Consensus development of digital measures of activity and movement for use in clinical trials

10th Winter Symposium of The Human Motion Project

Scottie Kern – Executive Director, eCOA Consortium

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C-Path funding acknowledgement

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- *The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.*

Critical Path Initiative and C-Path

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- In 2004, FDA launched the Critical Path Initiative (CPI) with a report titled "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"

- In 2005, in response to CPI, the Critical Path Institute was formed as an independent nonprofit organization "… to foster development of new evaluation tools to inform medical product development"

Tucson, AZ. USA

Amsterdam, NL

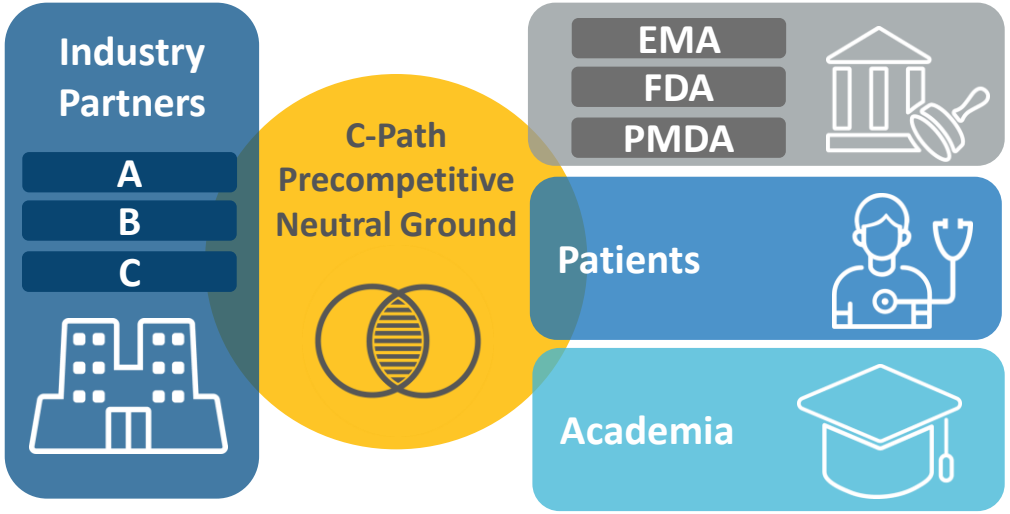
What We Do

CRITICAL PATH INSTITUTE

- Foster development of new evaluation tools to inform medical product development and regulatory decision-making
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise

The best science

- ✓ The broadest experience
- ✓ Active consensus building
- ✓ Shared risks and costs



- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Obtain official regulatory endorsement of novel methodologies and drug development tools

PRO CONSORTIUM
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PARKINSON'S CONSORTIUM

