Convention vs. Innovation II: Time To Abandon Clinician-Administered Scales As The Primary Outcome Measure Of Symptomatic And Disease Modifying Trials In Parkinson Disease

Tiago A. Mestre

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Overview

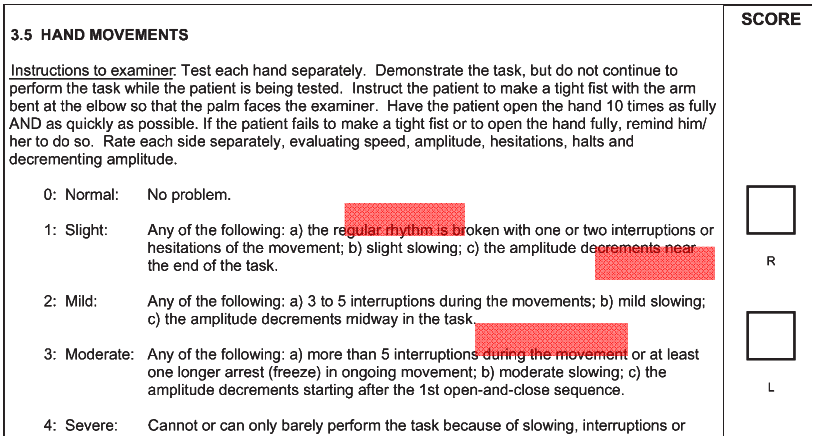
- PD clinical trials and outcomes
  - Clinician-administered scales
  - Patient-reported outcomes
- Digital outcome measures: opportunities, challenges
- Is it time?
- Clinical trials of the future (now!)

PD clinical trials and outcomes

- PD is a multi-domain fluctuating progressive condition
- Types of clinical outcome assessments (FDA):
  - Clinician-reported outcomes (ClinROs)
  - Patient-reported outcomes (PROs)
  - Observer-reported outcomes (ObsROs)
  - Performance outcomes (PerfOs)
- Symptomatic trials and disease-modifying trials

Clinician-administered scales

MDS-UPDRS part III (example)



3.5 HAND MOVEMENTS — SCORE

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problem.	
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.	R ☐
2: Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.	
3: Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.	L ☐
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or	

‘some’ limitations of the MDS-UPDRS

- ‘Snapshot’ measurement of a patient condition
- Inherent subjectivity (patient and physician)
- Risk of recall bias:
  - mood
  - (non-)motor fluctuations
  - sleep/rest
- Time expenditure
- Investigator and location dependency

Lim, 2018

‘more’ limitations of the MDS-UPDRS

- Inaccurate reporting (part I and II):
  - dyskinesia *vs.* tremor
  - physical fatigue *vs.* mental fatigue
  - ICBs
- Reliability (training requirement)
- Meaning of a compound score
- Non-linearity
- Floor effect, may not detect subtle clinical changes

Lim, 2018

Patient-reported outcomes

Information on the patient's health condition as directly reported by the patient, without outside interpretation from anyone.

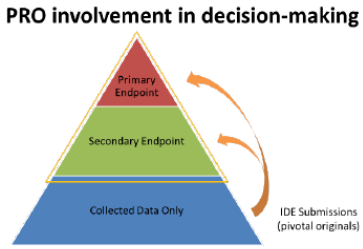


Figure 2. Upgrade of PROs involved in regulatory decision making.

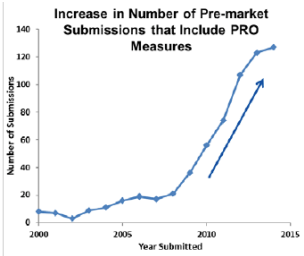
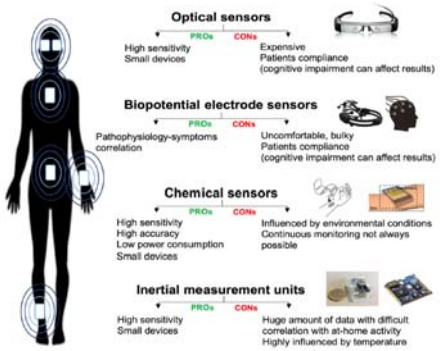


Figure 1: Number of submissions including PRO measures for calendar years 2000 – 2015.

Digital outcome measures

opportunities, challenges



mobile health technologies (mHealth)

310.4 million wearable devices sold in 2017

504.6 million wearable devices to be sold (2021)

not if, but how!

