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**ADVANCES IN ALZHEIMER'S  
AND PARKINSON'S THERAPIES  
AN AAT-AD/PD™ FOCUS MEETING**

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2 - 5 APRIL 2020 | VIENNA, AUSTRIA



**Critical Path for Parkinson's 3DT initiative:  
*Early regulatory engagement to optimize paths for efficient  
use of digital health technologies in PD clinical trials***

**Diane T. Stephenson, PhD**

**Executive Director, Critical Path for Parkinson's  
Critical Path Institute, Tucson, Arizona USA**

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## Disclosures

|                                     |                         |
|-------------------------------------|-------------------------|
| <input checked="" type="checkbox"/> | No, nothing to disclose |
| <input type="checkbox"/>            | Yes, please specify:    |



## Critical Path for Parkinson's 3DT initiative: Early regulatory engagement to optimize paths for efficient use of digital health technologies in PD clinical trials

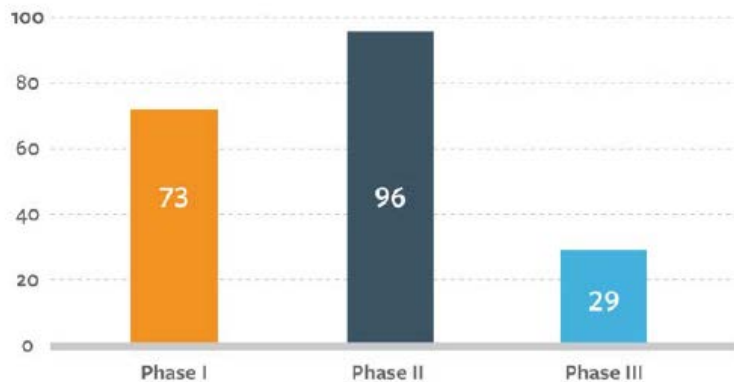
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Coeruleus Clinical Sciences
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Parkinson's UK
- **Michael Lindemann**  
F. Hoffman-La Roche Ltd
- **Ole Graff**  
GSK
- **Luis Garcia-Gancedo**  
GSK
- **H.E. Sengoku**  
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- **Bastiaan R. Bloem**  
Radboud University Medical Center
- **Michele T. Hu**  
University of Oxford
- **E. Ray Dorsey**  
University of Rochester

# The PD therapeutic pipeline is rich... Yet clinical trialists face many challenges



## Active Trials by Phase

FEB 2019



Total estimated number of active interventional drug trials by Phase. Programs in "Phase IV" or other undefined stages of clinical assessment are not included. Note that the number of trials does not reflect number of unique therapies as some therapies may have multiple trials underway in parallel.

Source: Cyteline's Trialtrove, data accessed February 2019

*Michael J Fox Foundation, Parkinson's Priority  
Therapeutic Pipeline Report, Feb 2019*

## Obstacles in PD Drug Development:

- Disease pathogenesis is unknown
- PD is characterized by phenotypic and genotypic heterogeneity
- Biomarkers that reflect disease presence, progression and severity are lacking
- Unpredictable placebo responses
- Concurrent symptomatic therapy may mask efficacy
- **Outcome measures lack precision**

*Lang A. et al. Mov Disord. 2018 May;33(5):660-677*

# People living with Parkinson's tell us early intervention is key

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## The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative

- **Patients note that non-motor features of PD are most burdensome early in disease**  
*Nonmotor symptoms significantly and negatively impair Quality of Life in people living with PD (e.g. Hermanowicz et al., 2019; Neuropsychiatric Disease and Treatment 2019:15 2205–2212)*
- **STOPPING PROGRESSION AT AN EARLY STAGE** was the strongest desire of persons with Parkinson's in a survey of >700 people with PD carried out by Parkinson's UK
- FDA's voice of the patient report for Parkinson's disease highlights patients communicated the need for a greater focus of disease **prevention** in addition to treatment

