# The Parkinson disease e-Diary: Developing a Clinical and Research Tool for the Digital Age

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<td>Complete List of Authors:</td>
<td>Vizcarra, Joaquin Sanchez-Ferro, Alvaro; HM-CINAC, Neurology; Massachusetts Institute of Technology, Research Laboratory of Electronics Maetzler, Walter; Christian-Albrechts-Universitat zu Kiel Medizinische Fakultat, Dept. of Neurology Marsili, Luca Zavala, Lucia Lang, Anthony; Toronto Western Hospital, Martinez-Martin, Pablo; National Center of Epidemiology and CIBERNED, Carlos III Institute of Health Mestre, Tiago; The Ottawa Hospital Research Institute, University of Ottawa, Parkinson's Disease and Movement Disorders Clinic, Division of Neurology, Department of Medicine; Reilmann, Ralf; George-Huntington-Institute, Neurology Hausdorff, Jeffrey; Tel Aviv Sourasky Medical Center, Department of Neurology; Tel Aviv University, Dorsey, E; University of Rochester, Neurology Paul, Serene Dexheimer, Judith Wissel, Benjamin; University of Cincinnati, Movement Disorders Division Fuller, Rebecca Bonato, Paolo; Harvard School, Physical Medicine and Rehabilitation Tan, Ai Huey; University of Malaya, Neurology Bloem, Bastiaan Kopil, Catherine; The Michael J. Fox Foundation for Parkinson's Research Daeschler, Margaret Bataille, Lauren Kleiner, Galit; University of Toronto Cedarbaum, Jesse; Research &amp; Early Development; Klucken, Jochen; University Hospital Erlangen, Department of Molecular Neurology Merola, Aristide; University of Cincinnati, Gardner Family Center for Parkinson’s Disease and Movement Disorders, Department of Neurology Goetz, Christopher; Rush University Medical Center, Department of Neurological Sciences Stebbins, Glenn; Rush University Medical Center, Neurological Sciences Espay, Alberto; University of Cincinnati, Neurology</td>
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Viewpoint

The Parkinson disease e-Diary: Developing a Clinical and Research Tool for the Digital Age

Joaquin A. Vizcarra, MD;1 Álvaro Sánchez-Ferro, MD, PhD;2 Walter Maetzler, MD;3 Luca Marsili, MD, PhD;1 Lucia Zavala, MD;4 Anthony E. Lang, MD, FRCPC;5 Pablo Martinez-Martin, MD, PhD;6 Tiago A. Mestre, MD, MSc;7 Ralf Reilmann, MD;8 Jeffrey M. Hausdorff, PhD;9 E. Ray Dorsey, MD, MBA;10 Serene S. Paul, PhD;11 Judith W. Dexheimer, PhD;12 Benjamin D. Wissel, BS;1 Rebecca L. M. Fuller, PhD;13 Paolo Bonato, PhD;14 Ai Huey Tan, MD, MRCP;15 Bastiaan R. Bloem, MD, PhD;16 Catherine Kopil, PhD;17 Margaret Daeschler, BA;17 Lauren Bataille, MS;17 Galit Kleiner, MD, FRCPC;18 Jesse M. Cedarbaum, MD;19 Jochen Klucken, MD;20 Aristide Merola, MD, PhD;1 Christopher G. Goetz, MD;21 Glenn T. Stebbins, PhD;21 Alberto J. Espay, MD, MSc,1 On behalf of the MDS Technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee.

1 Gardner Family Center for Parkinson’s Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA

2 HM CINAC, Hospital Universitario HM Puerta del Sur, Móstoles, Madrid, Spain.

3 Department of Neurology, University of Kiel, Kiel, Germany

4 Hospital General de Agudos Jose Maria Ramos Mejia, Departamento de Neurología, Universidad de Buenos Aires, Buenos Aires, Argentina

5 The Edmond J. Safra Program in Parkinson’s Disease and the Morton and Gloria Shulman Movement Disorders Clinic, University of Toronto, Toronto, Canada
6 National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain
7 Parkinson’s Disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, Canada
8 George Huntington Institute and Dept. of Clinical Radiology, University of Muenster, Muenster and Dept. of Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany
9 Center for the Study of Movement, Cognition, and Mobility, Tel Aviv Sourasky Medical Center; Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Israel; Rush Alzheimer’s Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, Illinois, USA
10 Department of Neurology and Center for Health + Technology, University of Rochester Medical Center, Rochester, New York, USA
11 Discipline of Physiotherapy, Faculty of Health Sciences, University of Sydney, Sydney, Australia
12 Department of Biomedical Informatics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
13 CHDI Foundation/ CHDI Management, Inc., Princeton, New Jersey, USA
14 Department of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Charlestown, Massachusetts, USA
15 Division of Neurology and the Mah Pooi Soo & Tan Chin Nam Centre for Parkinson's & Related Disorders, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.
16 Radboud University Medical Center; Donders Institute for Brain, Cognition and Behaviour; department of neurology; Nijmegen; the Netherlands

17 The Michael J Fox Foundation for Parkinson’s Research, New York, New York

18 Jeff and Diane Ross Movement Disorders Clinic at ATC/Baycrest Health Sciences, Division of Neurology Department of Medicine University of Toronto, Canada.

19 Biogen, Cambridge, MA, USA

20 Department of Molecular Neurology, Movement Disorder Unit, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

21 Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

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Corresponding Author: Dr. Alberto J Espay. Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA Tel: +1 (513)558-4035

E-mail: alberto.espay@uc.edu

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INTRODUCTION

As a consequence of limitations in current pharmacotherapy, the symptoms of patients with Parkinson’s disease (PD) may fluctuate throughout the day, impacting functional ability and quality of life. A diary has been the most common method for assessing fluctuations of symptoms in research settings. Diaries enable patients to monitor daily symptoms at specified intervals and report their severity, frequency, and duration for a limited repertoire of predominantly motor symptoms dichotomized into “ON” (defined variably as “good” response to dopaminergic treatment) or “OFF” (poor response to dopaminergic treatment) states. Prioritizing simplicity, most diaries consider dyskinesia exclusively as “ON” state phenomena, and divide them into whether they interfere with overall function (“troublesome”) or not (“non-troublesome”). Emphasis on the development of treatments designed to “reduce OFF” or “increase ON” time has limited attention to common intermediate, transitional, and non-motor states that may not squarely fall into one of these two states.

