Huntington Study Group
Exploring Novel HD Assessment Tools
November 8, 2019
Sacramento, CA

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The HD Patient Report of Problems (HD-PROP):
What Outcomes Matter for Patients
Ira Shoulson MD: Disclosures

- Founder and Principal, Grey Matter Technologies (GMT) LLC, Sarasota, FL (2017)
- Work conducted by GMT, with the support of the Michael J Fox Foundation for Parkinson’s Research (MJFF) via the Pritzker Prize (2017) and Computational Science grants (2018-2020)
- Former PI of the Georgetown University (GU)-FDA Center of Excellence for Regulatory Science and Innovation (CERSI) (2011-2018)
- PI of Fellowship for Regulatory Science of Parkinson Disease (Monica Javidnia PhD, fellow) sponsored by the MJFF through grants to GU and the University of Rochester (2017-2020)

- Introduction
- The HD-PROP
- PD-PROP Learning
  - Cross-Sectional Patient-Reported Natural History
  - Longitudinal Changes
  - What People Say (PROP) and What They Do (Digital Markers)
- MyHDStory
The most important elements of clinical care and research are not being heard and utilized.

When captured, what patients say is recorded in categorical terms, usually after being filtered by clinicians or technicians, or as largely ignored free-text.

Verbatim patient reporting has been viewed as infeasible, variable, and too wordy for analysis.
The Patient History

- foundation of the patient/clinician relationship
- basis for 80-85% of accurate diagnoses\(^1,2,3\)
- BUT patients get only 11-27 seconds to report their problems

So, are the most crucial data being neglected?

\(^1\)British Medical Journal 1975, 2,486-489.
\(^3\)J Gen Int Med. 2018; 341(1): 36-40
The Challenge

• How best to hear what patients say?
• How best to capture what patients say?
• How best to analyze what patients say (quality and quantity)?
• How best to apply what patients say to clinical care and clinical research?
• How best to marry what patients say (PROP) with what they do (digital markers)

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Huntington Disease
Patient Report Of
Problems (HD-PROP)

Piloting the HD-PROP in the
HSG-Prana REACH2HD Clinical Trial
Ira Shoulson MD
Boston, MA
May 3, 2012
Safety, tolerability, and efficacy of PBT2 in Huntington’s disease: a phase 2, randomised, double-blind, placebo-controlled trial

Huntington Study Group Reach2HD Investigators* Lancet Neurol 2014 Published Online ClinicalTrials.gov, NCT01590888.

![Graph showing Trail Making Test Part B results]

Decreased time to complete = improvement
### Reach2HD

**HD PATIENT REPORTED OUTCOME PROBLEM ASSESSMENT (BL)**

<table>
<thead>
<tr>
<th>SUBJECT ID</th>
<th>VISIT NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SITE NO</th>
<th>VISIT DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DD MM YYYY</td>
</tr>
</tbody>
</table>

### Initial Assessment

At entry into the study, please ask the Patient/Research Participant the following questions:

1. **What is the most bothersome problem of your Huntington disease?**
   (record the reply verbatim)

   [Blank Line]

2. **In what way does this problem bother you by affecting your every day functioning or ability to accomplish what needs to be done?**

   [Blank Line]

3. **How much (severely) does this problem bother you by limiting your functioning?**

   - 1 = Not at all
   - 2 = Mildly (minimally or rarely)
   - 3 = Moderately (more often than not)
   - 4 = Severely (plenty or all the time)
Huntington Disease Patient Reported Outcome of Problems (HD-PROP)

1. What is the most bothersome problem from your Huntington disease?

2. In what way does this problem bother you by affecting your every-day functioning or ability to accomplish what needs to be done)?

3. How much (severely) does this problem bother you by limiting your functioning?

   1 = Not at all
   2 = Mildly (minimally or rarely)
   3 = Moderately (more often than not)
   4 = Severely (plenty or all of the time)
Patient Responses Examples

<table>
<thead>
<tr>
<th>Problem Code</th>
<th>Example Verbatim Reported Patient Thinking Problems</th>
</tr>
</thead>
</table>
| Memory       | “The fact that I lose my memory - I worry about that.”  
              | “My memory is not what I would like it to be. I struggle with names of relatives, acquaintances.”  
              | “I think the lack of memory and forgetting to do things like taking my medications.” |
| Attention    | “It's hard for me to concentrate.”  
              | “Concentration has gotten much worse.”  
              | “Lack of focus.”  
              | “Distractibility.” |
| Communication| “Sometimes trying to explain something to someone I can't get the words out.”  
              | “I guess the short term communication, connecting the dots etc.”  
              | “Sometimes when I want to say something to someone I can't get my thoughts out and it turns into an argument.” |
Applying Natural Language Processing (NLP) to Verbatim Patient-Reported Outcomes

