Clinically Meaningful Endpoints

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DISCLOSURES

- Advisory Boards: ACADIA, IMPAX, US WorldMeds
- Honoraria for talks: AAN, New York University, New York Presbyterian Hospital/Methodist, Rutgers
- Honoraria for editorials: NeuroAlert

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INTRODUCTION

- Clinical trial phase will steer focus to specific types of endpoints
- Endpoint choices will enhance scientific information to be gained
- Endpoints may address a variety of processes:
    - Treatment effects on physiology, cell biology and target engagement
    - Safety and tolerability
    - Efficacy

Measures important to patients

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CLINICALLY MEANINGFUL ENDPOINTS

- Measure how study participants
  - Feel
  - Function
  - Survive
- Condition-specific vs general
- May be incorporated into any clinical phase of development
- Important basis for drug approval

- Objective versus subjective
  - Objective
    - Clinical event
    - Change in disease status
    - Survival
  - Subjective
    - Symptoms score
    - Quality of life score

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PATIENT REPORTED OUTCOMES (PROs)

- Patient-reported outcomes (PROs)
- a report that comes directly from the patient
  - •symptoms
  - •activities
  - •global assessment from the subject's perspective.

- intuitively compelling
- reflect whether a participant feels better or capture benefits only noticed by the patient
- development and validation is challenging
  - need to be reliable
  - sensitive to differences at baseline and to changes over time
  - if they comprise multiple domains these must be appropriately weighted
  - interpretation may be difficult, for example in judging meaning of a score, or whether one item drove the result

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SUCCESSES & CHALLENGES IN USING CLINICALLY MEANINGFUL ENDPOINTS

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#1: INCORPORATING CLINICALLY RELEVANT MEASURES INTO OPEN LABEL TRIALS

- *Spinal cord-derived neural stem cell transplant for amyotrophic lateral sclerosis (ALS), phase 1 and 2 trials (Glass et al Neurol 2016;87:392-400).*
- open label trial of 15 study participants
- risk escalation strategy
- focus on safety and adverse events
- not designed to detect efficacy
- clinically meaningful endpoints enhance understanding of intervention
  - changes in disease were measured by the ALS Functional Rating Scale-Revised (ALSFRS-R), forced vital capacity (FVC) % predicted, and grip strength
  - comparing with “control” data from other ALS trials - no evidence that transplant exacerbated decline
  - distinct open label study of 6 recipients of human fetal neural stem cells, a transitory increase in the ALSFRS-R ambulatory subscore was observed in 2 patients (Mazzini et al J Transl Med 2015;13:17)

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#2: USE OF CLINICALLY MEANINGFUL OUTCOMES IN "PLACEBO" CONTROLLED TRIALS

- *AAV2-GAD gene therapy in advanced Parkinson's disease (LeWitt et al Lancet Neurol 2011;10:309-319)*
- Sham surgery controlled, randomized, double-blind study in 45 participants
- Clinically meaningful endpoints (objective and subjective) support efficacy
- Primary endpoint – difference in "off" medication UPDRS part 3 (motor) at 6 months
- Baseline mean score 34.8 ± 1.6 (AAV2-GAD) vs 39.0 ± 1.9 (sham)
  - 6month mean score 26.6 ± 2.0 (AAV2-GAD) vs 34.3 ± 2.5 (sham), (p=0.04)
    - *(analysis was not ITT)*
- Clinical global impression at 6 months
  - 3.4 ± 0.1 (AAV2-GAD) vs 3.9 ± 0.1 (sham), p=0.02

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A CLOSER LOOK AT A CLINICAL RATING SCALE