Current gaps in PD diaries and strategies to address them in an e-Diary

PD diaries have provided valuable information often as primary endpoints in clinical trials of symptomatic therapies over the past 20 years. Two diaries (Parkinson Disease Home Diary and CAPSIT-PD Diary) have been designated as “Recommended” by the MDS Task Force on Rating Scales. These two diaries, nonetheless, have the caveat that limited data exist regarding their validity, compliance, and completion, and their assessment is implicitly linked to the presence of motor fluctuations. A systematic literature search found total of 12 published PD diaries, for which a narrative review (Supplementary material 1) and quality criteria (Supplementary material 2) are available online. The
phenomenological, contextual, and clinimetric gaps identified in existing diaries as well as the potential strategies to correct them are listed in Table 1.

In recent years, the advent of new technologies has introduced the opportunity to redesign this diary tool. Current diaries are almost exclusively designed in paper format (or in an electronic format that resembles paper diaries). Newer digital methods should enable the capture of a wider range of individualized motor, non-motor, and circadian complex fluctuations with greater accuracy as an electronic diary/tracker interface (e-Diary). With the aim of bringing the PD diary into the digital age, the MDS Technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee elaborated a set of desirable characteristics and developmental steps for a technology-enhanced e-Diary, usable in both clinical practice and treatment trials. At the request of Movement Disorders editors, a draft of this manuscript was made available on the MDS website (movementdisorders.org/MDS/Resources/2018/PD-Diary.htm) to facilitate public comments on the proposed roadmap between October 7 and November 7, 2018. The MDS Secretariat sent an email invitation to MDS members and two reminders within that time frame. Supplementary material 3 contains a summary of the feedback, highlighting the suggestions that prompted changes into the final document contained in this manuscript.

**Desirable characteristics of a PD e-Diary**

1. **Phenomena recognition.** A diary must focus on capturing key symptoms and signs that correlate with clinically pertinent fluctuations in motor and non-motor function. Two archetypal states have been defined in research settings, anchored on motor fluctuations (MF) but adaptable also to non-motor fluctuations (NMF): “OFF”, the clinical condition
reflective of no treatment effect, and “ON”, associated with full and effective treatment. However, patients often experience partial, transitional, or “gray-zone” states throughout the day that cannot be dichotomized into full ON or OFF states. Further, dyskinetic and dystonic behaviors can develop during ON, OFF, and transitional states, so that diaries that restrict them as subcategories of ON are conceptually and operationally inadequate.

Another important metric with direct implications in therapeutic decisions is functional status, which can vary independently of the duration and severity of fluctuations. Finally, because the biological, pharmacological and clinical relationships between MF and NMF have not been clarified, an ideal diary tool should not implicitly link them and must allow for independent registration of different symptoms.

2. Patient language. If the terms “OFF” and “ON” are to be used, definitions must be clearly outlined. The definitions should incorporate both motor and non-motor symptoms. Testing patients’ understanding of definitions must be conducted during the development phases to ensure adequacy of language, content, and health literacy. This practice can lead to the modification of items to increase the precision of self-reported measures. Video-based training sessions and standardized instructions can be developed for ensuring validation. Following these steps should render the final diary intuitive to patients, minimizing the need for additional training in subsequent clinical or research uses.

3. Administration and data collection. The adequate frequency or duration of recording needed to capture MF and NMF, in order to define a baseline pattern and to evaluate treatment response, is still unknown. Regardless, frequency of assessments and method of state determination (averaged over a period of time or in real-time) must be tailored to
Clinical or research settings. Current diaries predominantly use the “averaged over a period of time” method. Even with these efforts, however, studies using similar instructions stress the “peak-end rule” that dominates human behavior, judging an epoch for its worst or best point or its state at the moment of the assessment. Such averaging can be cognitively challenging and may increase measurement errors and recall bias, even in the absence of cognitive impairment. Compliance of data recording and frequency of missing or erroneous data collection must be recorded. Accurate sleep and wakefulness detection is necessary. Medication—and possibly meal—intake tracking is required to recognize their influence on MF and NMF. One advance of electronic methods is that alerts and interactive involvement may enhance valid data collection. Finally, data should be protected and kept confidential.

4. Diary format and data visualization. An accessible interface would ideally include visual results and feedback to the patient in the form of percent completed and progress reports, independently tailored for clinical care and research settings. Visualization of the evolution of fluctuations over time could be an added value of such e-Diary. An inviting interface, such as currently applied by wearable fitness technologies and exercise devices, may serve to stimulate long-term compliance with an e-Diary. Flexibility in this capacity (on-off switch for “shared feedback”) could help adaptability for research and clinical settings.

5. Data and clinimetric properties. Desirable measurement formats include active (requiring input by patients, e.g., questions or tasks) and passive data collection (not requiring input by patients). Visual analog scales (VAS) are ideal to use for non-dichotomous questions in active data collection, can be used by patients with cognitive
impairment, and are very sensitive to small intrapersonal changes. Wearable sensors (see below) may be ideal for passive MF and NMF assessments. Regardless of the methods employed, understanding the instruments’ clinimetric properties is important. Validation methods may include internal consistency (Cronbach’s alpha), construct validity (convergent, divergent, known groups), patient-clinician agreement, predictive validity calculations, cross-cultural validation, and factor analyses, among other methods. Reliability assessments with test-retest calculations are acceptable, but not desirable as a sole method due to the fluctuating nature of the latent variables. Above all, demonstration of how patients feel or function is of utmost importance in defining utility and relevance.

6. Technology-based objective measures. An e-Diary/tracker would allow tools such as surveys and VAS to be administered regardless of time or place. Advanced hardware components, such as accelerometers, gyroscopes, microphones, radio signals, among other wearable sensors, can provide complementary action-dependent and action-independent objective measures. Active data collection should be tailored for motor and non-motor symptoms. Examples for motor symptoms include spiral drawing, finger tapping, and voice characteristics; for non-motor symptoms, assessments of visual performance and short-term memory. Passive measures should be obtained in an unsupervised and unobtrusive fashion, recorded preferentially during patients’ daily regular activities. One hope is that passive tracking should, in the future, capture a subset of relevant MF and NMF. Smartphones, increasingly being used across all age groups, are ideally suited for the e-Diary development, allowing for an ever-present yet unobtrusive and ecologically valid data collection. Challenges related to the technological development include the costs associated with software and hardware development and maintenance, patient/health
provider interface configuration, and regulatory difficulties with data storage, confidentiality, and management. Challenges related to usability, on the other hand, include possible issues of long-term compliance with active measures and the requirement to navigate an application, which might be difficult in the setting of motor disability or poor literacy of digital health technologies. Incorporation of artificial intelligence methods would be expected to minimize the need for active measures as “learning” from their initial integration into passive data serves to eventually “predict”, in their absence, the patient-relevant motor, non-motor, and functional states.