Developing endpoint measures in isolation

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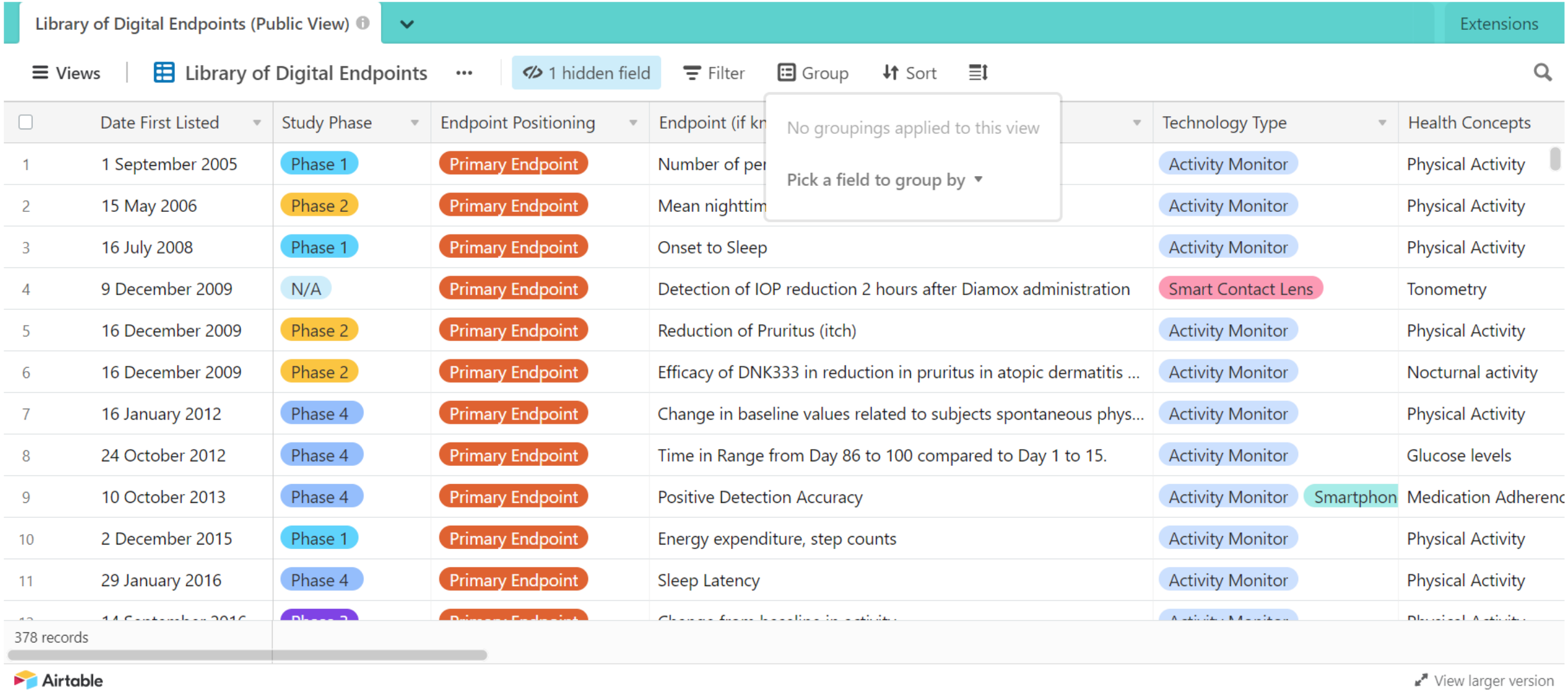

Taken from Digital Medicine Society's *Library of Digital Endpoints* https://dimesociety.org/

PRO Consortium's CHF Working Group

Development of activity monitor-based COA for CHF clinical trials

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FDA COA Qualification Program

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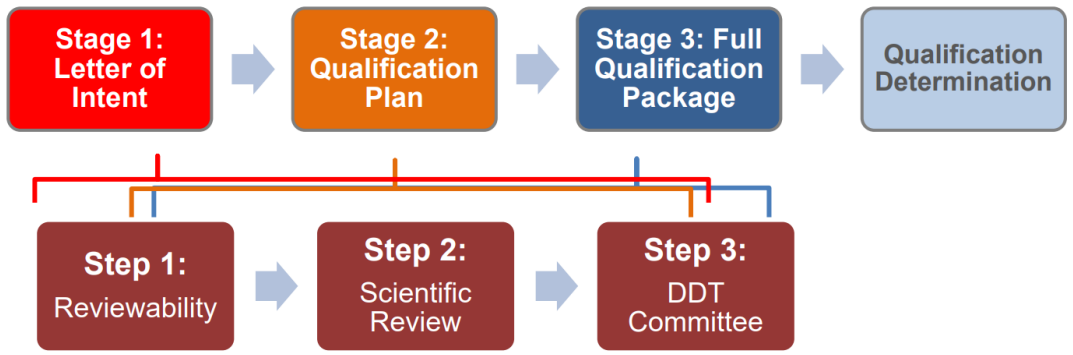
What is 'Qualification'

- A conclusion that within the qualified COU, the COA can be relied upon to have a specific interpretation and application in drug development and regulatory review.
- Once qualified, the COA can be included in IND/NDA/BLA submissions without needing FDA to reconsider and reconfirm its suitability

CDER COAQP Stages



Qualification Stage	Review Clocks
Letter of Intent (LOI)	3 months (calendar days)
Qualification Plan (QP)	6 months (calendar days)
Full Qualification Package (FQP)	10 months (calendar days)

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Chronic Heart Failure (CHF)	DDT COA #000084: Kansas City Cardiomyopathy Questionnaire (KCCQ)	CHF symptoms and their impact on physical limitations	Patients with CHF	PRO