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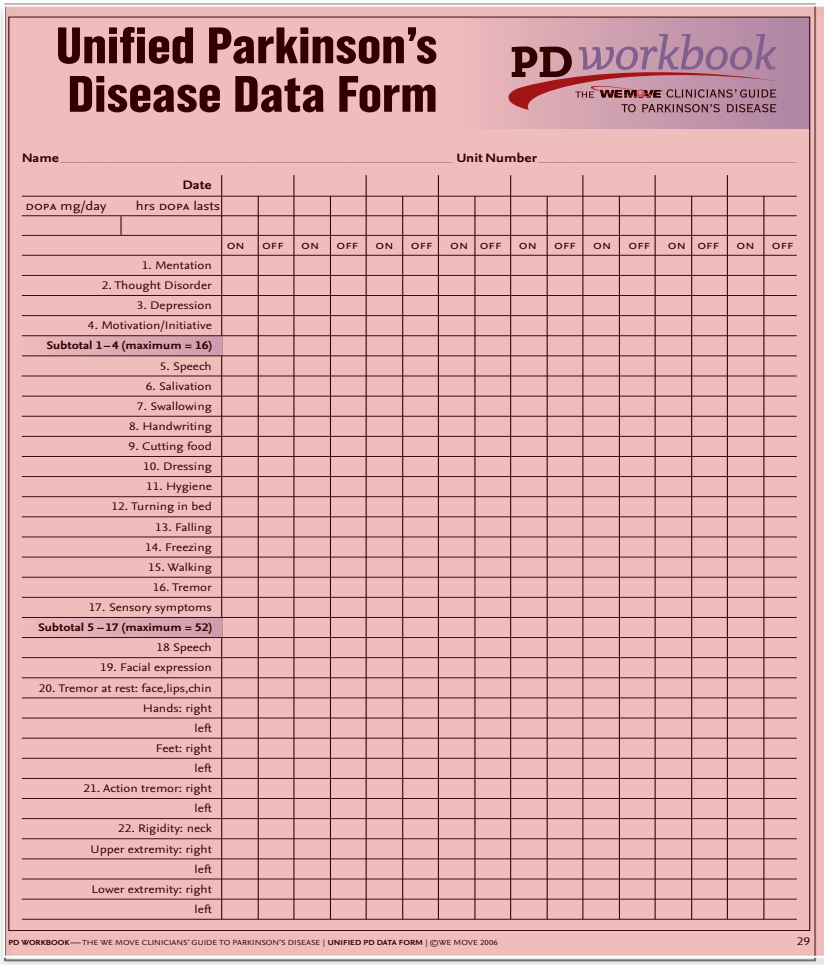
THE UNIFIED PARKINSON DISEASE RATING SCALE (UPDRS): A"GOLD STANDARD"



Unified Parkinson's Disease Data Form

PD workbook — THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

Name _____ Unit Number _____

Date																
DOPA mg/day / hrs DOPA lasts																
	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
1. Mentation																
2. Thought Disorder																
3. Depression																
4. Motivation/Initiative																
Subtotal 1–4 (maximum = 16)																
5. Speech																
6. Salivation																
7. Swallowing																
8. Handwriting																
9. Cutting food																
10. Dressing																
11. Hygiene																
12. Turning in bed																
13. Falling																
14. Freezing																
15. Walking																
16. Tremor																
17. Sensory symptoms																
Subtotal 5 – 17 (maximum = 52)																
18 Speech																
19. Facial expression																
20. Tremor at rest: face,lips,chin																
Hands: right																
left																
Feet: right																
left																
21. Action tremor: right																
left																
22. Rigidity: neck																
Upper extremity: right																
left																
Lower extremity: right																
left																

PD WORKBOOK — THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE | UNIFIED PD DATA FORM | ©WE MOVE 2006 29

Unified Parkinson's Disease Data Form

PD workbook — THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

Date																
	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
23. Finger taps: right																
left																
24. Hand grips: right																
left																
25. Hand pronate/supinate: right																
left																
26. Leg agility: right																
left																
27. Arise from chair																
28. Posture																
29. Gait																
30. Postural stability																
31. Body bradykinesia																
Sub-total:18–31 (maximum=108)																
Total points: 1–31 (max=176)																
32. Dyskinesia (duration)																
33. Dyskinesia (disability)																
34. Dyskinesia (pain)																
35. Early morning dystonia																
36. "Offs" (predictable)																
37. "Offs" (unpredictable)																
38. "Offs" (sudden)																
39. "Offs" (duration)																
40. Anorexia, nausea, vomiting																
41. Sleep disturbance																
42. Symptomatic orthostasis																
Blood Pressure: seated																
supine																
standing																
Weight																
Pulse: seated																
standing																
Name of Examiner																
	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST
Hoehn & Yahr Stage																
% ADL Score (PD)																
% ADL (with dyskinesia)																

Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 153-163, 293-304

30 PD WORKBOOK — THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE | UNIFIED PD DATA FORM | ©WE MOVE 2006

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AN EXAMPLE OF SCORING THE UPDRS

VIDEO

Voice volume/clarity
Facial expression
Rest tremor
Pauses and decrements on finger taps, hand grips, pronation-supination, foot taps
Gait
Flexed posture

Balance
Rigidity

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CHARACTERISTICS OF THE UPDRS

- Test-retest reliability
  - Intra-class correlation coefficient (ICC)
  - Total: 0.92; mental: 0.74; ADL: 0.85; motor: 0.90
- Inter-rater reliability judged “satisfactory”
  - Good-to-excellent on rest tremor, rapid repeated movements, standing from seated, gait
  - Poor on hypophonia, hypomimia
- Part II and Part III may be useful in measuring progression
- Can help define a minimal clinically significant change

- Floor effects, lack of sensitivity in early PD, and missing non-motor effects have been suggested as criticisms
  - New “MDS-UPDRS” may address these problems

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#3: PROS AND CONS OF OBJECTIVE AND SUBJECTIVE CLINICAL TRIAL ENDPOINTS

- *Transplantation of embryonic mesencephalic tissue to the bilateral putamen for advanced Parkinson's disease (Freed et al N Engl J Med 2001;344(10):710-719)*
- Sham surgery controlled, randomized, double-blind study in 40 participants
- PRO as primary endpoint - change from baseline in a Likert scale determining a subjective global rating from participants
- PRO and objective measures provide differing information

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#3: PROS AND CONS OF OBJECTIVE AND SUBJECTIVE CLINICAL TRIAL ENDPOINTS

- "subjective global rating of the change in the severity of disease, scored on a scale of –3.0 to 3.0 at one year, with negative scores indicating a worsening of symptoms and positive scores an improvement"
  - subjects chose a phrase (ranging from "parkinsonism markedly worse" (-3 points), through "no change" (0 points) to "parkinsonism markedly improved as compared with before surgery" (+3 points)
  - scores were submitted by study participants at 12 months
- Mean changes in scores:
  - Transplantation arm: 0.0 ± 2.1
  - Sham surgery arm: -0.4 ± 1.7

#3: PROS AND CONS OF OBJECTIVE AND SUBJECTIVE CLINICAL TRIAL ENDPOINTS

- Does this signify a failed study?
  - Fiber outgrowth from the transplant was observed by neuroimaging in 17/20 patients by 18F-fluorodopa PET or at postmortem
  - Benefit in younger patients in total UPDRS, a standardized test of Parkinson's disease severity
- the PRO was subsequently judged to be an inaccurate reflection of function, since measures differed when patients were shown videos of themselves pre-operatively (Freed et al 2011 Neurotherapeutics 8:549)

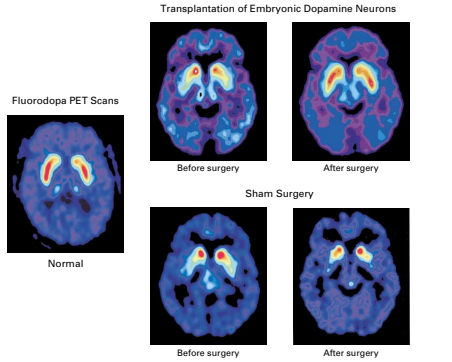


Figure 2. Change in ^{18}F-Fluorodopa Uptake in the Brains of Patients with Parkinson's Disease after Transplantation, as Shown in Fluorodopa PET Scans.

In the panel on the far left, an axial section through the caudate and putamen of a normal subject shows intense uptake of ^{18}F-fluorodopa (red). On the right side, the upper panels show preoperative and 12-month postoperative scans in a patient in the transplantation group. Before surgery, the uptake of ^{18}F-fluorodopa was restricted to the region of the caudate. After transplantation, there was increased uptake of ^{18}F-fluorodopa in the putamen bilaterally. The lower panels show ^{18}F-fluorodopa scans in a patient in the sham-surgery group. There was no postoperative change in ^{18}F-fluorodopa uptake.