Opportunities

Wider accessibility
Ecological validity
Continuous monitoring
Multi-domain assessment

Better monitoring
Better patient engagement
Better outcomes

Positive Impacts of Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials*

	SPECIFIC BENEFITS		
	SHORT-TERM	MEDIUM-TERM	LONG-TERM
Patient Centricity	Development of high-quality, patient-centric, mobile technology-derived endpoints	Greater use of endpoints that matter to patients in clinical trials Reduced participation burden (patient and caregiver) in clinical trials Fewer barriers to trial participation Larger, more inclusive, and more generalizable trials	Increase in clinical trials that yield more complete information on how therapies affect aspects of disease most important to patients Increase in clinical trials that yield better information to inform regulatory and labeling claims as well as subsequent reimbursement decisions Increase in participation and retention of patients in clinical trials through the development and selection of measures that matter to patients
Efficacy	Inclusion of mobile technology-derived endpoints in early-phase trials and in postmarket surveillance	Improved predictability rates for advancement from phase II to phase III trials Increased efficiency of postmarket surveillance	Increase in number of potentially successful treatments taken forward for testing in phase III trials, particularly in high-risk therapeutic areas
Efficiency	Generation of data needed by payers to make coverage determinations during clinical trials	Prevention of delays in coverage, payment, and use decisions	Prevention of delays in patient access to therapies

CLINICAL TRIALS TRANSFORMATION INITIATIVE

*The term "clinical trial" is used here to refer to studies done to support regulatory approval for marketing.
Source: Clinical Trials Transformation Initiative's [Mobile Clinical Trials – Novel Endpoints Project]

Challenges

ADVANCES IN TECHNOLOGIES FOR PD SERIES: REVIEW

New Methods for the Assessment of Parkinson's Disease (2005 to 2015): A Systematic Review

Álvaro Sánchez-Ferro, MD, MSc,[1,2*] Morad Elshehabi, MD, MSc,[3,4] Catarina Godinho, PhD,[5,6,7] Dina Salkovic, MD, MSc,[3,4] Markus A. Hobert, MD,[3,4] Josefa Domingos, MSc,[5,7] Janet MT. van Uem, MSc,[3,4] Joaquim J. Ferreira, MD, PhD,[5,7,8] and Walter Maetzler, MD[3,4]

Systematic review (2005 - 2015)
588 original articles assessed

65% included fewer than 30 patients
< 50% employed a standard methodology to validate diagnostic tests,
8% confirmed their results in a different dataset
87% occurred in a clinic or lab

Axial features domain was the most frequently studied, followed by bradykinesia.
Rigidity and nonmotor domains were rarely investigated.

6% of the systems reached a maturity in technology to hope for a clinical use

Challenges

Standardized development and validation processes

Integration of devices from different companies in a comprehensive data platform

Streamline regulatory approval of health technologies

Challenging the effort, cost, and the risk of 'failure' of novel outcomes in clinical trials

Patient engagement

Provider engagement (clinical vs. technical know-how)

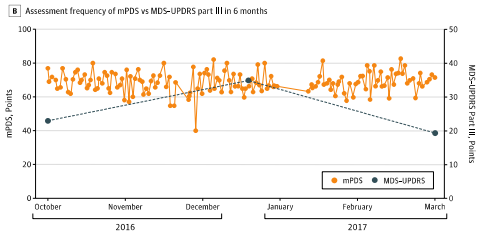
Ethical and legal issues

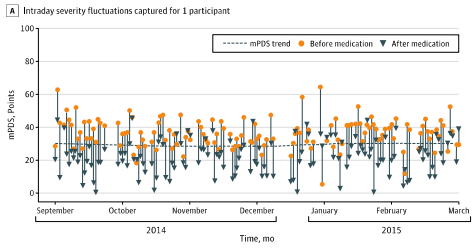
JAMA Neurology | Brief Report

Using Smartphones and Machine Learning to Quantify Parkinson Disease Severity

The Mobile Parkinson Disease Score

Andong Zhan, MS; Srihari Mohan; Christopher Tarolli, MD; Ruth B. Schneider, MD; Jamie L. Adams, MD; Saloni Sharma, MD; Molly J. Elson, BA; Kelsey L. Spear, MPH; Alistair M. Glidden, BS; Max A. Little, PhD; Andreas Terzis, PhD; E. Ray Dorsey, MD; Suchi Saria, PhD





CONCLUSIONS AND RELEVANCE Using a novel machine-learning approach, we created and demonstrated construct validity of an objective PD severity score derived from smartphone assessments. This score complements standard PD measures by providing frequent, objective, real-world assessments that could enhance clinical care and evaluation of novel therapeutics.