Next steps: milestones for the development of the PD e-Diary

We propose a development plan to construct an e-Diary that harnesses the complementary role of diaries (e.g., assessments of data meaningfulness based on patient feedback) and wearable sensors (e.g., continuous, objective measures, independent from patient feedback). The scope and features of an e-Diary/tracker will require tight collaboration in all developmental phases between all stakeholders, including clinicians, technology developers, regulatory experts, scientists from industry, caregivers, patient advocacy groups, and especially patients. This tool development may benefit from guidelines from the Food and Drug Administration, the Clinical Trials Transformation Initiative, and the Electronic Patient-Reported Outcome Consortium, among others. The new e-Diary should be built on an open-access data management concept, preferentially with the endorsement of the International Parkinson and Movement Disorders Society to standardize the mechanism for technology developers to gain regulatory approval, assist in improvements of the instrument over time, and contribute to its wide acceptance and adherence. Here, we outline the specific developmental milestones suggested by consensus.
• **First milestone: minimal viable product.** A fully functional “minimal viable product” would consist of a wireless-enabled, secured, web-based e-Diary of patient-reported outcomes. The elements to be considered for this first step will require the prioritization of patient-relevant outcomes, as outlined in a parallel ongoing effort by the MDS Task Force on Technology. Optimization of existing data-capturing methods and technologies could facilitate the assessment of partial medication states, NMF reporting, medication tracking, and functional assessments. Some existing instruments (e.g., NMSQuest, NoMoFa, Wearing-Off Questionnaire) and PROMIS® (Patient-Reported Outcomes Measurement Information System) could assist this process by providing relevant items to the construction of the e-Diary. Verification and validation processes should start at this step and continue throughout the development.

• **Second milestone: integration of action-dependent metrics.** Selection of hardware components (e.g., accelerometers, gyroscopes, microphones, among others) and development of software will be tailored to acquire action-dependent data. Individualized assessments for motor (e.g., spiral drawing, finger tapping) and non-motor symptoms (e.g., visual performance, memory) could be selected according to patient-reported relevance and feasibility.

• **Third milestone: incorporation of action-independent metrics.** Hardware components selected in previous steps, potentially including available wearable
devices, could be optimized for passive data gathering, enabling the “tracker” functionality.

- **Fourth milestone: algorithm development, improvement and simplification.** A desired final step will be the analysis and integration of diary data and the active and passive recordings with hypothesis-driven and machine learning algorithms. Such algorithms must control for the state and setting in which patients enter action-dependent measures into the diary (for instance, dyskinesia might be interpreted differently in a patient with versus without anxiety, the former possibly magnifying its severity). The endpoint is the transformation of patient data into individualized current and predictive feedback to patients themselves, providers, and caregivers for both self-guided behavioral changes and facilitation of personalized management decisions by clinicians.

The feasibility of an e-Diary has been demonstrated by recent smartphone-based “rating scores”. A recently introduced mobile application combines active and passive data gathering,\(^\text{40}\) while another mobile application uses active-only data.\(^\text{25}\) In both cases, data were processed with machine-learning algorithms, yielding adequate reliability and validity metrics.\(^\text{25,40}\) Major unknown variables include the heterogeneity of PD and the extent to which integration of an e-Diary, daily or intermittently, is capable of enhancing patient empowerment for long-term sustainability. Further, the use of a new tool will be different if applied in clinical research (limited time) or “in real life” both for patients and, through a separate interface, for their caregivers.
Conclusions

The highly dynamic and user-friendly technological advances of recent years enable the development and validation of an accepted e-Diary/tracker that simultaneously assesses MF and NMF and utilizes action-dependent and action-independent endpoints for clinical management and research efforts. An e-Diary can be patient-friendly and intuitive as well as capable of providing real-time feedback to the patient (empowered to influence any state) and clinician in order to ensure widespread use and long-term adherence. The time has come to move beyond the simplistic dualism of “ON” and “OFF” states of paper diaries and reconfigure this important source of clinical information for care and research.

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Dr. Reilmann is founding director and owner of the George-Huntington-Institute, a private research institute focused on clinical and preclinical research in Huntington’s disease, and QuantMedis, a clinical research organization providing Q-Motor (quantitative motor) services in clinical trials and research. He provided consulting services, advisory board functions, clinical trial services, quantitative motor analyses, and/or lectures for Teva, Pfizer, uniQure, Ipsen, Vaccinex, WAVE, Novartis, Raptor, Omeros, Siena Biotech,
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Viewpoint

The Parkinson disease e-Diary: Developing a Clinical and Research Tool for the Digital Age

Joaquin A. Vizcarra, MD;1 Álvaro Sánchez-Ferro, MD, PhD;2 Walter Maetzler, MD;3 Luca Marsili, MD, PhD;1 Lucia Zavala, MD;4 Anthony E. Lang, MD, FRCPC;5 Pablo Martínez-Martin, MD, PhD;6 Tiago A. Mestre, MD, MSc;7 Ralf Reilmann, MD;8 Jeffrey M. Hausdorff, PhD;9 E. Ray Dorsey, MD, MBA;10 Serene S. Paul, PhD;11 Judith W. Dexheimer, PhD;12 Benjamin D. Wissel, BS;1 Rebecca L. M. Fuller, PhD;13 Paolo Bonato, PhD;14 Ai Huey Tan, MD, MRCP;15 Bastiaan R. Bloem, MD, PhD;16 Catherine Kopil, PhD;17 Margaret Daeschler, BA;17 Lauren Bataille, MS;17 Galit Kleiner, MD, FRCPC;18 Jesse M. Cedarbaum, MD;19 Jochen Klucken, MD;20 Aristide Merola, MD, PhD;1 Christopher G. Goetz, MD;21 Glenn T. Stebbins, PhD;21 Alberto J. Espay, MD, MSc;1 On behalf of the MDS Technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee.

1 Gardner Family Center for Parkinson’s Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA
2 HM CINAC, Hospital Universitario HM Puerta del Sur, Móstoles, Madrid, Spain.
3 Department of Neurology, University of Kiel, Kiel, Germany
4 Hospital General de Agudos Jose Maria Ramos Mejia, Departamento de Neurología, Universidad de Buenos Aires, Buenos Aires, Argentina
5 The Edmond J. Safra Program in Parkinson’s Disease and the Morton and Gloria Shulman Movement Disorders Clinic, University of Toronto, Toronto, Canada
6 National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain
7 Parkinson’s Disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, Canada
8 George Huntington Institute and Dept. of Clinical Radiology, University of Muenster, Muenster and Dept. of Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany
9 Center for the Study of Movement, Cognition, and Mobility, Tel Aviv Sourasky Medical Center; Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Israel; Rush Alzheimer’s Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, Illinois, USA
10 Department of Neurology and Center for Health + Technology, University of Rochester Medical Center, Rochester, New York, USA
11 Discipline of Physiotherapy, Faculty of Health Sciences, University of Sydney, Sydney, Australia
12 Department of Biomedical Informatics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
13 CHDI Foundation/ CHDI Management, Inc., Princeton, New Jersey, USA
14 Department of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Charlestown, Massachusetts, USA
15 Division of Neurology and the Mah Pooi Soo & Tan Chin Nam Centre for Parkinson's & Related Disorders, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.
Radboud University Medical Center; Donders Institute for Brain, Cognition and Behaviour; department of neurology; Nijmegen; the Netherlands

The Michael J Fox Foundation for Parkinson’s Research, New York, New York

Jeff and Diane Ross Movement Disorders Clinic at ATC/Baycrest Health Sciences, Division of Neurology Department of Medicine University of Toronto, Canada.