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Major Depressive Disorder (MDD)	DDT COA #000008: Symptoms of Major Depressive Disorder Scale (SMDDS)	Overall symptoms of MDD	Adults (>18 years) with a clinical diagnosis of MDD and: • treated in an ambulatory setting • experienced a major depressive episode within the last 6 months	PRO

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Non-Small Cell Lung Cancer (NSCLC)	DDT COA #000009: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)	Symptom severity (cough, pain, dyspnea, fatigue, and appetite)	Adult patients (> 18 years) with Stage IIIB or IV NSCLC that are: • Treatment naïve (i.e., treatment naïve to current chemotherapy and not having received chemotherapy for the past 6 months from study enrollment) • Treated (i.e., received chemotherapy in the last 6 months and recovered from any prior treatment related toxicities/adverse events to CTCAE v4.03 grade 1 or better)	PRO

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Acute Bacterial Exacerbation of Chronic Bronchitis in patients with Chronic Obstructive Pulmonary Disease (ABECB-COPD)	DDT COA #000003: Exacerbations of Chronic Pulmonary Disease Tool (EXACT)	Symptoms of ABECB-COPD	Outpatients with ABECB-COPD who meet the clinical trial entry criteria as described in the FDA Guidance: *Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment.*	PRO

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Irritable Bowel Syndrome (IBS)	DDT COA #000005: Diary for Irritable Bowel Syndrome Symptoms- Constipation (DIBSS-C)	Aspects of symptom experience associated with irritable bowel syndrome with constipation	Patients 18 years and older with a diagnosis of IBS-C as defined by the Rome Criteria and the final FDA IBS Guidance	PRO

Disease/Condition	DDT COA Number and Instrument Name	Concept of Interest	Context of Use	COA Type
Asthma	DDT COA #000006: Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)	Asthma symptoms	Adolescent (12 -17 years) and adult patients	PRO
Chronic Obstructive Pulmonary Disease (COPD)	DDT COA #000017: Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD)	Respiratory symptoms of stable COPD	Adult outpatients with stable COPD	PRO

CHF WG Background

- PRO Consortium member representatives and FDA advisors identified CHF as a priority area with an unmet need for a 'fit-for-purpose' clinical outcome assessment (COA) approach to evaluate clinical benefit in CHF clinical trials.
- The Chronic Heart Failure (CHF) Working Group has been developing evidence for the qualification of 3 clinical outcome assessments (COAs) for use in CHF clinical trials:
  - Two patient-reported outcome (PRO) measures
    - *Chronic Heart Failure-Symptom Scale* (*CHF-SS*)
    - *Chronic Heart Failure-Impact Scale* (*CHF-IS*)
  - One activity monitor-based endpoint measure

- Letters of Intent (LOIs) were submitted to FDA, and all measures were accepted into FDA's COA Qualification Program in April 2019.
  - In its response to the LOIs, FDA requested a Qualification Plan for each COA.

Activity Monitor-based Endpoint Measure: Strategy

- Main challenge: determining what variable(s) from an activity monitor will be used to derive an endpoint that would reflect a meaningful aspect of physical activity to persons with CHF.

Concept elicitation

Qualitative evidence regarding day-to-day physical activities most meaningful to patients

- Activity types
- Activity Dimensions
- Narrative analysis

Literature review

Review of recent literature was performed as an informal step to guide the overall efforts

Observational study

Parallel study using an activity monitor, funded by Amgen

Advisory Panel

- Provide feedback on the proposed metrics for an activity monitor-based endpoint measure in CHF.
- 2 meetings

Observational study: defining the metric

- Study data donated by Working Group Member Firm
  - Reliance on donation of data
- Tri-axial accelerometry data for 108 patients
- Wrist-worn activity monitor – targeted 28 days of passive data collection
- Obtained raw data and deidentified
- **Algorithm selection**
  - Types of algorithm
  - Context of use
  - Rules and conditions
- Intent is to apply to any wrist-worn activity monitor
- Technical requirements
  - e.g., Sample rate
- Analyse data in context of PRO completions
- Endpoint package licensable for use in clinical trials