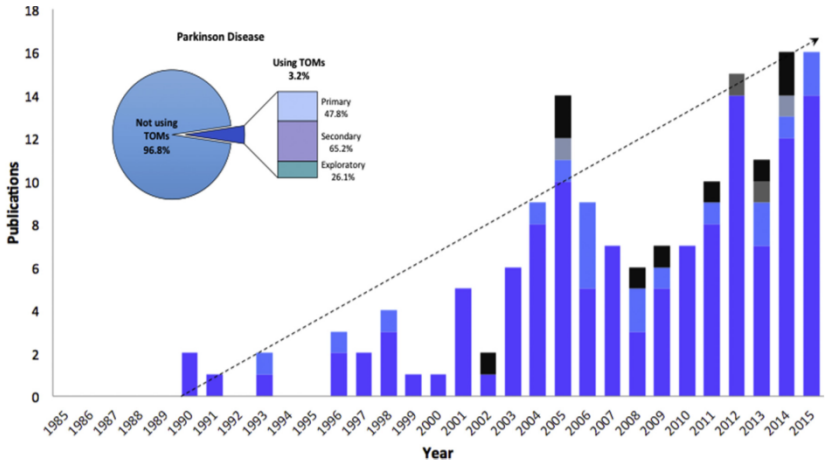
Limitations

This study has several limitations. Participants were generally white, college-educated, people who owned Android smartphones and thus were not representative of the broader PD population. Only 51.6% of those who downloaded the application met criteria for inclusion in the development cohort. Additionally, the clinic cohort included only 7 assessments to evaluate the responsiveness of the mPDS to dopaminergic therapy administration, and only 16 smartphone and in-person assessment pairs met criteria for the correlation analysis. However, to our knowledge, this

Is it time?

Clinical trials and technology-objective outcomes

C.A. Artusi et al. / Parkinsonism and Related Disorders 46 (2018) S53–S56



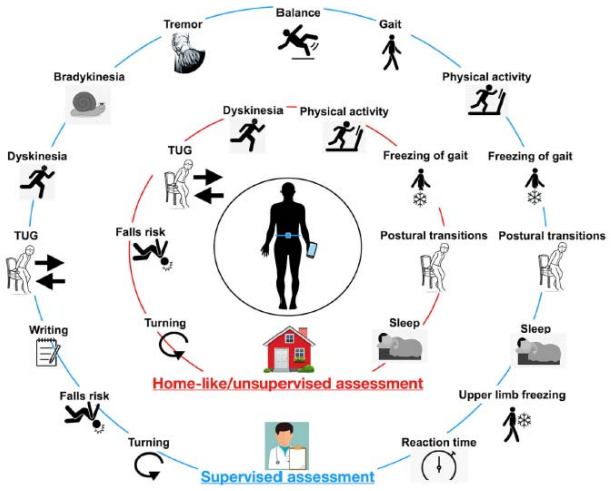
Evidence is Needed to Establish Clinical Trial Endpoints Derived from mHealth