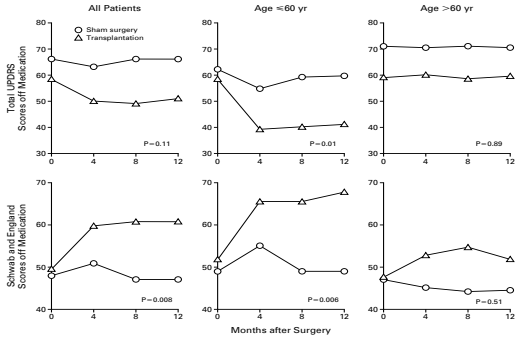


Figure 1. Unified Parkinson's Disease Rating Scale (UPDRS) Scores and Schwab and England Scores for Patients in the Sham-Surgery and Transplantation Groups while off Medication.

For the UPDRS scores, the higher the score, the worse the parkinsonism (worst possible score, 176; best possible score, 0). For the Schwab and England scores, the higher the score, the better the performance in the activities of daily living (worst possible score, 0; best possible score, 100). The scores at 0 months are the average of the scores on two base-line tests. The P values are for the comparisons between the scores in the two groups at 12 months.

Freed et al N Engl J Med 2001;344(10):710-719

THE PROMISE OF REMOTE ASSESSMENTS

REMOTE ASSESSMENTS OF PATIENTS AND STUDY PARTICIPANTS

- Although early in development, the possibilities for use of new technology to allow remote data collection are promising
- Offers a look at various aspects of patient function “in the wild”
- May provide an adjunct to face-to-face evaluation for patients engaged in clinical trials

- “mPower” app
  - Available since March 2015 via Apple App Store
  - study demonstrated use of app to gather data from patients “in the wild” for provision to researchers
  - Used surveys and sensor-based recordings
  - Individuals (PD and controls) may download, navigate inclusion/exclusion criteria, and provide e-consent
  - baseline survey/tasks provided on a dashboard
    - From 48000 downloads, 9520 consented, demographic data were provided by 6800
    - Task completion varied (968 for memory tasks, 8003 for tapping task)

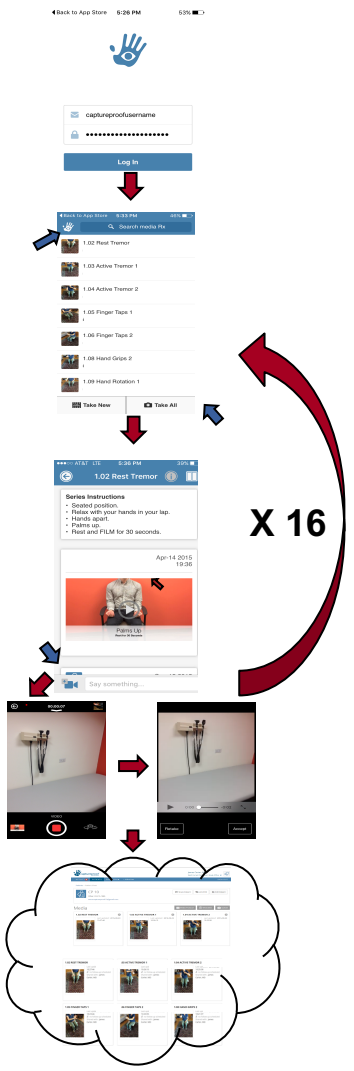
Espay, A.J., et al., Technology in Parkinson’s disease: challenges and opportunities. Mov Disord 2016. ***31****(9): p. 1272-82*

Bot, B.M., et al., The mPower study, Parkinson disease mobile data collected using ResearchKit. Sci Data, 2016. ***3****: p. 160011x*

VIRTUAL VISITS

- 6-month randomized pilot study (n=20) of home video visits for Parkinson's disease
  - feasible, outcomes comparable to traditional in-person clinic care, saved 3 hours/100 miles of travel per visit on average

- 12-month, multicenter national randomized comparative effectiveness study (Connect.Parkinson)
  - Comparing usual care in the community to usual care + four virtual house calls from a PD specialist
  - High interest from patients
    - barriers: "Digital Divide"; lack of diversity