Biogen, Cambridge, MA, USA

Department of Molecular Neurology, Movement Disorder Unit, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

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Corresponding Author: Dr. Alberto J Espay. Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA Tel: +1 (513)558-4035

E-mail: alberto.espay@uc.edu

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INTRODUCTION

As a consequence of limitations in current pharmacotherapy, the symptoms of patients with Parkinson’s disease (PD) may fluctuate throughout the day, impacting functional ability and quality of life.¹ A diary has been the most common method for assessing fluctuations of symptoms in research settings. Diaries enable patients to monitor daily symptoms at specified intervals and report their severity, frequency, and duration for a limited repertoire of predominantly motor symptoms dichotomized into “ON” (defined variably as “good” response to dopaminergic treatment) or “OFF” (poor response to dopaminergic treatment) states. Prioritizing simplicity, most diaries consider dyskinesia exclusively as “ON” state phenomena, and divide them into whether they interfere with overall function (“troublesome”) or not (“non-troublesome”).²³ Emphasis on the development of treatments designed to “reduce OFF” or “increase ON” time has limited attention to common intermediate, transitional, and non-motor states that may not squarely fall into one of these two states.

Current gaps in PD diaries and strategies to address them in an e-Diary

PD diaries have provided valuable information often as primary endpoints in clinical trials of symptomatic therapies over the past 20 years. Two diaries (Parkinson Disease Home Diary and CAPSIT-PD Diary) have been designated as “Recommended” by the MDS Task Force on Rating Scales. These two diaries, nonetheless, have the caveat that limited data exist regarding their validity, compliance, and completion,⁴ and their assessment is implicitly linked to the presence of motor fluctuations.⁵⁶ A systematic literature search found total of 12 published PD diaries, for which a narrative review (Supplementary material 1) and quality criteria (Supplementary material 2) are available online. The
phenomenological, contextual, and clinimetric gaps identified in existing diaries as well as the potential strategies to correct them are listed in Table 1.

In recent years, the advent of new technologies has introduced the opportunity to redesign this diary tool. Current diaries are almost exclusively designed in paper format (or in an electronic format that resembles paper diaries). Newer digital methods should enable the capture of a wider range of individualized motor, non-motor, and circadian complex fluctuations with greater accuracy as an electronic diary/tracker interface (e-Diary). With the aim of bringing the PD diary into the digital age, the MDS Technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee elaborated a set of desirable characteristics and developmental steps for a technology-enhanced e-Diary, usable in both clinical practice and treatment trials. At the request of Movement Disorders editors, a draft of this manuscript was made available on the MDS website (movementdisorders.org/MDS/Resources/2018/PD-Diary.htm) to facilitate public comments on the proposed roadmap between October 7 and November 7, 2018. The MDS Secretariat sent an email invitation to MDS members and two reminders within that time frame. Supplementary material 3 contains a summary of the feedback, highlighting the suggestions that prompted changes into the final document contained in this manuscript.

Desirable characteristics of a PD e-Diary

1. *Phenomena recognition.* A diary must focus on capturing key symptoms and signs that correlate with clinically pertinent fluctuations in motor and non-motor function. Two archetypal states have been defined in research settings, anchored on motor fluctuations (MF) but adaptable also to non-motor fluctuations (NMF): “OFF”, the clinical condition
reflective of no treatment effect, and “ON”, associated with full and effective treatment. However, patients often experience partial, transitional, or “gray-zone” states throughout the day that cannot be dichotomized into full ON or OFF states. Further, dyskinetic and dystonic behaviors can develop during ON, OFF, and transitional states, so that diaries that restrict them as subcategories of ON are conceptually and operationally inadequate.

Another important metric with direct implications in therapeutic decisions is functional status, which can vary independently of the duration and severity of fluctuations. Finally, because the biological, pharmacological and clinical relationships between MF and NMF have not been clarified, an ideal diary tool should not implicitly link them and must allow for independent registration of different symptoms.

2. Patient language. If the terms “OFF” and “ON” are to be used, definitions must be clearly outlined. The definitions should incorporate both motor and non-motor symptoms. Testing patients’ understanding of definitions must be conducted during the development phases to ensure adequacy of language, content, and health literacy. This practice can lead to the modification of items to increase the precision of self-reported measures. Video-based training sessions and standardized instructions can be developed for ensuring validation. Following these steps should render the final diary intuitive to patients, minimizing the need for additional training in subsequent clinical or research uses.

3. Administration and data collection. The adequate frequency or duration of recording needed to capture MF and NMF, in order to define a baseline pattern and to evaluate treatment response, is still unknown. Regardless, frequency of assessments and method of state determination (averaged over a period of time or in real-time) must be tailored to
clinical or research settings. Current diaries predominantly use the “averaged over a period of time” method. Even with these efforts, however, studies using similar instructions stress the “peak-end rule” that dominates human behavior, judging an epoch for its worst or best point or its state at the moment of the assessment.\textsuperscript{12} Such averaging can be cognitively challenging and may increase measurement errors and recall bias, even in the absence of cognitive impairment.\textsuperscript{13,14} Compliance of data recording and frequency of missing or erroneous data collection must be recorded. Accurate sleep and wakefulness detection is necessary. Medication –and possibly meal– intake tracking is required to recognize their influence on MF and NMF. One advance of electronic methods is that alerts and interactive involvement may enhance valid data collection. Finally, data should be protected and kept confidential.

4. Diary format and data visualization. An accessible interface would ideally include visual results and feedback to the patient in the form of percent completed and progress reports, independently tailored for clinical care and research settings. Visualization of the evolution of fluctuations over time could be an added value of such e-Diary. An inviting interface, such as currently applied by wearable fitness technologies and exercise devices, may serve to stimulate long-term compliance with an e-Diary.\textsuperscript{15} Flexibility in this capacity (on-off switch for “shared feedback”) could help adaptability for research and clinical settings.