CLINICAL TRIALS TRANSFORMATION INITIATIVE

FDA U.S. FOOD & DRUG ADMINISTRATION

Evidentiary portfolio for device implementation in clinical trials

CLINICAL TRIALS TRANSFORMATI(INITIATIVE



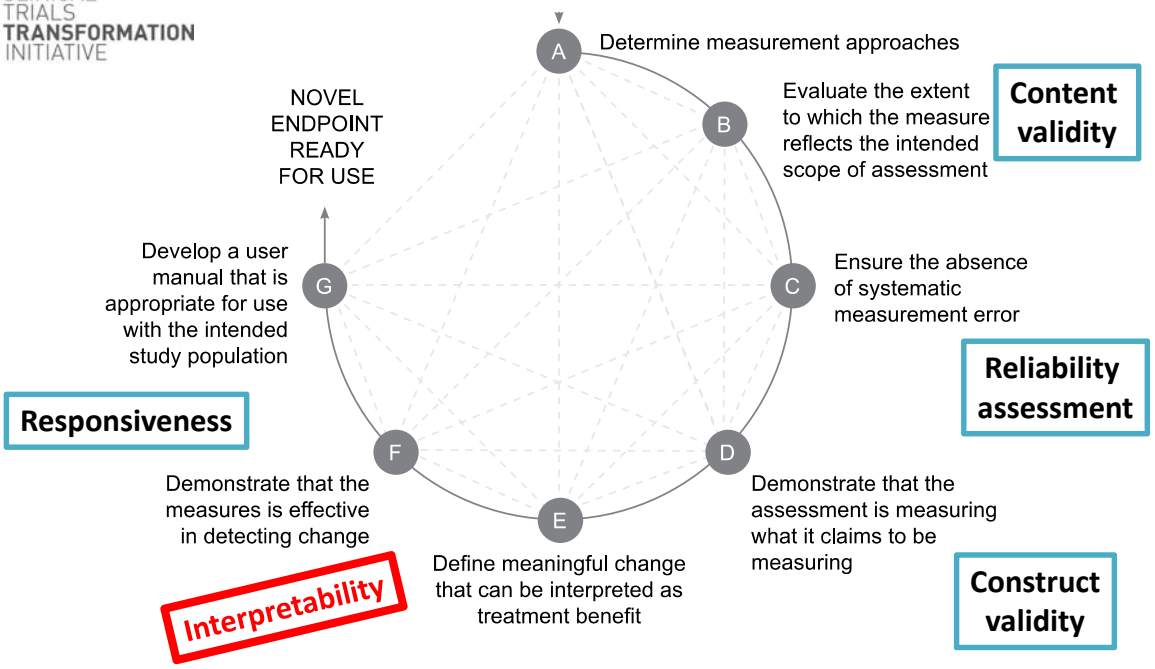
meaningful health aspect

concept of interest

outcome assessment

Izmailova 2018; CITI 2017, Artusi 2020

CLINICAL TRIALS TRANSFORMATION INITIATIVE



MDS COMMISSIONED REVIEW

A Roadmap for Implementation of Patient-Centered Digital Outcome Measures in Parkinson's Disease Obtained Using Mobile Health Technologies

Alberto J. Espay, MD, MSc,[1] Jeffrey M. Hausdorff, PhD,[2,3,4] Álvaro Sánchez-Ferro, MD, MSc,[5] Jochen Klucken, MD,[6,7] Aristide Merola, MD, PhD,[1] Paolo Bonato, PhD,[8] Serene S. Paul, PhD, BAppSc(Phty)(Hons),[9] Fay B. Horak, PhD, PT,[10,11] Joaquin A. Vizcarra, MD,[1] Tiago A. Mestre, MD, MSc,[12] Ralf Reilmann, MD, PhD,[13,14,15] Alice Nieuwboer, PhD,[16] E. Ray Dorsey, MD, MBA,[17] Lynn Rochester, PhD,[18,19] Bastiaan R. Bloem, MD, PhD,[20] and Walter Maetzler, MD[21] on behalf of the Movement Disorder Society Task Force on Technology

ROADMAP FOR DIGITAL MEASURES IN PD

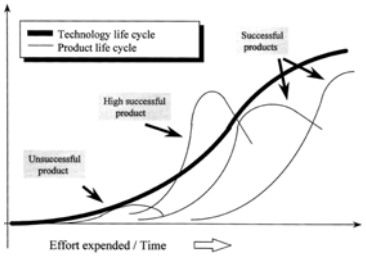
	Prerequisites	Testing	Output
What to measure?			
Domains relevant for assessment	Active involvement of large patient organizations, MJFF (Fox Insight questionnaire)	Mixed methods (quantitative / qualitative) evaluation	Definition of a targetable set of PD-relevant symptoms and resources
How to measure?			
Selection of software and hardware	Agreement on sensor and hardware selection, App interface	Implementation and measurement of adherence and data reliability	Validation of a set of sensors and software capturing patient-relevant data, best balance of compatible hardware/software
What to display?			
Open-source platform and interface integration	Agreement on protocol, platform design, and algorithm development	Run-in phase, test rules, Website development for data compatibility, and synchronization	High-quality interfaces for sensor data integration and visualization
How to disseminate?			
Regulatory pathway and commercialization	Assessing costs of development, implementation, and maintenance	Incentives for financial reimbursement Stakeholders adoption	**Application ready for patients, clinicians, regulators, and health care systems**

VISION

VISION IMPLEMENTATION

PROCESS

Is it time? YES



to thread the RIGHT path with confidence

Clinical trials of the future (now!)