Critical Path for Parkinson's

Consensus development of movement-based measures of PD progression

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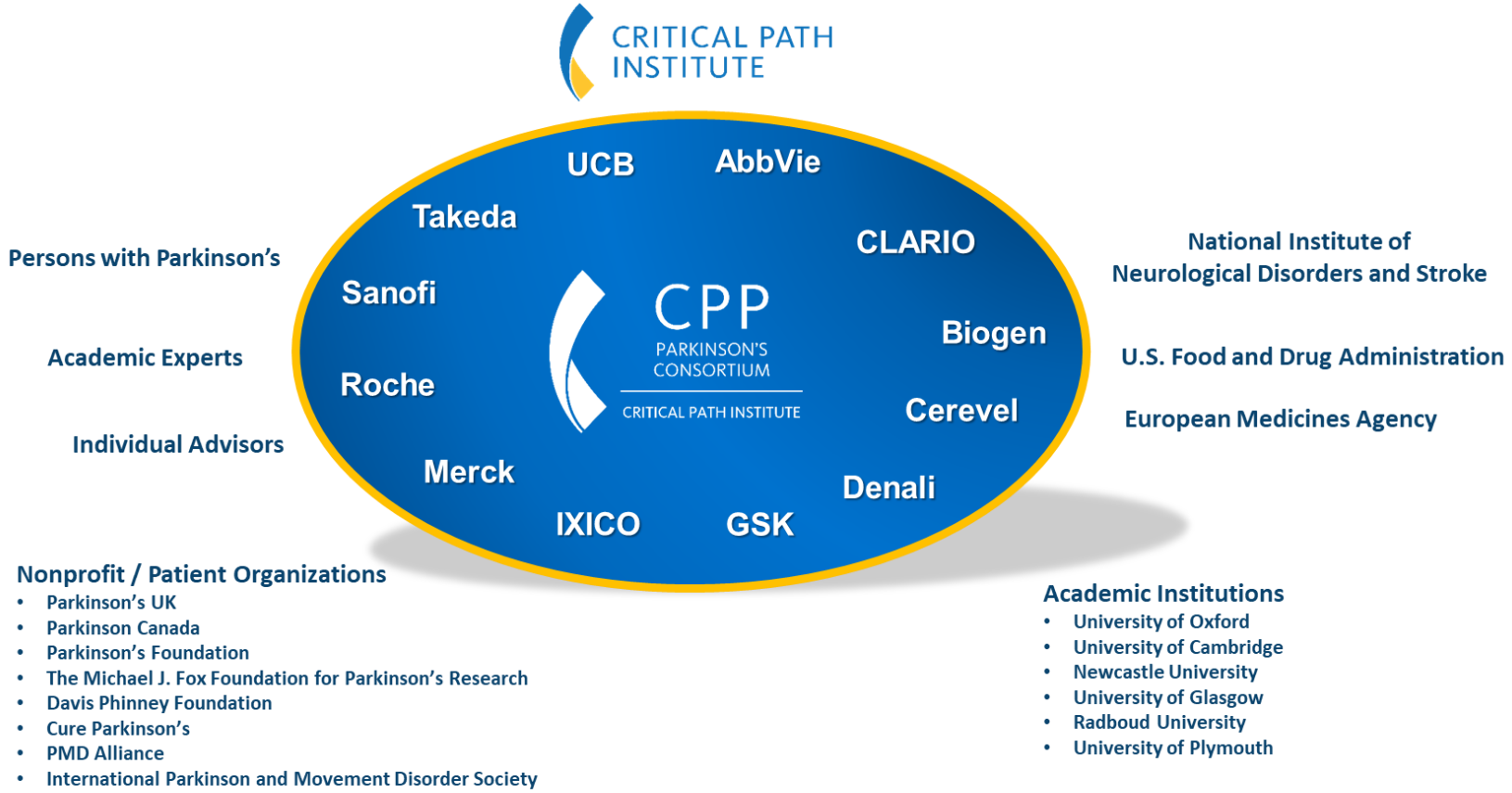
Critical Path for Parkinson's Consortium

Mission: ***To serve as a leading international consortium to collectively advance data driven collaborative research under the advisement of worldwide regulatory agencies***

- CPP was launched in 2015 with a major goal to develop tools to quantify disease progression
- Successfully acquired and integrated patient level data from >12,500 PD patients
- Current CPP focus is regulatory endorsement of PD drug disease trial model
- Digital Drug Development Tools (3DT) team was launched under CPP with the goal of advancing regulatory readiness of digital health technologies in early PD studies