5. Data and clinimetric properties. Desirable measurement formats include active (requiring input by patients, e.g., questions or tasks) and passive data collection (not requiring input by patients). Visual analog scales (VAS) are ideal to use for non-dichotomous questions in active data collection, can be used by patients with cognitive
impairment, and are very sensitive to small intrapersonal changes.\textsuperscript{16–19} Wearable sensors (see below) may be ideal for passive MF and NMF assessments. Regardless of the methods employed, understanding the instruments’ clinimetric properties is important. Validation methods may include internal consistency (Cronbach’s alpha), construct validity (convergent, divergent, known groups), patient-clinician agreement, predictive validity calculations, cross-cultural validation, and factor analyses, among other methods.

Reliability assessments with test-retest calculations are acceptable, but not desirable as a sole method due to the fluctuating nature of the latent variables. Above all, demonstration of how patients feel or function is of utmost importance in defining utility and relevance.

6. Technology-based objective measures. An e-Diary/tracker would allow tools such as surveys and VAS to be administered regardless of time or place. Advanced hardware components, such as accelerometers, gyroscopes, microphones, radio signals, among other wearable sensors, can provide complementary action-dependent and action-independent objective measures.\textsuperscript{20,21} Active data collection should be tailored for motor and non-motor symptoms. Examples for motor symptoms include spiral drawing, finger tapping, and voice characteristics; for non-motor symptoms, assessments of visual performance and short-term memory.\textsuperscript{20,22–25} Passive measures should be obtained in an unsupervised and unobtrusive fashion,\textsuperscript{26} recorded preferentially during patients’ daily regular activities. One hope is that passive tracking should, in the future, capture a subset of relevant MF and NMF.\textsuperscript{27–30} Smartphones, increasingly being used across all age groups, are ideally suited for the e-Diary development, allowing for an ever-present yet unobtrusive and ecologically valid data collection.\textsuperscript{6,31,32} Challenges related to the technological development include the costs associated with software and hardware development and maintenance, patient/health
provider interface configuration, and regulatory difficulties with data storage, confidentiality, and management. Challenges related to usability, on the other hand, include possible issues of long-term compliance with active measures and the requirement to navigate an application, which might be difficult in the setting of motor disability or poor literacy of digital health technologies.\textsuperscript{33} Incorporation of artificial intelligence methods would be expected to minimize the need for active measures as “learning” from their initial integration into passive data serves to eventually “predict”, in their absence, the patient-relevant motor, non-motor, and functional states.

Next steps: milestones for the development of the PD e-Diary

We propose a development plan to construct an e-Diary that harnesses the complementary role of diaries (e.g., assessments of data meaningfulness based on patient feedback) and wearable sensors (e.g., continuous, objective measures, independent from patient feedback). The scope and features of an e-Diary/tracker will require tight collaboration in all developmental phases between all stakeholders, including clinicians, technology developers, regulatory experts, scientists from industry, caregivers, patient advocacy groups, and especially patients. This tool development may benefit from guidelines from the Food and Drug Administration,\textsuperscript{34} the Clinical Trials Transformation Initiative,\textsuperscript{35} and the Electronic Patient-Reported Outcome Consortium,\textsuperscript{36} among others. The new e-Diary should be built on an open-access data management concept, preferentially with the endorsement of the International Parkinson and Movement Disorders Society to standardize the mechanism for technology developers to gain regulatory approval, assist in improvements of the instrument over time, and contribute to its wide acceptance and adherence. Here, we outline the specific developmental milestones suggested by consensus.
First milestone: minimal viable product. A fully functional “minimal viable product” would consist of a wireless-enabled, secured, web-based e-Diary of patient-reported outcomes. The elements to be considered for this first step will require the prioritization of patient-relevant outcomes, as outlined in a parallel ongoing effort by the MDS Task Force on Technology. Optimization of existing data-capturing methods and technologies could facilitate the assessment of partial medication states, NMF reporting, medication tracking, and functional assessments. Some existing instruments (e.g., NMSQuest, NoMoFa, Wearing-Off Questionnaire) and PROMIS® (Patient-Reported Outcomes Measurement Information System) could assist this process by providing relevant items to the construction of the e-Diary. Verification and validation processes should start at this step and continue throughout the development.

Second milestone: integration of action-dependent metrics. Selection of hardware components (e.g., accelerometers, gyroscopes, microphones, among others) and development of software will be tailored to acquire action-dependent data. Individualized assessments for motor (e.g., spiral drawing, finger tapping) and non-motor symptoms (e.g., visual performance, memory) could be selected according to patient-reported relevance and feasibility.

Third milestone: incorporation of action-independent metrics. Hardware components selected in previous steps, potentially including available wearable
devices, could be optimized for passive data gathering, enabling the “tracker” functionality.

- **Fourth milestone: algorithm development, improvement and simplification.** A desired final step will be the analysis and integration of diary data and the active and passive recordings with hypothesis-driven and machine learning algorithms. Such algorithms must control for the state and setting in which patients enter action-dependent measures into the diary (for instance, dyskinesia might be interpreted differently in a patient with versus without anxiety, the former possibly magnifying its severity). The endpoint is the transformation of patient data into individualized current and predictive feedback to patients themselves, providers, and caregivers for both self-guided behavioral changes and facilitation of personalized management decisions by clinicians.

The feasibility of an e-Diary has been demonstrated by recent smartphone-based “rating scores”. A recently introduced mobile application combines active and passive data gathering,\(^40\) while another mobile application uses active-only data.\(^25\) In both cases, data were processed with machine-learning algorithms, yielding adequate reliability and validity metrics.\(^25,40\) Major unknown variables include the heterogeneity of PD and the extent to which integration of an e-Diary, daily or intermittently, is capable of enhancing patient empowerment for long-term sustainability. Further, the use of a new tool will be different if applied in clinical research (limited time) or “in real life” both for patients and, through a separate interface, for their caregivers.
Conclusions

The highly dynamic and user-friendly technological advances of recent years enable the development and validation of an accepted e-Diary/tracker that simultaneously assesses MF and NMF and utilizes action-dependent and action-independent endpoints for clinical management and research efforts. An e-Diary can be patient-friendly and intuitive as well as capable of providing real-time feedback to the patient (empowered to influence any state) and clinician in order to ensure widespread use and long-term adherence. The time has come to move beyond the simplistic dualism of “ON” and “OFF” states of paper diaries and reconfigure this important source of clinical information for care and research.

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2) Manuscript: A. Writing of the first draft, B. Review and Critique.

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Dr. Maetzler is co-chair of the MDS Technology Task Force and receives or received funding from the European Union, the Michael J. Fox Foundation, Robert Bosch Foundation, Neuroalliance, Lundbeck and Janssen, and holds part of a patent for the assessment of dyskinesias (German patent office, 102015220741.2). He received speaker honoraria from GlaxoSmithKline, Abbvie, Bayer, UCB, Licher MT and Rölke Pharma, and was invited to Advisory Boards of Market Access & Pricing Strategy GmbH, Abbvie, Roche and Biogen.

