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Gonzalez-Robles, C; Bartlett, Michèle; Burnell, Matthew; Clarke, Caroline S.; Haar, Shlomi; Hu, Michele T.; Huxford, Brook; Jha, Ashwani; Lawton, Michael; Noyce, Alastair; Piccini, Paola; Pushparatnam, Kuhan; Rochester, Lynn; Siu, Carroll; van, Wamelen D; Williams-Gray, CH; Zeissler, Marie Louise; Zetterberg, Henrik; Carroll, Camille B.; Foltynie, Thomas; Weil, Rimona S.; Schrag, Anette

Published in:
Movement Disorders

DOI:
[10.1002/mds.29691](https://doi.org/10.1002/mds.29691)

Publication date:
2023

Link:
[Link to publication in PEARL](#)

Citation for published version (APA):

Gonzalez-Robles, C., Bartlett, M., Burnell, M., Clarke, C. S., Haar, S., Hu, M. T., Huxford, B., Jha, A., Lawton, M., Noyce, A., Piccini, P., Pushparatnam, K., Rochester, L., Siu, C., van, W. D., Williams-Gray, CH., Zeissler, M. L., Zetterberg, H., Carroll, C. B., ... Schrag, A. (2023). Embedding Patient Input in Outcome Measures for Long-Term Disease-Modifying Parkinson Disease Trials. *Movement Disorders*, 0(0). <https://doi.org/10.1002/mds.29691>

BRIEF REPORT

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

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

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Funding agency: This work was done as part of the Edmond J. Safra Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) Initiative, which is funded by the Edmond J. Safra Foundation.

Received: 22 June 2023; **Revised:** 30 October 2023; **Accepted:** 30 November 2023

Published online in Wiley Online Library ([wileyonlinelibrary.com](https://www.wileyonlinelibrary.com)). DOI: 10.1002/mds.29691

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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 Engagement (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

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

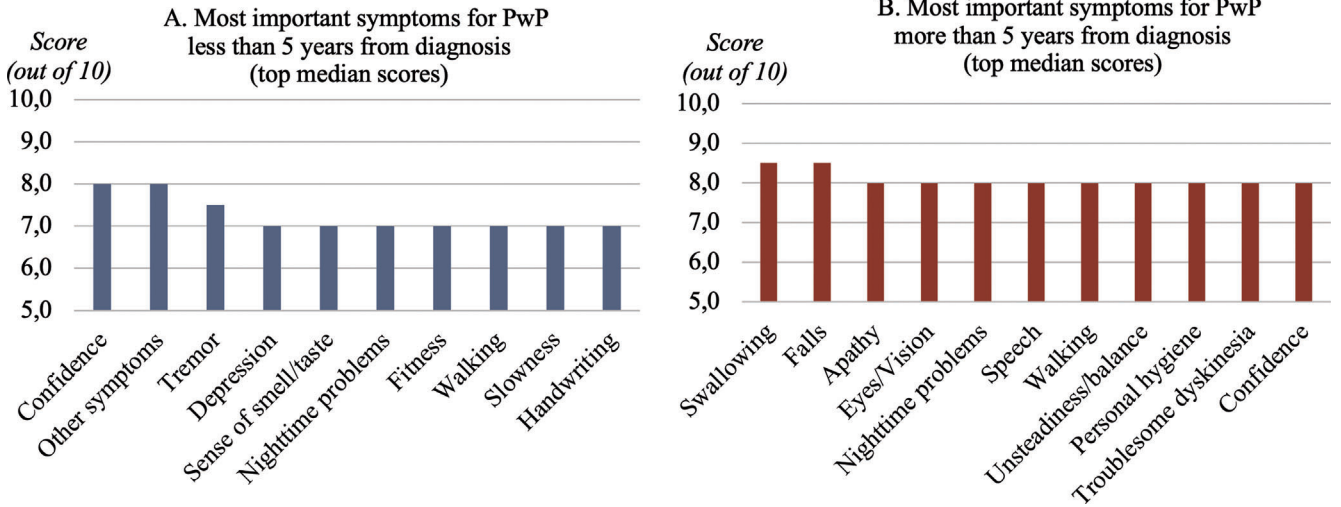


FIG 1. (A, B) Most important symptoms in our PPIE survey. Reported under “Other symptoms”: “chronic nasal drip,” “double vision,” “hearing loss,” “orthostatic hypotension leading to giddiness and fainting,” “embarrassment of certain symptoms in public, such as tremors, drooling, etc.” [Color figure can 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 disability²⁶ and functional mobility²⁷ 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 valid²¹ 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. ■