CPP target population for drug development tools

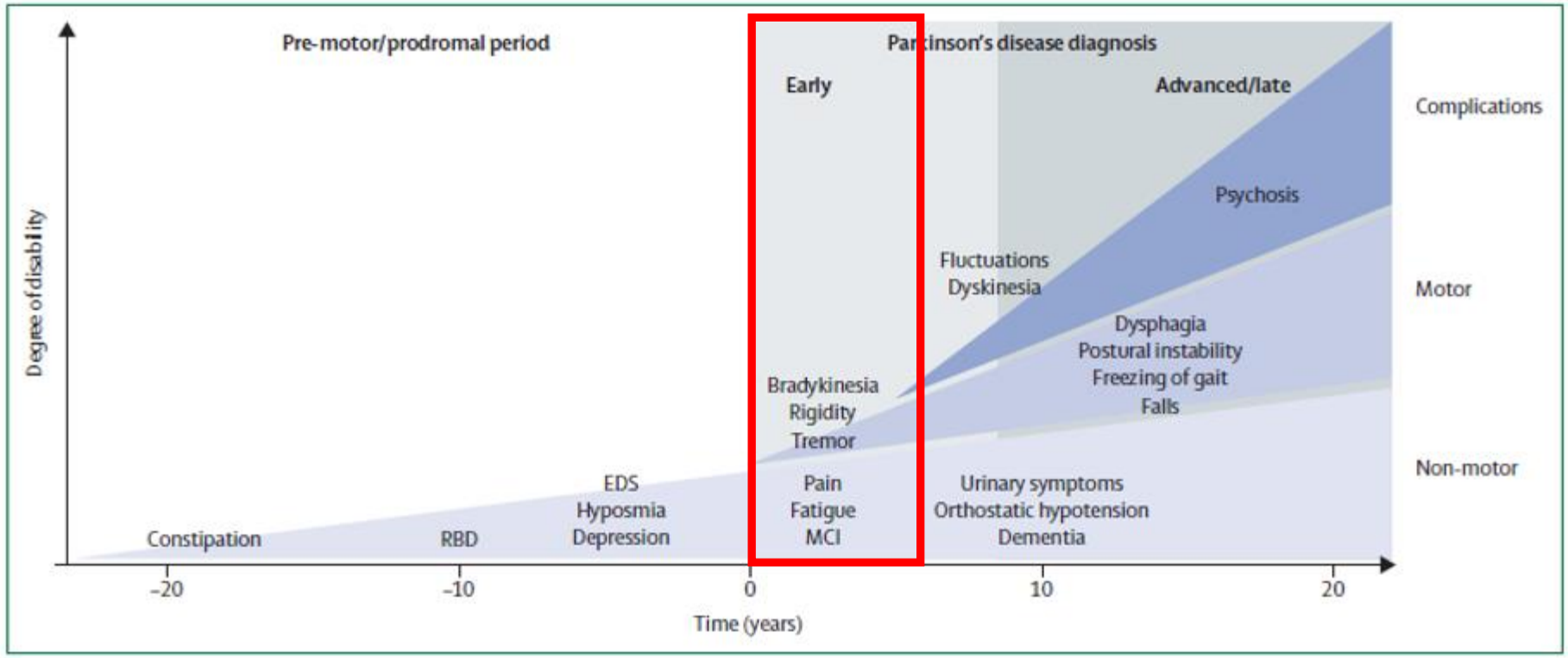


Figure 1: Clinical symptoms and time course of Parkinson's disease progression

Adapted from: Kalia et al., Parkinson's disease, Lancet 386: 896-912.

WATCH-PD (Wearable Assessments in The Clinic and Home in PD)

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WATCH-PD USES THREE TECHNOLOGIES

IPHONE, APPLE WATCH, AND APDM WEARABLE SENSORS

IPHONE

iPhone applications can provide a convenient, comfortable way to frequently report symptoms and see how you're doing. During the study, we'll ask you to track your symptoms and perform motor and cognitive assessments on the phone.

APPLE WATCH

The Apple Watch has many sensors that can detect tremor, gait, balance, and other features of movement. During the study, we'll ask you to complete a set of motor activities while wearing the watch.