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**Dr. Reilmann** is founding director and owner of the George-Huntington-Institute, a private research institute focused on clinical and preclinical research in Huntington’s disease, and QuantiMedis, a clinical research organization providing Q-Motor (quantitative motor) services in clinical trials and research. He provided consulting services, advisory board functions, clinical trial services, quantitative motor analyses, and/or lectures for Teva, Pfizer, uniQure, Ipsen, Vaccinex, WAVE, Novartis, Raptor, Omeros, Siena Biotech,
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References


Table 1. Gaps of current (paper) diaries and Strategies to address them in an e-diary

<table>
<thead>
<tr>
<th>Gap of current diaries</th>
<th>Strategies for correction into an e-diary</th>
</tr>
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<tbody>
<tr>
<td>Absence of non-motor fluctuations</td>
<td>While separate non-motor fluctuations tools are under development, non-motor fluctuations assessment within a diary is needed.</td>
</tr>
<tr>
<td>Incomplete definitions of OFF and ON States</td>
<td>Expand the repertoire of motor behaviors and include non-motor fluctuations. Combine real-time assessments with wearable sensors and e-diary tracking.</td>
</tr>
<tr>
<td>Underrepresentation of partial states</td>
<td>Partial states can be recognized by patients and add granularity to transitional states. OFF and ON states may be replaced with measurement of symptom and disability severity along a continuum.</td>
</tr>
<tr>
<td>Inaccurate and partial reporting of motor complications</td>
<td>Allow for independent recognition of peak dose and diphasic dyskinesia, and OFF-associated dystonia. Allow for separate/complementary input by spouse or other immediate caregiver.</td>
</tr>
<tr>
<td>Lack of functional assessment</td>
<td>Allow for quantification of functioning that accounts for the wide nature, duration and severity of OFF periods at any “level” of fluctuation.</td>
</tr>
<tr>
<td>Absent cognitive debriefing</td>
<td>Conduct cognitive debriefing to improve items and increase the precision of self-reported measures.</td>
</tr>
<tr>
<td>Heterogeneous frequency of assessments</td>
<td>Evaluate real-time assessments with or without variably spaced frequency of assessments.</td>
</tr>
<tr>
<td>Data integrity limitations</td>
<td>Compliance assessment and improved patient interface can be implemented with electronic diaries.</td>
</tr>
<tr>
<td>Absent medication tracking</td>
<td>Implement medication tracking to correlate with function and assist with management strategies.</td>
</tr>
<tr>
<td>Absent meal type and sleep quality</td>
<td>Implement meal tracking and sleep quality recording to determine effect on response to medications.</td>
</tr>
<tr>
<td>Subjective information without objective measures (trackers)</td>
<td>Implement a smartphone based application with integrated action-dependent and action-independent (wearable sensors) symptom measures.</td>
</tr>
<tr>
<td>Heterogeneous measurement formats and validations methods</td>
<td>Adopt visual analog scales as measurement format and anchor metrics on patient-relevant outcomes.</td>
</tr>
</tbody>
</table>

Other limitations for all diaries include episodic and categorical assessment for continuous behaviors, lack of determination when assessment is completed, and undefined time to completion.
Supplementary material 1: Review of Parkinson’s Disease diaries

METHODS

Search strategy

We searched for eligible diary studies in Pubmed and Embase until December 2017 using the following search terms: ("Parkinson Disease"[Mesh] OR parkinson disease OR parkinsons OR parkinson) AND (patient diary OR diary OR fluctuation diary OR diary assessment).

Selection of studies and data extraction

Abstracts were reviewed for eligibility criteria by two investigators (J.A.V. and A.J.E.). Reference lists of eligible articles were screened for additional diaries.

RESULTS

Out of the 437 citations derived from the initial search strategy, 17 publications (12 original diaries, four validations or modifications, one e-diary) were identified.

1. Parkinson Disease Home Diary\textsuperscript{1–4}

The Parkinson Disease Home Diary was developed by Hauser and colleagues in 2000 and further validated and modified in 2004 and 2006. It is the most used motor fluctuation diary. It asks patients to retrospectively characterize their predominant motor states in 30-minute intervals as Asleep, ON, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia. An electronic version of the diary was created in 2007 by Lyons and Pahwa. Validation efforts in the original development included correlating ON and ON with non-troublesome dyskinesia to patient-defined "Good" time, and OFF and ON with troublesome dyskinesia to patient-defined "Bad" time. The 2004 version conducted test-
retest reliability procedures (intraclass correlation coefficient calculation=0.715); predictive
validity was assessed with Pearson correlation between patient diaries and visual analog scale
responses (0.36-0.57). The 2006 version assessed patient understanding of functional terms,
where less than half of patients interviewed (22/50 [44%]) had good understanding of the
terms OFF, ON without dyskinesia, and ON with dyskinesia before being shown a training
video (47/50 [94%] reported that the training video was useful).

2. CAPSIT-PD Diary

The core assessment program for surgical interventional therapies in Parkinson's Disease
(CAPSIT-PD) Diary was developed by Reimer and colleagues in 2004 to assess motor status
following the CAPSIT-PD committee recommendations: over a day, waking hours, 30-
minute fractions, divided into four conditions: complete OFF, partial OFF, complete ON, and
ON with dyskinesias. Validation efforts included patient-clinician agreement during a 4-hour
observation period (kappa=0.62; weighted kappa=0.84). Predictive value was assessed in 4
time points compared to full 4 week diary collections (one week yielded good prediction
\[ r^2 \geq 0.736 \] except for Partial-Off.

3. WiiPD

The WiiPD diary was developed by Synnott and colleagues in 2012. It is a 4-times daily,
electronic, real-time, motor assessment interphase that combines Nintendo Wii remote
minigames and diary input of symptom severity to quantify tremor and bradykinesia. It has
been tested in 10 participants (n=8, young healthy adults; n=1, elderly PD patient, n=1,
elderly healthy subject). Validation included blinded clinician evaluations of patient self-
rating based on amplitude, prevalence and impact of tremor on minigames-task completion
(agrément=72.2%).
4. **SCOPA-DC**\textsuperscript{7,8}

The Scales for Outcomes in Parkinson’s disease diary card (SCOPA-DC) is part of the larger SCOPA research project. It was constructed by Marinus and colleagues in 2002 and further modified and validated in 2011. It is a 7-times daily, retrospective, motor (n=4) and non-motor (n=7) symptoms severity assessment, that has undergone multiple validation tests. Validation included a Cronbach's $\alpha$ of 0.80 for walking, changing position and difficulty using hands. Test-retest reliability in patients without fluctuations was 0.91 at 2 weeks and 0.68 at 3 months; for fluctuating patients, it was 0.37 at 3 months. Clinician-patient agreement (r=0.81) and partner-patient agreement (r=0.70) were good. Construct validity was 0.46 compared to H&Y stage, 0.57 compared to SPES-ADL, and 0.62 compared to UPDRS-ADL. Total score prediction of patient’s own estimation of ON and OFF was good (r=0.75). Binary logistic regression of total score predicted being ON or OFF in 93% of the cases. The 2011 version conducted factorial analyses resulting in a 3-domain structure with item-scale correlations of 0.59-0.83 and Cronbach's $\alpha$ values 0.83-0.87. All these domains had moderate ability to predict OFF-time.