Jennifer L. Purks, BS 1Michael Harris, MS 1Karen E. Anderson, MD and 1Ira Shoulson, MD
1Georgetown University, Washington DC, United States

Introduction
• REACH2HD examined the safety and benefits of PBT2, an experimental modulator of metal ionophores, on cognitive impairment, the major and untreatable source of disability in early HD. 1
• Huntington Disease Patient Reported Outcome of Problem (HD-PROP) captures bothersome problem verbatim descriptions reported by individual patients.
• Natural Language Processing (NLP) extracts relationships and meaning from large text-based resources. 1 One tool is word clouds (images composed of words from a text where the size of the word indicates frequency or importance).

Objective: Apply Natural Language Processing (NLP) to analyze verbatim patient-reported outcomes (PROs) among Huntington Disease (HD) research participants in the Phase 2 REACH2HD randomized-controlled trial

Methods
• The HD-PROP were administered to the 109 REACH2HD participants at baseline (BL), Week 12 (W12), and Week 26 of experimental treatment (W26) (randomly assigned to PBT2 250 mg/day (n=36), PBT2 100 mg/day (n=38), or placebo (n=35).
• NLP, specifically word clouds, was applied to the HD-PROP problem and consequence data in the REACH2HD trial at BL, W12, W26, and all time points to extract relationships and meaning from large text-based resources.

Table 1: Most commonly reported single word from Word Cloud with Example Verbatim Reported Problem Responses

<table>
<thead>
<tr>
<th>Word</th>
<th>Example Verbatim Reported Problem Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance</td>
<td>“Not riding bike-balance” “balance, not so good question if my balance is good.” “I’ve been having trouble with balance”</td>
</tr>
<tr>
<td>Memory</td>
<td>“Memory is not what I would like it to be” “the fact that my memory is not what it used to be”</td>
</tr>
<tr>
<td>Movements</td>
<td>“The fact that my movements are still around even with medication” “the fact that my movements are still around even with medication”</td>
</tr>
</tbody>
</table>

Results
• The Problem Word Cloud showed that: “BALANCE” (60 counts), “MEMORY” (66 counts) and “MOVEMENTS” (48 counts) were the most bothersome reported problems (Figure 1).
• There was a decrease from 8 “MEMORY” counts at BL to 4 “MEMORY” counts at W26 in the PBT2 250mg group (Figure 3).
• However the Functional Consequence Word Cloud (Figure 2) did not show a clear informative pattern.

Figure 3: Verbatim Problems by treatment group over time

Conclusion
• The NLP word clouds for verbatim-reported problems and consequences help to quantify and visually depict patterns in the HD-PROP dataset of the REACH2HD trial.
• Verbatim problems are more uniformly informed by NLP than verbatim consequences, perhaps related to the complexity of the questions and replies. This may reflect lack of insight or impaired cause and effect reasoning between problem and its functional consequence in this patient population.
• Some PBT2 250mg treatment effect on MEMORY is suggested by these results.

Future Directions
• More advanced NLP may provide more informative analysis of PROs:
  • Tri-grams (frequencies of three words reported together)
  • Text metrics (number of characters or words in a response)
  • Sentence parsing (model of grammatical sentence structure)

Acknowledgements & References
REACH2HD examined the safety and benefits of PBT2, an experimental modulator of metal ionophores, on cognitive impairment, the major and untreatable source of disability in early HD.


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Fox Insight (www.foxinsight.org)

Dynamic online clinical study sponsored by The Michael J. Fox Foundation (MJFF) where people with Parkinson’s disease and control volunteers contribute data longitudinally (3-6 months) on their experiences. The study also involves a genetic testing component, through 23&me.

Participants consent to sharing de-identified data for research and option to be contacted about future research.
The Parkinson Disease Patient Report of Problems
(PD-PROP©)

Devised to capture the *verbatim* accounts of PD patients about:

1. **Bothersome Problems:**
   What bothers you the most about your Parkinson Disease?

2. **Functional Consequences:**
   In what way does this problem bother you by affecting your daily functioning?

3. **Problem severity:** *(0-1-2-3 categorical scale)*

4. **Remedies:** *(PROP version 2.0)*
   What do you do to lessen or relieve the problem?