Patient-centric clinical trials

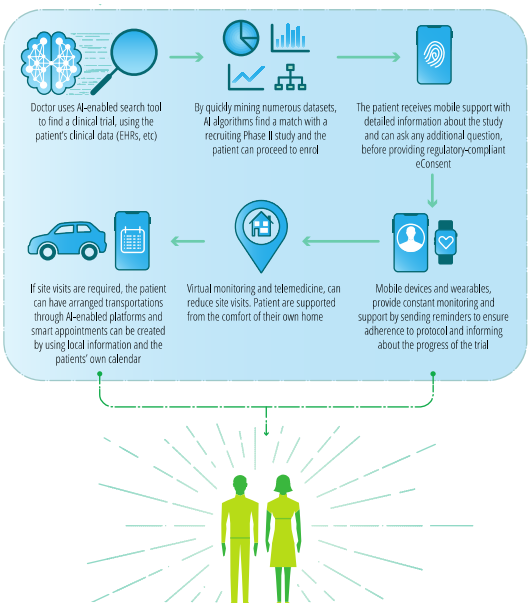
Decentralized Clinical Trials
- Inclusive patient participation
- (Quasi) continuous stream of objective data
- Reduced participation burden

Reliable and noise-minimal data

Streamlined remote data access and monitoring

Longer trials to more adequately address clinical questions (symptoms, disease progression)

Less expensive



Motor Working Group Survey on health technology and motor Parkinson disease (2020)

Q5 In which areas of PD, can health technology solutions have the greatest impact in 5 years? (please rank response options and assign the number 1 to the most impactful area)

Answered: 127 Skipped: 0

	1	2	3	4	TOTAL
Therapeutic development and clinical trials	37.80% 48	18.90% 24	18.90% 24	24.41% 31	127
Symptom assessment and management in clinical practice	30.71% 39	25.98% 33	28.35% 36	14.96% 19	127
Patient-physician communication	13.39% 17	25.20% 32	26.77% 34	34.65% 44	127
Patient self-management and empowerment	18.11% 23	29.92% 38	25.98% 33	25.98% 33	127

An example in PD in 2021

Design of a virtual longitudinal observational study in Parkinson's disease (AT-HOME PD)

Ruth B. Schneider[1,2], Larsson Omberg[3], Eric A. Macklin[4,5], Margaret Daeschler[6], Lauren Bataille[6], Shalini Anthwal[2], Taylor L. Myers[2], Elizabeth Baloga[2], Sidney Duquette[2], Phil Snyder[3], Katherine Amodeo[1], Christopher G Tarolli[1,2], Jamie L. Adams[1,2], Katherine F Callahan[7], Joshua Gottesman[6], Catherine M. Kopil[6], Codrin Lungu[8], Alberto Ascherio[9], James C. Beck[10], Kevin Biglan[1,11], Alberto J. Espay[12], Caroline Tanner[13], David Oakes[14], Ira Shoulson[1,2,15], Dan Novak[10], Elise Kayson[1,2], Earl Ray Dorsey[1,2], Lara Mangravite[3], Michael A. Schwarzschild[7], Tanya Simuni[16] & the Parkinson Study Group AT-HOME PD Investigators

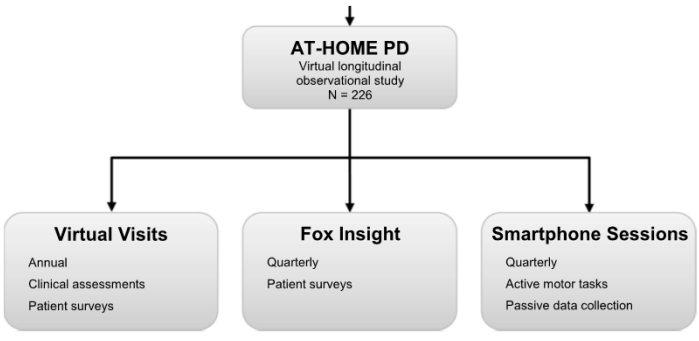


Figure 1. Overview of AT-HOME PD Study.

Convention vs. Innovation II: Time To Abandon Clinician-Administered Scales, validate and use digital outcomes As The Primary Outcome Measure Of Symptomatic And Disease Modifying Trials In Parkinson Disease

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