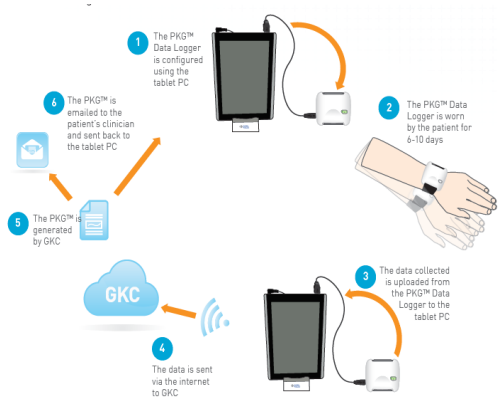
CAPTURE-PD: use of CaptureProof™ app with HIPAA-compliant cloud-based platform to communicate photos and videos (Carter et al, unpublished)

Dorsey, E.R., et al., National Randomized Controlled Trial of Virtual House Calls for People with Parkinson's Disease: Interest and Barriers. Telemed J E Health, 2016. ***22****(7): p. 590-8; Dorsey, E.R., et al., Feasibility of Virtual Research Visits in Fox Trial Finder. J Parkinsons Dis, 2015.* ***5****(3): p. 505-15; Carter et al unpublished*

WEARABLE DEVICES AND APPS

- For objective measures, multiple devices now exist that will objectively measure various features of movement, such as gait
- A systematic review identified 22 wearables

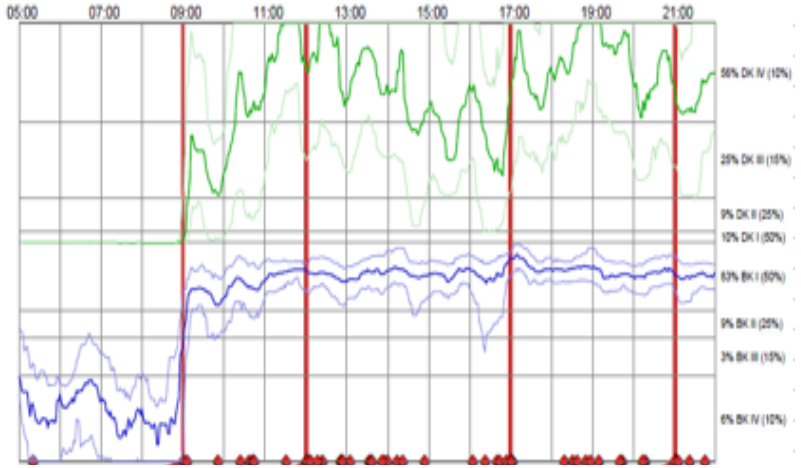
- Personal KinetiGraph (PKG™)
  - FDA-clearance for second generation device in 2016



Godinho, C., et al., A systematic review of the characteristics and validity of monitoring technologies to assess Parkinson's disease. J Neuroeng Rehabil, 2016. ***13****: p. 24; Horne, MK et al., An objective fluctuation score for Parkinson's disease. PLoS ONE 10(4):e0124522*

PKG RECORDING OF MOTOR STATUS

VIDEO



Parkinson's Kinetigraph Data Reports representing an average measure of movements recorded over a 6 day period for all subjects. Recordings were measured over a period of 17 hrs/day.
•PD Graft 02 - Severe dyskinesia appears to arise in the morning and persists for the rest of the day

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CONCLUSIONS

- Benefit for the patient is important and measures may be included in all clinical phases of development
  - Clinically meaningful endpoints in early phase trials can provide valuable preliminary information
- Disease-specific clinical rating scales are available that are validated and have adequate performance characteristics
  - Many correlate with quality of life or other patient-reported outcomes
- Patient-reported outcomes are affected by multiple uncontrolled factors
  - may not be sensitive enough to detect statistically significant changes
  - BUT are important for a broader grasp of an intervention's effects
- Use of standardized and well validated measures and harmonization where possible enhances contribution to the scientific field
  - BUT new technologies could provide clinically meaningful information in an objective and "ecological" way

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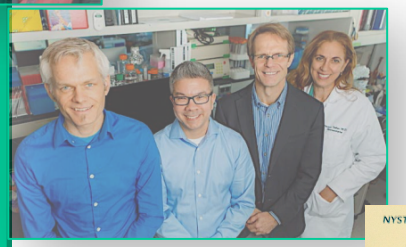

TEAM-PD "at home": Yaa Obeng-Aduasare, Natalie Hellmers CH, James Carter

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Thank you.

Questions?