   *(questioned and answered re 2nd most bothersome, up to 5th most bothersome)*

Modeled after the Huntington Disease (HD)-PROP *(Ann Neurology 80, S69–S69, 2016)*
The Parkinson Disease Patient Report of Problems: Verbatim Examples of GAIT DISORDER

<table>
<thead>
<tr>
<th>Subject</th>
<th>Problem</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>gait issues. This can hinder some of the activities I want to participate in.</td>
<td>it reduces my ability to participate in activities I enjoy like walking with my spouse.</td>
</tr>
<tr>
<td>2</td>
<td>foot cramps when walking more than 10 minutes outside</td>
<td>it is quite painful to go about my daily life (i.e. go to work, shopping, etc)</td>
</tr>
<tr>
<td>3</td>
<td>abnormal shuffling gait, freezing, slow movement</td>
<td>slow gait and freezing sometimes results in falling</td>
</tr>
</tbody>
</table>
## Parkinson Disease Patient Report of Problems: Verbatim Examples of BALANCE

<table>
<thead>
<tr>
<th>Subject</th>
<th>Problem</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>constantly feeling off-balance, afraid to climb stairs, and feeling that I need to move slowly so that I don't fall.</td>
<td>it makes it difficult for me to want to go out for fear of falling, or holding people up, or just looking ridiculous.</td>
</tr>
<tr>
<td>2</td>
<td>I have trouble walking because I have trouble standing up straight and often I am off balance, so usually I use a walking cane.</td>
<td>it bothers me because I used to walk miles every day for exercise.</td>
</tr>
<tr>
<td>3</td>
<td>my most bothersome problem would be balance or lack of it.</td>
<td>I have had several falls including one where I broke my hip. I now use either a walking stick or two nordik poles.</td>
</tr>
</tbody>
</table>
The Parkinson Disease Patient Report of Problems: Verbatim Examples of FALLING

<table>
<thead>
<tr>
<th>Subject</th>
<th>Problem</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>not being able to walk very well &amp; falling.</td>
<td>it's very hard to go any place when your worried about walking &amp; falling</td>
</tr>
<tr>
<td>2</td>
<td>mobility issues, such as frozen feet in crowded public areas causing a sense of concern in falling.</td>
<td>how easy it is to have a fall with the likelihood of personal injury. I've experienced a number of these already.</td>
</tr>
<tr>
<td>3</td>
<td>falling and fear of falling</td>
<td>very self-conscious and less willing to be in the public eye</td>
</tr>
</tbody>
</table>
Distribution of Years Since Diagnosis (YSD)  
(N = 18607, Range 0-10 YSD)

Data Source Date: July 5th, 2019
Distribution of Number of Most Bothersome PROBLEMS (1st, 2nd, 3rd, 4th, 5th, if applicable)
PATIENT REPORT OF PROBLEMS (PROP)
VERBATIM REPORT TO ANALYZABLE OUTPUT

PROP CAPTURE
- Build the PROP Platform
- Recruit and Consent Patients
- Capture PROP into Database

DATA MINING
- Extract, Transform, Load (ETL)
- Natural Language Processing (NLP)
- Data Extraction for Curation

CLINICAL CURATION
- Define Symptom Bins
- Perform Independent Curation
- Create Gold Standard Labels

ADVANCED ANALYTICS
- Machine Learning
- Map to UMLS
- Extract Insightful Data
# ANALYSIS OF POSTURAL INSTABILITY

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Synonyms</th>
<th>Sub-categories</th>
<th>Terms within the verbatim used for extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural Instability</td>
<td>balance, fall, freeze, gait, imbalance, stagger, unsteady, walk</td>
<td>Gait disorder</td>
<td>difficulty walking, foot cramps (appearing in the context of the term “walking”), gait, limp, short steps, shuffling, stumbling, twisting, walk/walking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slowness</td>
<td>bradykinesia, can't keep up, slow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Balance</td>
<td>balance, imbalance, instability, off balance, stability while walking, stagger, unstable walking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stiffness</td>
<td>stiffness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Falling</td>
<td>fall/fallen/falling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Freezing</td>
<td>festination, freeze/freezing/frozen, freezing when walking, stutter step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posture</td>
<td>bending over, keep body straight, leaning backward, posture</td>
</tr>
</tbody>
</table>
### PD-PROP

**CLINICALLY-CURATED MOTOR SUB-SYMPTOMS**

<table>
<thead>
<tr>
<th>Motor Signs and their Sub-Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
## PD-PROP
### CLINICALLY-CURATED NON-MOTOR SUB-SYMPTOMS