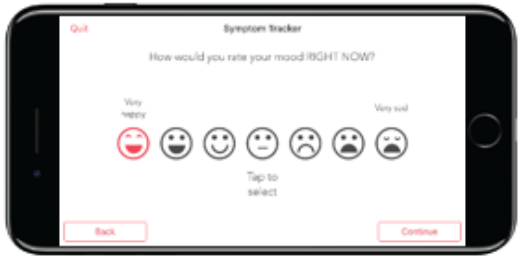
APDM WEARABLE SENSORS

APDM Opal sensors make up a state-of-the-art system for measuring many aspects of your movement. At study visits, we'll ask you to complete a set of motor activities while wearing the sensors.

WATCH-PD Study Design – Clinic Visits

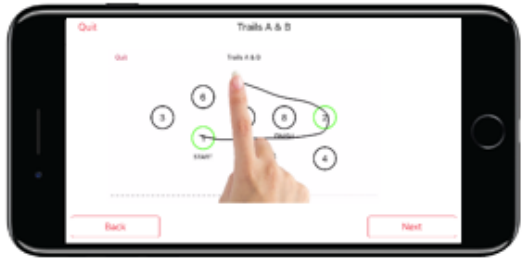
Mobile test battery (twice monthly)

Symptom PRO (2 min)



- Mood
- Fatigue
- Cognition
- Tremor
- Bradykinesia

Cognitive/Psychomotor Tasks (10 min)



- Trailmaking
- Digit Symbol Substitution (DSST)
- Visual Working Memory
- Alternate Finger Tapping
- Fine Motor
- Speech

Instrumented Motor Tasks (5 min)

- Gait
- Balance
- Tremor

Continuous passive data collection (for 7 days after each visit)

Apple Watch

- Accelerometer
- Gyroscope
- Apple Movt. Disorders API for continuous tremor monitoring

WATCH-PD Baseline Results are Promising

News > Medscape Medical News > Conference News > MDS 2021

Apple Devices Identify Early Parkinson's Disease

Daniel M. Keller, PhD

September 24, 2021

1 Read Comment

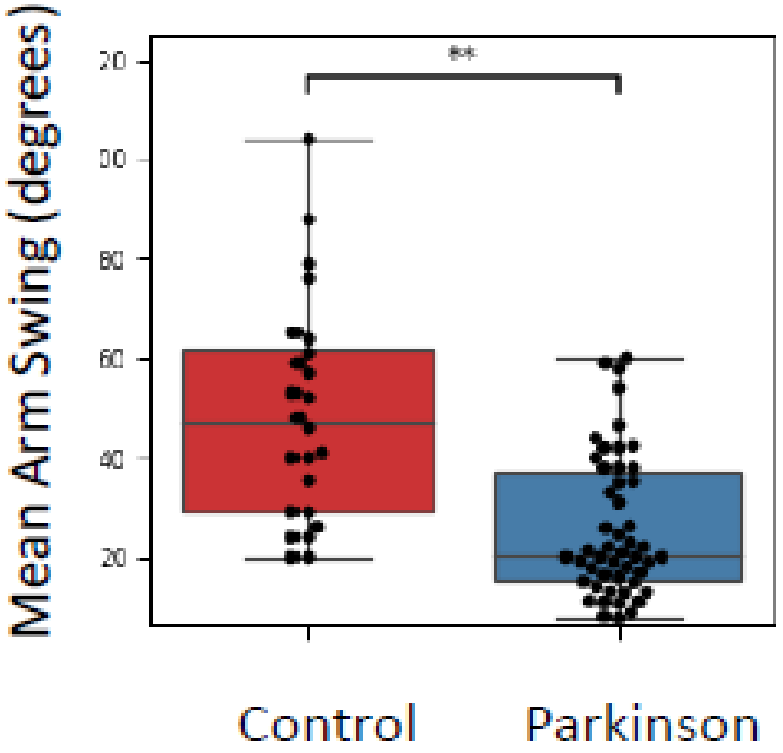
Add to Email Alerts

Apple Watches and iPhones can differentiate between individuals with early, untreated Parkinson's disease (PD) and healthy controls, new research shows.