Acknowledgments: We sincerely thank the PPIE members in EJS ACT-PD for their invaluable contribution to this work.

Additional Statement

For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) license to any author accepted manuscript version arising from this submission.

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.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Statistical analysis: A. Design, B. Execution, C. Review and critique. (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

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A.S.: 1A, 1B, 1C, 3B.

Financial Disclosures

C.G.R. has no conflict of interest to report and has received research support from the Edmond J. Safra (EJS) Foundation (EJS Accelerating Clinical Trials in Parkinson's Disease [EJS ACT-PD] project). M.B. is appointed to a Patient Council for UCB on shaping a phase II clinical trial and will receive an honorarium for this role. M. Bu. has received research support from the Edmond J. Safra (EJS) Foundation (EJS Accelerating Clinical Trials in Parkinson's Disease [EJS ACT-PD] project) and has no conflict of interest to report. C.S.C has no conflict of interest to report and reports grant funding from National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) (ref. 15/59/17); NIHR HTA (ref. 128699); NIHR Programme Grants for Applied Research (PGfAR) (ref. NIHR201608); NIHR PGfAR (RP-PG-0614-20011); NIHR Health and Social Care Delivery Research (HSDR) (ref. NIHR130693); NIHR Research for Patient Benefit (RfPB) (ref. PB-PG-0418-20006); NIHR RfPB (ref. NIHR201934); NIHR RfPB (PB-PG-1216-20042); NIHR Biomedical Research Centre Moorfields Eye Hospital (NIHR Default Scheme); NIHR Evidence Synthesis Groups Commissioning Committee, call: 22/5 ESP Evidence Synthesis Groups 2023–2028 (ref. NIHR153783); Asthma + Lung UK Mesothelioma Clinical Trials Award (ref. MCTA22F\7); JP Moulton; European Association of Urology Research Foundation, National Cancer Imaging Translational Accelerator, The John Black Charitable Foundation, The Deickmann Foundation; SBRI (Small Business Research Initiative) Healthcare Cancer Programme. S.H. has no conflict of interest to report and is supported by the Edmond and Lily Safra Fellowship and the UK Dementia Research Institute Care Research & Technology Centre. M.T.H. has received consultancy fees from Lundbeck, CuraSen Therapeutics, Evidera, and Manus Neurodynamica. M.T.H. received payment for advisory board attendance/consultancy for Lundbeck, ESCAPE Bio, Evidera, Manus Neurodynamica, Biogen MA, CuraSen Therapeutics, Roche Products Ltd. M.T.H. is an advisory founder of