<table>
<thead>
<tr>
<th>SLEEP</th>
<th>FATIGUE</th>
<th>COGNITION</th>
<th>MOOD</th>
<th>PAIN</th>
<th>BOWEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Fatigue (intrinsic to PD)</td>
<td>Language/Word Finding</td>
<td>Anxiety</td>
<td>Pain</td>
<td>Constipation</td>
</tr>
<tr>
<td>Unspecified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>Sleep problem</td>
<td>Memory</td>
<td>Depression</td>
<td>Cramp</td>
<td>Bloating</td>
</tr>
<tr>
<td>Fragmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Sleepiness</td>
<td>Depression/Anxiety disorders</td>
<td>Concentration/Attention</td>
<td>Frustration</td>
<td>Discomfort</td>
<td>Other</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness Unspecified</td>
<td>Muscle Over-use</td>
<td>Cognitive Slowing</td>
<td>Apathy</td>
<td>Headache</td>
<td>Bowel pain</td>
</tr>
<tr>
<td>Sleepiness Unspecified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLS</td>
<td>Other (specify)</td>
<td>Confusion</td>
<td>Irritability</td>
<td>Painful dystonia</td>
<td>Bowel incontinence</td>
</tr>
<tr>
<td>RBD</td>
<td>Indeterminant</td>
<td>Learning Difficulty</td>
<td>Sadness</td>
<td></td>
<td>Bowel frequency</td>
</tr>
<tr>
<td>Sleep onset insomnia</td>
<td></td>
<td>Hallucination/Delusion</td>
<td>Other</td>
<td></td>
<td>Bowel urgency</td>
</tr>
<tr>
<td>Vivid Dreams</td>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td>Bowel obstruction</td>
</tr>
</tbody>
</table>

*PD-PROP: PD-Proposed Observation Protocol, a list of non-motor signs and their sub-symptoms.*
METHODOLOGY – Initial analysis

- Word cloud for the Uni-Gram of Most Bothersome Problem by years since diagnosis (0-5 & 6-10 years).

10,362 patients and 45,232 problems
Motor ~51.5%, Non-Motor ~48.5% of symptom terms
TERM DISTRIBUTION OF EACH SYMPTOM BY PATIENT PRIORITY (1=MOST BOTHERSOME...TO 5 = 5TH MOST BOTHERSOME)

10,362 patients and 45,232 problems
Motor ~51.5%, Non-Motor ~48.5% of symptom terms

Data Source Date: MJFF Aug 2nd 2018
FREQUENCY OF POSTURAL INSTABILITY SYMPTOMS COMPARING PATIENT AGE AND YEARS SINCE DIAGNOSIS (YSD)
CURATION of TERMS
VIDEO 3-d visualization of sub-categories
FREQUENCY OF TERMS BY PATIENT REPORTED AGE AND YSD
Original Investigation

Natural History of Huntington Disease

E. Ray Dorsey, MD, MBA; Christopher A. Beck, PhD; Kristin Darwin, BS; Paige Nichols, BA; Alicia F. D. Brocht, MS; Kevin M. Biglan, MD, MPH; Ira Shoulson, MD; for the Huntington Study Group COHORT Investigators

ANALYSIS OF POSTURAL INSTABILITY

Distribution of sub-categories within symptom – curated data
NLP Post Clinical Curation

Analysis of frequency of problems related to Postural Instability and its sub-symptoms (Gait Disorder, Balance and Falling) by age and years since diagnosis
CURATION OF TERMS
3-D VISUALIZATION OF POSTURAL INSTABILITY SUB-CATEGORIES

FREQUENCY OF TERMS BY PATIENT REPORTED AGE AND YSD

Analyes of Symptoms Facilitates Trial Recruitment and Enrollment
Company They Keep Analysis

Terms and their co-occurrence relative to three sub-symptoms Balance, Falling and Gait Disorder of the Postural Instability domain

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July 2019 Dataset

Data Source Date: July 5th, 2019
WORD CLOUD ACROSS STUDY VISITS ALL PREFERENCES AND SEVERITIES

PROP Visit #1

PROP Visit #2

PROP Visit #3

PROP Visit #4

PROP Visit #5

Data Source Date: March, 2019
WORD CLOUD ACROSS STUDY VISITS ALL PREFERENCES AND SEVERITIES (N-GRAM TREMOR REMOVED)