Results from the WATCH-PD study show clear differences in a finger-tapping task in the PD vs control group. The finger-tapping task also correlated with "traditional measures," such as the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), investigators report.

Adams J et al., Movement Disorders Congress, Sept 2021
Funded by Biogen, Takeda, CPP 3DT and led by University of Rochester

A smartwatch can differentiate arm swing between individuals with Parkinson's disease and controls



Engage Regulatory Agencies Early and Often

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: 7/10/2019

Subject: Critical Path Innovation Meeting: Parkinson's Disease Digital Drug Development Tools

Date of meeting: 5/14/2019

Requestor: Critical Path Institute, Critical Path for Parkinson's

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

FDA Representatives

Center for Drug Evaluation and Research
Office of Business Informatics (OBI)

EMA initiatives to support drug development

EUROPEAN MEDICINES AGENCY

What do we provide?

2. Innovation Task Force (ITF) platform and meetings

5 August 2019

ITF Briefing Meeting Report

Critical Path Institute Ltd, Critical Path for Parkinson's (CPP) Consortium

Briefing meeting held at the European Medicines Agency (EMA) on 15th July 2019.

The objective of the ITF briefing meetings is to provide for a preparatory discussion on scientific and regulatory topics relevant to the development of new medicinal products and technologies complementing and reinforcing existing formal procedures.

U.S. FOOD & DRUG ADMINISTRATION

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Critical Path Innovation Meetings (CPIM)

Advice from Regulatory Agencies Informs the Path

The importance of properly evaluating clinically meaningful aspects of motor, non-motor, and mood-related manifestations of PD.

The importance of assessing patients' perspective on how digital measures assess how patients function and feel.

A recommendation to conduct exit interviews to gather patient feedback on their experience with DHTs.

Technical issues related to the impact of hardware/software changes on results, data quality issues, how to address missing data, and the need for transparency of algorithms.

The importance of establishing **normative databases** of metrics that will be collected with wearable devices.

A suggestion that it may be beneficial to enroll subjects at the earliest point possible in disease progression to identify sensitive measures that are uniquely applicable to early PD.

Tackling Clinical Meaningfulness by Listening to Patients:
WATCH-PD Qualitative Sub-study

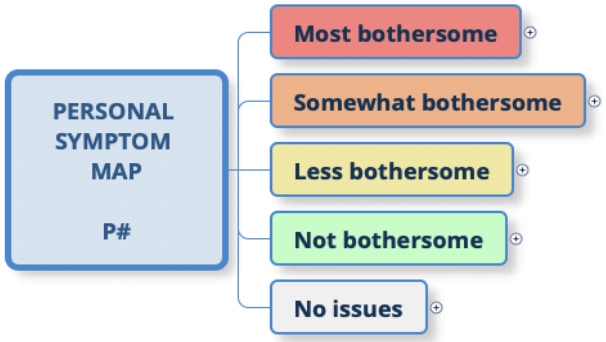
Surveys (N=80 – all participants in WATCH-PD)

- Sliding scale ratings of relevance of tasks
- Open response evaluation of symptoms and tasks
- Approx 100 mins/participant

Interviews (N=40 – purposeful subset)

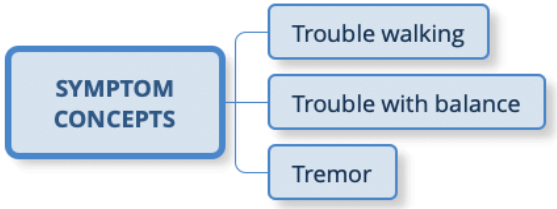
1. Map Patient Reported Symptoms (PRS)
   - with details on defining characteristics
2. Cognitive debriefing re:WATCH-PD tasks
3. Map WATCH-PD tasks to PRS
4. Map symptom concepts to PRS

Step 1: Map Patient Reported Symptoms



Step 2: Debrief on WATCH Tasks
Step 3: Map tasks back to PRS

Step 4: Map Symptom Concepts to PRS



In summary

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- Progress through collaboration
- Development in isolation does not advance the science
- Regulatory science driving clinical development
- Facilitate and embed regulatory direction and commentary
  - Learnings to accelerate the process
- Clinically meaningful within-person change
  - Patients tell us what matters to them

Thank you

skern@c-path.org

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