# Critical Path for Parkinson's Consortium

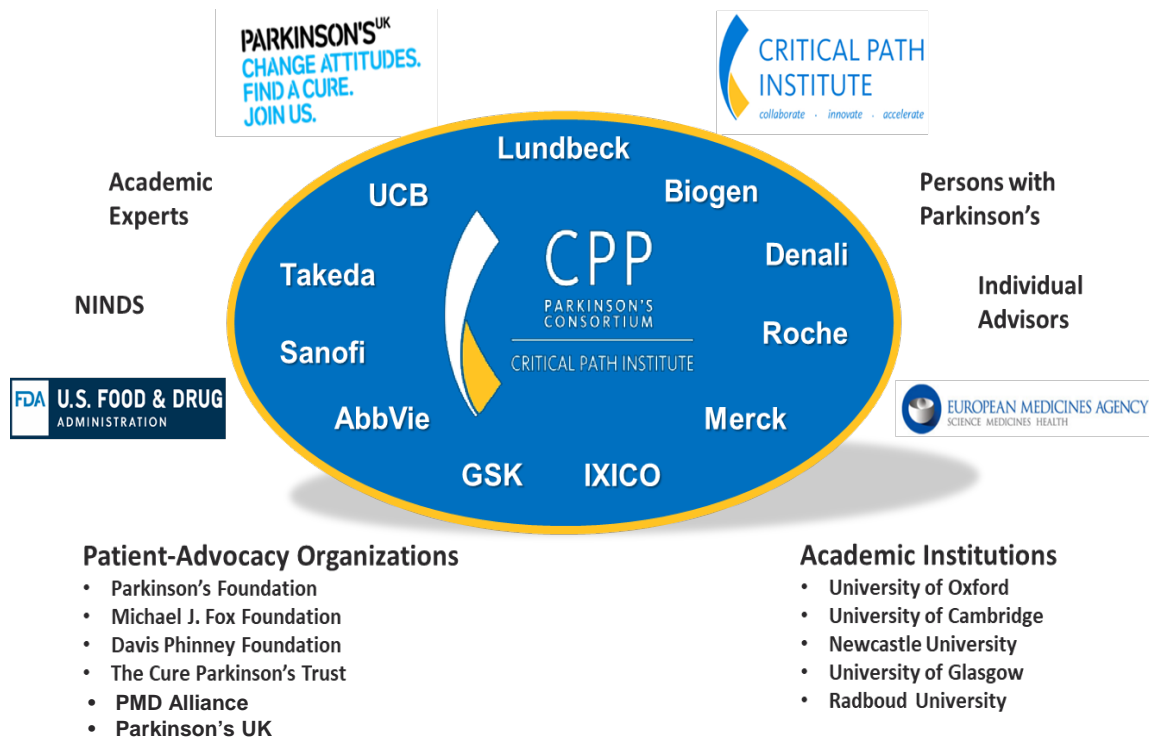
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**Mission:** *To serve as a leading International consortium to collectively advance data driven collaborative research under the advisement of worldwide regulatory agencies*

- CPP was launched in 2015 with a major goal to develop tools to quantify disease progression
- Successfully acquired and integrated patient level data from >9600 PD patients from around the world
- Qualification of imaging biomarker for enrichment of trials in early PD
- 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**





- Bastiaan R. Bloem, Radboud University
- Ray Dorsey, University of Rochester Medical Center
- Michele Hu, Oxford Univ
- Derek Hill, University College London
- Karl Kieburtz, University of Rochester
- Eric Macklin, Massachusetts General Hospital
- Ken Marek, Institute for Neurodegenerative Disorders
- Walter Maetzler, Kiel Univ, Germany
- Jesse Cedarbaum, Coeruleus Clinical Sciences
- Monica Javidnia, University of Rochester
- David Russell, Institute for Neurodegenerative Disorders
- Michael A. Schwarzschild, Massachusetts General Hospital
- John Seibyl, Institute for Neurodegenerative Disorders
- Ira Shoulson, Georgetown University
- Tanya Simuni, Northwestern University
- Glenn Stebbins, Rush University
- Charles Venuto, University of Rochester
- Daniel Weintraub, University of Pennsylvania
- Camille Carroll, Plymouth Univ, UK
- George Roussos, University of London



- A subset of CPP member organizations\* have convened to collaborate pre-competitively with the goal of optimizing the efficiency of paths for developing digital tools for PD drug development.
- 3DT is leveraging a prospective study called WATCH-PD (Wearable Assessments in The Clinic and Home in PD), a 12-month multi-center, longitudinal, digital assessment study of PD progression in subjects with early, untreated PD as an exemplar pilot study to collect digital data in an early PD target population for the purpose of facilitating discussion and alignment with regulatory agencies.

*Biogen, Takeda, UCB, Merck, Roche, Lundbeck, GSK  
Academic advisors: University of Rochester, Rush  
University, Parkinson's UK, Michael J Fox Foundation*

*Ray Dorsey,  
Principal Investigator*



# Why is CPP engaging in digital health technologies and why now?



- The PD field is in need of optimizing outcome measures of disease progression; digital measures have potential to assess aspects of the disease in a more accurate way or assess aspects of the disease that are not currently measured
- A number of public, academic and industry activities are implementing DHTs in PD (PPMI, academic research studies [1], industry clinical trials [2,3]); CPP can leverage its unique role in bringing stakeholders together for pre-competitive collaboration and regulatory discussions