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. M.L. is core funded by the University of Bristol and reports grants from Parkinson's UK and the National Institute for Health and Care Research. A.N. has been involved in the development of the Bradykinesia-Akinesia Incoordination (BRAIN) test. A.N. reports grants from Parkinson's UK, Barts Charity, Cure Parkinson's, National Institute for Health and Care Research, Innovate UK, Virginia Keiley benefaction, Solvemed, the Medical College of Saint Bartholomew's Hospital Trust, Alchemab, Aligning Science Across Parkinson's Global Parkinson's Genetics Program (ASAP-GP2), and The Michael J. Fox Foundation. A.N. reports consultancy and personal fees from AstraZeneca, AbbVie, Profile, Roche, Biogen, UCB, Bial, Charco Neurotech, uMedeor, Alchemab, Sosei Heptares, and Britannia, outside the submitted work. A.N. is an associate editor for the *Journal of Parkinson's Disease*. P.P. has no conflict of interest to report and reports grants from Parkinson's UK, Michael J. Fox Foundation (US), Medical Research Council, CHDI foundation, Agencie Nationale de la Recherche (France), Joint Programming Neurodegenerative Disease Research (Germany), Research Council of Norway, TEVA Pharmaceutical Ltd, and EUROPEAN COMMISSION Theme "Health" (FP7-program). K.P. has no conflict of interest to report and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. L.R. has no conflict of interest to report. L.R. receives funding from The Michael J. Fox Foundation for serving on its executive board. L.R. receives research funding from The Michael J. Fox Foundation, PDUK, MRC, NIHR, Dunhill Medical Foundation and from the EU. C.S. has no conflict of interest to report and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. D.V.W. reports consultancy and speaker fees from Bial and Britannia. C.H.W.G. has no conflicts of interest relating to the work in the manuscript. C.H.W.G. has received grant funding from the Medical Research Council (MR/W029235/1), Cure Parkinson's, Parkinson's UK, and the Rosetrees Trust, and is supported by the Cambridge Centre for Parkinson-Plus and the NIHR Cambridge Biomedical Research Centre (NIHR203312). C.H.W.G. has received consultancy payments from Evidera. M.-L.Z. has received research support from the Edmond J. Safra (EJS) Foundation (EJS Accelerating Clinical Trials in Parkinson's Disease [EJS ACT-PD] project) and has no conflict of interest to report. H.Z. has served at scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018), the European Union's Horizon Europe research and innovation program under grant agreement no.: 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärtfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement no.: 860197 (MIRIADE), the European Union Joint Programme—Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). C.B.C has received honoraria from Bial, GKC, AbbVie, Kyowa Kirin, Lundbeck, Britannia, and Medscape. She has received service grants from AbbVie and Bial, and research grants from Parkinson's UK, Cure Parkinson's, National Institute for Health Research, and the Edmond J. Safra Foundation. She receives salary from Newcastle University, University of Plymouth, University Hospitals Plymouth National Health Service Trust, Parkinson's UK, and National Institute of Health and Care Research. She is a Cure Parkinson's Linked Clinical Trials (LCT) committee member, a Cure Parkinson's Research Committee member, and a Parkinson's UK College of Experts Panel member. T.F. has received grants from National Institute of Health Research, Edmond J. Safra Foundation, Michael J. Fox Foundation, John Black Charitable Foundation, Cure Parkinson's Trust, Innovate UK, Janet Owens Research Fellowship, Rosetrees Trust, Van Andel Research Institute, and Defeat MSA. T.F. has served on advisory boards for Pepton, Voyager Therapeutics, Handl Therapeutics, Gain Therapeutics, Living Cell Technologies, AbbVie, Bluerock, Bayer & Bial. T.F. has received honoraria for talks sponsored by Bial, Profile Pharma, Boston Scientific & Novo Nordisk. R.S.W. has received speaking honoraria from GE Healthcare and

writing honoraria from Britannia. R.S.W. has received fees for consulting for Therakind. R.S.W. is supported by the Wellcome Trust: 205167/Z/16/Z and from the National Institute of Health Research Biomedical Research Centre. R.S.W. has also received support from the British Medical Association Vera Down Award and from the Rosetrees and Stoneygate Trusts. A.S. has received research funding or support from University College London, National Institute of Health (NIHR), National Institute for Health Research ULCH Biomedical Research Centre, the International Parkinson and Movement Disorder Society (IPMDS), the European Commission, Parkinson's UK, GE Healthcare, and the Economic and Social Research Council. A.S. is a member of the MDS-UPDRS Development Group, the MDS-NMS Development Group, the NINDS CDE QoL Group, the MDS Rating Scales Review Committee, and the MDS COA Early and Prodromal PD Working Group. A.S. has been involved in the development of the MDS-UPDRS, the MDS-NMS, and the PQoL. A.S. reports consultancy fees from Biogen, AbbVie, Roche, Bial, and GE Healthcare; license fees from University College London; and royalties from Oxford University Press.