based on the above, we reconsidered the choice of the primary OM to include a measure of nonmotor symptoms, specifically the MDS-UPDRS Part I. The MDS Non-Motor Symptoms Scale (MDS-NMS) was also considered but not deemed suitable as it only assesses nonmotor features, is long, requires clinician administration and, to our knowledge, there are no

TABLE 1 *Overview of features, strengths, and limitations of the considered primary outcome measures*

	MDS-UPDRS Part II	MDS-UPDRS Parts I + II sum score
Reflects features prioritized by PwP[18–20]	✓	✓✓
Assesses timeframe of past week (not just a snapshot)[6]	✓	✓
Includes nonmotor symptom assessment[6]	X	✓
Sensitive to change over 3 years[30]	✓	✓
Reflects features of long-term disease progression[12]	✓	✓✓
Deliverable remotely (ie, no need for face-to-face assessment)	✓	✓
Acceptable to regulators[35]	✓	?
Acceptable clinimetric properties[6,21,22,31]	✓	✓
Previous experience of use as a phase 3 efficacy measure	✓	X
Includes patient-reported items[6]	✓	✓✓

Abbreviations: MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PwP, People with Parkinson's.

clinimetric data on its combination with a different motor scale as a primary OM.

Advantages and Disadvantages of Different MDS-UPDRS Parts as Primary OM

Table 1 summarizes the strengths and limitations of the most relevant candidates for primary OM. MDS-UPDRS Part II was initially considered the best option for a ≥2-year disease-modifying trial, as it is patient-completed, addresses functionally relevant aspects of PD, and is responsive to change. Nevertheless, PPIE input prompted reconsideration of MDS-UPDRS Parts I + II sum score as the primary OM. To our knowledge, there is no previous experience with this combination as a primary endpoint in phase 3 PD trials, which may limit its acceptability to regulators. However, it comprises motor and nonmotor features, including milestones; addresses the top symptoms flagged by our PPIE group; is mostly patient-completed; can be administered remotely; and has reported validity.[22]

Discussion

The MDS-UPDRS Part II is a functionally and clinically relevant patient-reported OM (PROM) with acceptable validity and sensitivity to change.[6,23,24] Although the MDS-UPDRS Part III has been reported as more sensitive to difference between treatment arms in a recent phase 2 disease-modification RCT at 1 year,[7] and was the most sensitive measure of change in a recent 1-year disease-modification trial in early PD,[25] Part II has greater content validity as a meaningful functional OM. It has recently been recommended in systematic reviews of disability[26] and functional mobility[27] measures, and an algorithm derived from it can define functional dependency.[28] The combined emergence of patient-reported symptoms in MDS-UPDRS Parts IB and II has also shown promise as a sensitive endpoint.[29]

MDS-UPDRS Part I measures nonmotor symptoms and their functional impact, some of the most disabling long-term problems in PD,[12] but it is less sensitive to change than Parts II or III in the short term.[7] Although Parts II and III have been reported to have limitations in early PD,[30] both Parts I and II have been shown to be sensitive to disease progression over the first decade of the PD,[31] and their sum score has been shown to be a valid[21] and applicable endpoint.[32] Limited current evidence suggests that this combination is the most tightly related to health-related quality of life (HR-QoL) measures.[33] Its main caveats are the lack of experience of its use as an endpoint and its potentially complex interpretability (ie, if significant change is seen in only one part).

Despite its broad experience of use, MDS-UPDRS Part III omits nonmotor symptoms, is affected by dopaminergic medication, and is clinician-reported. The scale developers recommended avoiding summation with other parts,[6] which has been confirmed recently.[34] Moreover, the requirement of face-to-face assessments for its full administration can impact participant retention. Although sensitive in the shorter term (1 year),[7,25] long-term PD progression is dominated by L-dopa-resistant and nonmotor symptoms,[11,12,35] which may deem Part III unsuitable for longer duration trials. Lastly, regulatory input increasingly favors PROMs and endpoints relevant to patients, which is the case for the MDS-UPDRS Parts I and II.[36] Although we could not find direct data on sensitivity to change over time of MDS-UPDRS Parts I + II in the literature, it has been described as an applicable outcome measure with available minimal clinically important difference (MCID) thresholds,[32] already exceeded in previous studies.[37] Furthermore, results of some studies in abstract form have favored Part II over III.[38,39]

The selection of the primary OM is critical for the success of disease-modifying PD trials. Particularly for longer-duration trials this requires a compromise between acceptable clinimetric properties, responsiveness over an adequate time period, ability to capture meaningful change, and avoidance of undue burden on participants. The sum of MDS-UPDRS Parts I + II represents a relevant, patient-reported, acceptable, valid, and deliverable endpoint for a large, long-term trial; is based on PPIE preferences; has promise for capturing change; and reflects relevant features of PD progression including nonmotor symptoms. Moreover, it represents a good compromise between the implementation of PROMs,[40,41] and the use of a scale with wide experience as an endpoint in clinical trials. ■

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Additional Statement

Data Availability Statement

Data sharing is not applicable.

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APPENDIX

Additional EJS ACT-PD consortium members (further details are provided in the Supplementary material): Roger Barker, James Carpenter, Yoav Ben Shlomo, Mark Edwards, Alan Whone, Carl Counsell, Dorothy Salathiel, Sue Whipps, Anna Jewell, Priti Gros, Tom Barber, K. Ray Chaudhuri, Anthony H.V. Schapira, Oliver Bandmann, Simon Stott, George Tofaris, Esther Sammler, Heather Mortiboys, Li Wei, Alan Wong, Susan Duty, David Dexter, Paula Scurfield, Keith Martin, Edwin Jabbari, Stephen Mullin, Huw Morris, David Breen, Christian Lambert, Prasad Korlipara, Monty Silverdale, Kailash Bhatia, Alison Yarnall, Raj Khengar, Helen Collins, Fleur Hudson, Gareth Baxendale, Rebecca Croucher, Sandra Bartolomeu-Pires, Jennifer Allison, Jodie Forbes, Alex Edwards, Sheila Wonnacott, Dilan Athauda, Joy Duffen, Sonia Gandhi, Emily Henderson, Maryanne Graham, Shona Clegg, Karen Matthews, Vince Greaves, Eric Deeson, Laurel Miller, Joel Handley, David Dexter, Helen Matthews, Kevin McFarthing, Amit Batla, Nikul Bashi, Emma Lane, Miriam Parry, Natasha Ratcliffe, Georgia Mills, Romy Ellis-Doyle, Sally L. Collins, Rebecca Chapman, Jesse Cedarbaum, Anthony Lang, Brian Fiske, Richard Wyse, Mahesh Parmar, Adam Boxer, Denise Wilson, Jean Christophe Corvol, Jennifer Harris.

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NeuHealth Digital Ltd (company number: 14492037), a digital biomarker platform to remotely manage condition progression for Parkinson's. M.T.H. is a co-applicant on a patent application related to smartphone predictions in Parkinson's (PCT/GB2019/052522) pending. B.H. has no conflict of interest nor funding information to report. A.J. has been involved in the development and clinical assessment of a smartphone-based tool for Parkinson's disease (cloudUPDRS). A.J. has received support to attend scientific conferences from Merz and Britannia and fees from Sanofi/Genzyme, and Novartis. A.J. is currently funded by the Wellcome Trust and the National Institute of Health Research University College London Hospitals Biomedical Research Centre. M.L. received fees for advising on a secondary analysis of a Parkinson's RCT (GDNF) sponsored by North Bristol NHS trust. 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