## Overall:

- CPP consortium model, including alignment with regulatory agencies and excellence in data science, is well placed to fill gaps to enable efficiencies in the use of digital health technologies in PD

- 1) *Academic: Silva de Lima AL, Hahn T, Evers LJW, de Vries NM, Cohen E, Afek M, et al. (2017). PLoS ONE 12(12):e0189161. <https://doi.org/10.1371/journal.pone.0189161>*
- 2) *Industry – Lipsmeier, F. et al. Movement Disorders(2018). doi:10.1002/mds.27376*
- 3) *Industry - Boroojerdi, B., Parkinsonism and Related Disorders, <https://doi.org/10.1016/j.parkreldis.2018.11.024>*



The primary goal of this study is to **generate a set of candidate objective digital measures** with optimized performance (e.g., improved sensitivity, reduced variability, closing of measurement gaps, etc.) to complement standard clinical assessments in measuring the progression of Parkinson's disease and response to treatment in clinical studies targeting early stages following clinical diagnosis.

A secondary goal is to understand the relationship between standard clinical assessments, research-grade digital tools used in a clinic setting, and more user-friendly consumer digital platforms to **develop a scalable approach for objective, sensitive, and frequent collection of motor and non-motor data in early PD.**



## 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.



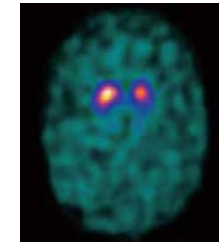
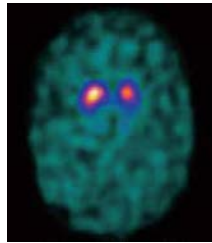
### APDM WEARABLE SENSORS

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.





## Clinic Visits at Baseline, 1, 3, 6, 9, 12 months



**APDM:** Ambulatory Parkinson's Disease Monitoring  
**DAT:** Dopamine Transporter  
**ESS:** Epworth Sleepiness Scale  
**I/E:** Inclusion/Exclusion  
**MDS-UPDRS:** Movement Disorder Society - Unified Parkinson's Disease Rating Scale  
**MoCA:** Montreal Cognitive Assessment  
**PIGD:** Postural Instability and Gait Disorder  
**PDQ-8:** Parkinson's Disease Questionnaire 8  
**PPMI:** Parkinson's Progression Markers Initiative  
**RBD:** Rapid Eye Movement (REM) Sleep Behavior Disorder  
**SCOPA:** Scales for Outcomes in Parkinson's Disease  
**SWEDD:** Scans without evidence of dopamine deficiency



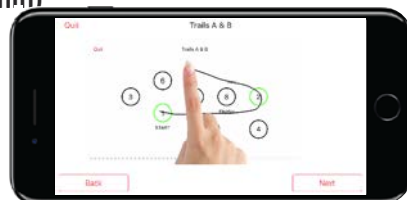
## Mobile test battery (twice monthly)

### 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

## How is WATCHPD unique as compared to other PD digital studies?



- Target population is focused on early PD, de novo patients to align with current and emerging trials
- Motor and nonmotor symptoms are being collected
- Assessments are being collected In clinic and at home
- Patient reported outcome measures are being collected at all visits
- Inclusion criteria similar to PPMI
- Study is non-interventional. Standard of care / DA therapy will serve as control for response to approved symptomatic Rx
- DAT imaging at baseline is used for screening to exclude SWEDD subjects
- Technology includes both commercial device and custom smartphone app
- The data will inform the concepts of interest (as advised by regulators)



We seek Agency feedback on how to maximize the value of the Wearable Assessments in the Clinic and Home in PD (WATCH-PD) pilot study design in advancing the regulatory maturity of digital technologies to monitor disease progression, in order to optimally inform sponsors on their use in future clinical trials.