5. **Parkinson's Symptoms Diary**\textsuperscript{9}

The Parkinson's Symptoms Diary was developed by Montgomery and colleagues in 1990. It is a 4-times daily, retrospective, motor symptoms (balance loss, freezing of gait, tremor, and difficulties walking or using hands/arms) severity assessment. Test-retest reliability in subjects with stable antiparkinsonian medication (n=28) revealed stable results (Wilcoxon matched-pairs signed-ranked test=p>0.40; Spearman rank correlations=rho>0.85) at 1 month. Physician rating of patients video recordings performing nine simulated activities of daily living was compared to patient-reported diary scores and Parkinson’s disease impairment
scale (PDIS), revealing moderate correlation. Criterion validity compared to the PDIS revealed modest correlation for loss of balance and freezing of gait (rho=0.36 and 0.35, respectively).

6. Ahlskog 1994

Ahlskog and colleagues conducted a clinical trial in 1994 assessing cabergoline efficacy to control motor fluctuations. Motor diary cards were developed as a secondary outcome measurement instrument for this study, allowing for retrospective characterization of the predominant motor state every 30-minute interval as ON, OFF, or ON with dyskinesia. No formal validation testing was conducted.

7. Dyskinesia Diary Rating

In 2001, the Parkinson Study Group conducted a clinical trial comparing several methods of rating dyskinesia to evaluate the effect of remacemide hydrochloride in patients with advanced PD. Motor diary cards were developed for the study, allowing for retrospective characterization of the predominant motor state every 30-minute interval as Full OFF, Partial OFF, ON without dyskinesias, ON with mild dyskinesias, ON with severe dyskinesias.

Validation efforts included clinician-patient agreement for percentage of ON with dyskinesias (intraclass correlation coefficients = 0.89 and 0.91 at baseline and at week 2, respectively) and the percentage of ON with severe dyskinesias (intraclass correlation coefficients = 0.99 and 0.98 at baseline and at week 2, respectively). For the percentage of time spent ON with dyskinesias, the diary demonstrated Spearman correlations= 0.33 and 0.50 at baseline and at week 2, respectively, compared to the Modified Goetz dyskinesia rating scale, and Spearman correlations = 0.33 and 0.34 at baseline and at week 2, respectively, compared to the Lang-Fahn activities of daily living dyskinesia scale.
8. Richard 2001

In 2001, Richard and colleagues developed a motor and non-motor states diary. It allowed for hourly, retrospective characterization of the predominant mood, anxiety, and motor states using visual analog scales. The anchors for mood were “extremely sad” and “extremely happy,” those for anxiety were “extremely calm” and “extremely anxious,” and those for motor were “extremely immobile (OFF)” and “excessively mobile (ON with dyskinesia)”.

No formal validation testing was conducted.

9. Nyholm 2004

In 2004, Nyholm and colleagues developed a motor and non-motor symptom diary in paper and electronic versions that combined check boxes and visual analog scales response formats. Participants were asked to retrospectively report the average of symptom severity on an hourly basis. No formal validation testing was conducted.

10. Westin 2010

Westin and colleagues developed a motor electronic diary (Qtek 2020i Pocket PC, personal digital assistant device) in 2010 that underwent further validation testing in 2012. It allowed participants to characterize 4-times daily their predominant past motor state and symptom severity, and to assess in real time their motor performance with finger tapping and spiral drawing. Validation methods included Cronbach’s $\alpha=0.85$, test-retest reliability 1 week later was 0.73 in non-fluctuators, 0.84 in fluctuators, and 0.88 for both groups combined. Convergent validity was significant for total UPDRS ($r = -0.64$, $p = 0.11$) and PDQ-39 ($r = -0.72$, $p=0.02$). Known-groups validity between fluctuators and non-fluctuators revealed a median overall score differing by 18% ($p=0.001$).
11. Schneider 2015\textsuperscript{16}

In 2015, Schneider and colleagues developed a motor diary as part of a study intended to characterize adequate stimulation parameters in PD patients who underwent deep brain stimulation. It allowed for retrospective characterization of the predominant motor state at 60-minute intervals as OFF, ON, Dyskinesia, and Not Ideal Mobility. No formal validation testing was conducted.

12. Ossig 2016\textsuperscript{17}

In 2016, Ossig and colleagues developed a non-motor symptom diary that incorporated a modified version of the Parkinson Disease Home Diary motor state characterization (Asleep, motor OFF, ON without dyskinesia, and ON with dyskinesia). It asked participants to retrospectively rate, at every 60-minute interval, the predominant motor state and presence or absence of anxiety, depressive mood, inner restlessness, difficulties with concentration, fatigue, excessive sweating, sialorrhea, bladder urgency, and dizziness. No formal validation testing was conducted.