Data Source Date: March, 2019
WORD CLOUD FOR SUBJECTS WHO REPORTED POSTURAL INSTABILITY SUB-SYMPTOM AS A BOTHERSOME PROBLEM AND WHO HAD AT LEAST 3 PROP VISITS (N=1712)

PROP visit #1 (Baseline)

PROP visit #2 (~ 6 months)

PROP visit #3 (~ 12-24 months)
FREQUENCY DISTRIBUTION FOR SUBJECTS WHO REPORTED POSTURAL INSTABILITY SUB-SYMPTOM AS A BOTHERSOME PROBLEM AND WHO HAD AT LEAST 3 PROP VISITS (N = 1712)

Data Source Date: MJFF July 5th, 2019
CALIBRATING THE PROP

Focus on BETTER-WORSE-SAME

1. Priority of bothersome problem (1st-5th most bothersome)
2. Severity of problem (0-1-2-3)
3. Verbatim NLP
   a. BETTER-WORSE-SAME
   b. Change in Curated Problem/Consequence
4. Rx change (e.g., initiation of DA Rx)
5. Clinical Global Impression of Change reported by patient (CGICp)
   -3, -2, -1, 0, +1, +2, +3
Fox Insight Rxs

Anti-PD Rxs reported by ~95% PD-PROP subjects (n~10,000) as of August 2018
EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON’S DISEASE

The Parkinson Study Group*

Abstract Background and Methods. In 1987 we began a multicenter controlled clinical trial of deprenyl (a monoamine oxidase inhibitor) and tocopherol (a component of vitamin E that traps free radicals) in the treatment of early Parkinson’s disease. We randomly assigned 800 patients to one of four treatments: placebo, active tocopherol and deprenyl placebo, active deprenyl and tocopherol placebo, or both active drugs. The primary end point was the onset of disability prompting the clinical decision to begin administering levodopa. An interim analysis showed that deprenyl was beneficial (N Engl J Med 1989;321:1364–71). We report the results of tocopherol treatment after a mean (±SD) follow-up of 14±6 months, as well as the follow-up results for deprenyl.

Results. There was no beneficial effect of tocopherol or any interaction between tocopherol and deprenyl. The beneficial effects of deprenyl, which occurred largely during the first 12 months of treatment, remained strong and significantly delayed the onset of disability requiring levodopa therapy (hazard ratio, 0.50; 95 percent confidence interval, 0.41 to 0.62; P<0.001). The difference in the estimated median time to the end point was about nine months. The ratings for Parkinson’s disease improved during the first three months of deprenyl treatment; the motor performance of deprenyl-treated patients worsened after the treatments were withdrawn.

Conclusions. Deprenyl (10 mg per day) but not tocopherol (2000 IU per day) delays the onset of disability associated with early, otherwise untreated Parkinson’s disease. The action of deprenyl that accounts for its beneficial effects remains unclear. (N Engl J Med 1893;328:176–83.)

Early (de novo) subjects at enrollment were followed for up to 7.5 years, including randomized changes in deprenyl (selegiline) and dopaminergic Rx.
UPDRS (Part 3) Postural Instability (‘Retropulsive Pull Test’) Posture ≥2 (3 or 4 ratings)
3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.
4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

(Karl Kieburtz circa 1991)

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Evaluation of Smartphone-Based Testing to Generate Exploratory Outcome Measures in a Phase 1 Parkinson’s Disease Clinical Trial

F. Lipsmaier, PhD,1 K. L. Taylor, PhD,1 T. Khenmann, MSc,1 D. Wolf, MSc,1 A. Scotland, MSc,1 J. Schipper-Eriksen, PhD,1 W. Y. Chang, PhD,1 I. Fernandez-Garcia, PhD,1 J. Siebourg-Polster, PhD,1 L. Jin, MD,1 J. Soto, BS,2 L. Versailles, MA,1 F. Boess, PhD,1 M. Koller, MD,2 M. Grundman, MD,2,3 A. U. Monsch, PhD,4 R. B. Postuma, MD,5 A. Ghosh, PhD,1 T. Kremer, PhD,1 C. Czeck, PhD,1 C. Gossens, PhD 1,6 and M. Lindemann, PhD1

1Roche Pharma Research and Early Development, pRED informatics, Pharmaceutical Sciences, Clinical Pharmacology, and Neuroscience, Ophthalmology, and Rare Diseases Discovery and Translational Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland
2Prothena Biosciences Inc., South San Francisco, California, USA
3Global R&D Partners, LLC, San Diego, California, USA
4Felix Platter Hospital, University Center for Medicine of Aging, Memory Clinic, Basel, Switzerland; University of Basel, Faculty of Psychology, Basel, Switzerland
5Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada

Movement Disorders, vol. 33, no. 8, 2018
FIG. 1. Screenshots of the smartphone application and workflow for the daily assessments. The smartphone (Galaxy S3 mini; Samsung, Seoul, South Korea) was provided with a single, preinstalled custom application (Roche PD Mobile Application v1; Roche, Basel, Switzerland). The application requested the completion of six active tests daily and subsequently recorded sensor data during daily living (“passive monitoring”), whereby participants were instructed to carry the smartphone in their trouser pocket, or a small bag around the waist.
Passive Digital Monitoring captures differences between PD (n=44; YSD=3.5) and age-matched healthy controls (n=35) for Turning and Gait activities.

**FIG. 2.** Machine-learning algorithms applied to passive monitoring data revealed multiple aspects of significantly reduced everyday motor behavior in PD participants compared with controls. See Results (Reliability of Testing) for details. **P < 0.01; ***P < 0.001. C, control group.
The HD Patient Report of Problems (HD-PROP):
What Outcomes Matter for Patients

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- MyHDStory
“Sharing HD Experiences. Improving HD Research. Shaping Future Care.”

HSG online observational research study to capture longitudinal data from the perspectives of people in the Huntington disease community – learning about individual “stories” – to seek better care and treatments for those affected by HD

➢ Researchers and sponsors can better identify research participants and facilitate the enrollment and conduct of HD clinical trials
➢ Research platform to track consenting participants and characterize long-term effects
➢ Enable and empower the HD community to improve care and advance treatments that make a difference
The Huntington Disease Patient Report of Problems (HD-PROP©)

Devised to capture the verbatim accounts of HD patients about:

1. **Bothersome Problems:**
   What bothers you the most about your Huntington Disease?

2. **Functional Consequences:**
   In what way does this problem bother you by affecting your daily functioning?

3. **Problem severity:** (0-1-2-3 categorical scale)

4. **Self-Interventions:** (PROP version 2.0)
   What do you do to lessen or relieve this problem?

   (questioned and answered re 2nd most bothersome, up to 5th most bothersome)
Devised to capture the verbatim accounts (‘tell us in your own words’) about:

1. **Bothersome Problems:**
   **What bothers you the most about your health?**

2. **Functional Consequences:**
   **In what way does this problem bother you by affecting your daily functioning?**

3. **Problem severity:** *(0-1-2-3 categorical scale)*

4. **Self-Interventions:** *(PROP version 2.0)*
   **What do you do to lessen or relieve this problem?**

   *(questioned and answered re 2nd most bothersome, up to 5th most bothersome)*
PsychoSocial Report of Problems
(PS-PROP©)
Devised to capture the verbatim accounts (‘tell us in your own words’) about:

1. Bothersome Problems:
   What bothers you the most about your day-to-day life as related, for example, to personal, family, financial, social, or other aspects?

2. Functional Consequences
   In what way does this problem bother you by affecting your daily functioning?

3. Problem severity: (0-1-2-3 categorical scale)

4. Self-Interventions: (PROP version 2.0)
   What do you do to lessen or relieve this problem?

(questioned and answered re 2nd most bothersome, up to 5th most bothersome)
Remote Platform Advantages

• Low burden for participants (avoids on-site travel and in-person reporting; comfort and privacy of home)
• Central IRB – eConsent
• Geographic and socio-economic diversity
• Characterizes stratification and validation cohorts in planning RCTs
• Enriches eligibility criteria and identifies target cohort
• Development of clinical outcome assessments
• Inherently patient-centered
• Rich data-sharing opportunity
Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at druginfo@fda.hhs.gov, (855) 543-3784, or (301) 796-3400 or (CBER) Office of Communication, Outreach, and Development at occod@fda.hhs.gov, 800-425-4709 or 240-402-8110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
Procedural
Despite modern medicine’s infatuation with high-tech gadgetry, the single most powerful diagnostic tool is the doctor-patient conversation, which can uncover the lion’s share of illnesses. However, what patients say and what doctors hear are often two vastly different things.

Listen to your patient; they are telling you the diagnosis.”

Dr. William Osler (circa 1903)

Because chat collects the full conversation, the patient voice is the medical record. No check boxes, no drop-down menu autofill. Artificial intelligence built on chat records can fulfill both Osler’s mandate to “listen” and Silicon Valley’s promise to “learn.”

Blake McKinney MD, September 30, 2019

STAT, Adobe
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