REFERENCES


John Wiley & Sons


### Supplementary Material 2: Quality Criteria of 12 available diaries (1/2)

<table>
<thead>
<tr>
<th>Phenomena recognition</th>
<th>Parkinson Disease Home Diary&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CAPSIT-PD Diary&lt;sup&gt;3&lt;/sup&gt;</th>
<th>WiiPD&lt;sup&gt;6&lt;/sup&gt;</th>
<th>SCOPA-DC&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Parkinson's Symptoms Diary&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Ahlskog 1994&lt;sup&gt;10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenomena recognition</td>
<td>Self-reporting of MF and NMF</td>
<td>MF only.</td>
<td>MF only.</td>
<td>Both.</td>
<td>MF only.</td>
<td>MF only.</td>
</tr>
<tr>
<td>Motor complications</td>
<td>PDD.</td>
<td>PDD.</td>
<td>Unclear.</td>
<td>PDD.</td>
<td>PDD, unclear reporting of DDys.</td>
<td>PDD, unclear reporting of DDys</td>
</tr>
<tr>
<td>Patient language</td>
<td>ON definition</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Not used.</td>
<td>Not used.</td>
<td>Yes.</td>
</tr>
<tr>
<td></td>
<td>OFF definition</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Not used.</td>
<td>Not used.</td>
<td>Yes.</td>
</tr>
<tr>
<td>Administration and data collection</td>
<td>Assessments and status determination</td>
<td>30 minutes. Average.</td>
<td>30 minutes. Average.</td>
<td>4 times a day. Real time.</td>
<td>7 times a day. Average.</td>
<td>4 times a day. Average.</td>
</tr>
<tr>
<td>Missing or erroneous data collection frequency</td>
<td>17-42%.</td>
<td>15%.</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>9%.</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Measurement format</td>
<td>Check boxes and VAS&lt;sup&gt;2, 3&lt;/sup&gt;</td>
<td>Check boxes.</td>
<td>Check boxes and sensor minigames.</td>
<td>Check boxes.</td>
<td>Check boxes.</td>
<td></td>
</tr>
<tr>
<td>Validation and Reliability methods</td>
<td>Predictive validity, test-retest reliability (ICC)&lt;sup&gt;2, 3&lt;/sup&gt;</td>
<td>Patient-clinician agreement, predictive validity.</td>
<td>Patient-clinician agreement.</td>
<td>Patient-clinician agreement, predictive validity, internal validity, construct validity, factorial analyses, item-scale correlations, test-retest reliability (ICC)&lt;sup&gt;8&lt;/sup&gt;.</td>
<td>Patient-clinician agreement, criterion validity, test-retest reliability (Spearman).</td>
<td>None.</td>
</tr>
</tbody>
</table>
Table 1: Quality Criteria of 12 available diaries (2/2)

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reporting of MF and NMF</td>
<td>MF only</td>
<td>Both</td>
<td>Both</td>
<td>MF only</td>
<td>MF only</td>
<td>Both</td>
</tr>
<tr>
<td>Motor complications</td>
<td>PDD.</td>
<td>PDD.</td>
<td>PDD, unclear reporting of DDys.</td>
<td>PDD and DP, Unclear reporting DDys.</td>
<td>PDD, unclear reporting of DDys.</td>
<td>PDD.</td>
</tr>
<tr>
<td>Patient language</td>
<td>ON definition</td>
<td>Yes.</td>
<td>Uncertain.</td>
<td>Not used.</td>
<td>Yes.</td>
<td>Yes.</td>
</tr>
<tr>
<td>Training components</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes.</td>
</tr>
<tr>
<td>Missing or erroneous data collection frequency</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>12% for electronic version, 2% for paper version.</td>
<td>14%.</td>
<td>Not reported.</td>
<td>22% for patients with fluctuations and 7% for non-fluctuators.</td>
</tr>
<tr>
<td>Measurement format</td>
<td>Check boxes.</td>
<td>VAS.</td>
<td>Check boxes and VAS.</td>
<td>Check boxes, VAS and sensor tasks.</td>
<td>Check boxes.</td>
<td>Check boxes.</td>
</tr>
<tr>
<td>Validation and Reliability methods</td>
<td>Patient-clinician agreement.</td>
<td>None.</td>
<td>None.</td>
<td>Internal validity, convergent validity, known-groups validity, test-retest reliability (ICC).</td>
<td>None.</td>
<td>None.</td>
</tr>
</tbody>
</table>
MF, Motor fluctuations; NMF, Non-motor fluctuations; PDD, Peak-dose dyskinesia; DDys, Diphasic dyskinesia; DP, Dystonic posturing; VAS, Visual analog scale; ICC, Intraclass correlation coefficient. Reference numbers correspond to Supplementary Material 1.
Supplementary material 3

Comments from MDS Members

A total of 33 MDS members provided comments. In many cases, multiple comments (C) per reader were received. Itemized responses are shown (R).

Suggestions that warranted changes or clarifications in the manuscript:

C1. Consider cloud application for data storage and protection.

R1. Added the term “cloud-secured” to the minimal viable product section.

C2. A separate access for caregiver data entry should be considered and rated as helpful for the e-diary.

R2. Caregiver input is helpful. A separate interface for them may be developed in parallel to the interface for patients. Added this concept in the proposed steps.

C3. Missing language validation as psychometric testing.

R3. Added language validation in the validation methods.

C4. The listed development steps seem linear, but a parallel development strategy that integrates achievements for continuous improvement seems more reasonable.

R4. We explicitly added this suggested parallel strategy of development.

C5. Please change the typo of “Wilconxon” to “Wilcoxon” in the supplement.

R5. Change made.
C6. Cite relevant regulatory guidances, such as the FDA ePRO guidance and outcome measures
guidance.

R6. We have added these additional regulatory guidelines.

C7. In addition to these [Roche V1 and HopkinsPD], you should acknowledge the PKG device,
which has gained regulatory approval in both the US and EU for detecting and managing
fluctuations, as well.

R7. We have added these as potential components of the tracker functionality.

C8. The diary should also include awake and asleep hours.

R8. We agreed and added this in the text.

C9. Notifications and remainders could be a desirable characteristics of an e-Diary.

R9. We agreed and added this in the text.

Suggestions that did not prompt changes to the manuscript:

C10. Nurses can aid in the training, analysis, and troubleshooting of the tool.

R10. To be discussed in future developments, not in this manuscript.

C11. Select non-motor symptom scales based on psychometric theories. Item-response theory
scales should be selected.

R11. Both Classical test theory and Item response theory are psychometric methods that can be
used later in the developmental process. Their use is not mutually exclusive.
C12. The MDS should explore 1. whether the published literature on sensor technology accurately reflects the various motor states of PD patients as defined by clinicians, 2. consider the simultaneous application of smart-phone based e-diary patient reporting of motor states, and 3. only when a reliable, objective wearable technology for monitoring motor fluctuations is available, should non-motor symptoms be addressed.

R12. Different scope than the one defined for this manuscript. However, some of these points are being addressed in the proposed roadmap for the MDS technology task force (separate paper).

C13. Is there a way to integrate summative data into a visual graph-style format, which can be used to guide treatment decisions?

R13. The processing of data with machine-learning algorithms should allow the visualization of clinically meaningful metrics for both clinicians and patients.

C14. Perform a survey among PD patients and caregivers on "how they imagine a PD e-diary", "which kind of symptoms they would like to continuously monitor", "what are the main difficulties they have in telling the fluctuations of their symptoms to the doctor".

R14. These issues are being addressed in a separate proposed roadmap for the integration of technology into monitoring by the MDS Technology Task Force.

C15. E-diaries will be need to be validated against the current paper diary, at least against the "Parkinson Disease Home Diary" or the "CAPSIT-PD Diary", currently considered as "recommended" by the MDS Task Force on Rating Scales.

R15. Validation against paper diaries may not be feasible due to different state characterization. In addition, we do not believe paper diaries should be considered the "gold-standard".