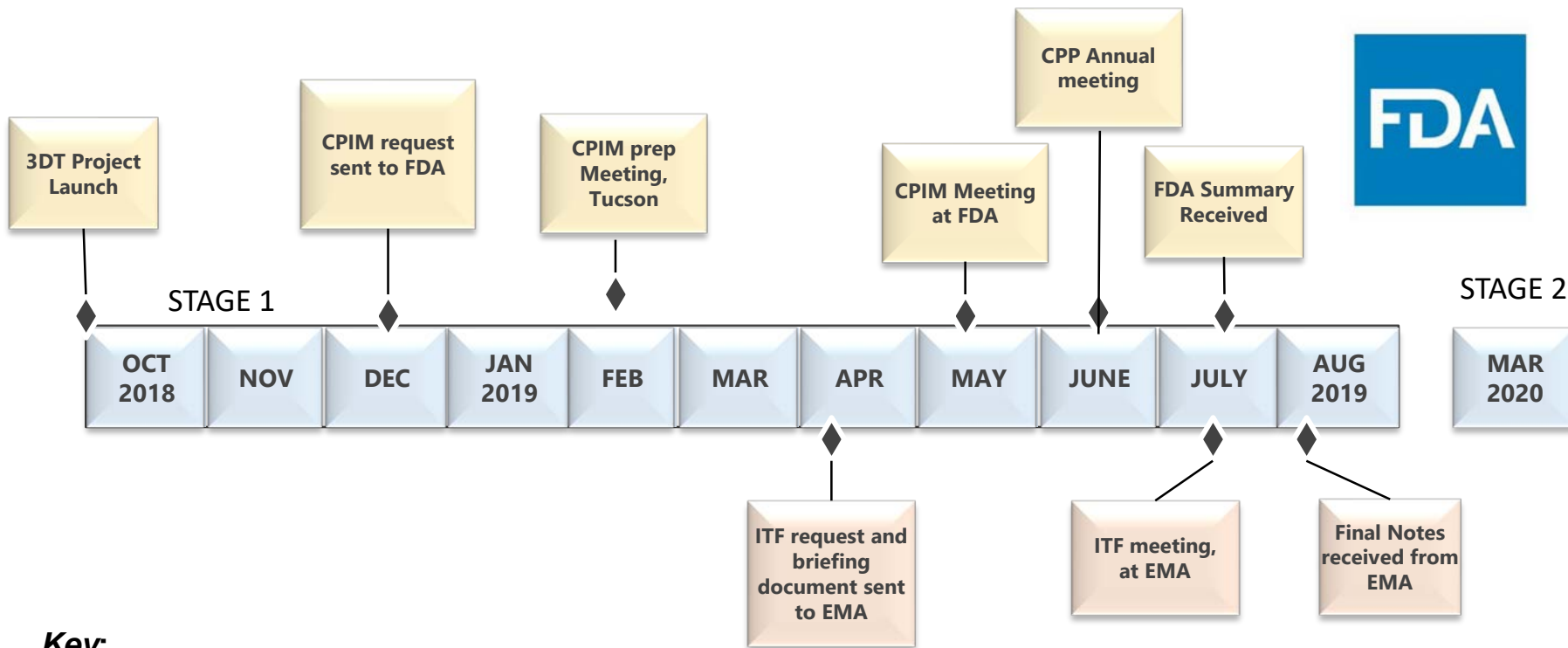
### *In scope:*

- Maximize the use of WATCH-PD pilot study to identify candidate digital measures for future discussions with regulators

### *Out of scope:*

- Qualification (as biomarker or clinical outcome assessment)
- Device clearance or approval with CDRH, CE Mark certification for medical devices

# CPP Timeline and Regulatory Interactions



## Key:

3DT = digital drug development tool team

CPIM = Critical Path Innovation Meeting

ITF = Innovative Task Force Meeting





# What is a Critical Path Innovation Meeting (CPIM)?



- A forum to meet with the FDA to discuss innovative drug development approaches
- The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development.
- Not all requests are accepted
- Meetings are informal and advice is non-binding



## Critical Path Innovation Meetings (CPIM)

Potential topics for a CPIM include, but are not limited to, the following:

- Biomarkers in the early phase of development and not yet ready for the Biomarker Qualification Program (BQP)
- Clinical Outcome Assessments in the early phase of development and not yet ready for the Clinical Outcome Assessment Qualification Program
- Natural history study designs and implementation
- Emerging technologies or new uses of existing technologies
- Innovative conceptual approaches to clinical trial design and analysis



### Well attended by wide range of FDA staff from across the agency

- Office of Medical Policy (OMP)
- Division of Neurology Products (DNP)
- Clinical Outcomes Assessments (COA)
- Office of Biostatistics (OB)
- Office of Science Policy (OSP)
- Center for Devices and Radiological Health (CDRH)
- Center for Biologics and Evaluation Research (CBER)
- Office of Clinical Pharmacology (OCP)
- Office of Business Informatics (OBI)

*36 FDA participants  
in person, 18 remote*

# What is an Innovation Task Force Meeting (ITF)?



## EMA initiatives to support drug development



EUROPEAN MEDICINES AGENCY

### What do we provide?

#### 2. Innovation Task Force (ITF) platform and meetings

- meetings are free and provide an open environment for a dialogue with experts
- a multidisciplinary group that includes **scientific, regulatory and legal competences**.
- provide regulatory advice to applicants on the eligibility to Agency procedures as a medicinal product
- **increase awareness and learning** in emerging therapies and technologies at the Agency

### What can it be used for?

- a discussion platform **for early dialogue** with applicants to proactively identify scientific, legal and regulatory issues **of emerging therapies and technologies** (e.g. growth factors, gene and cell therapy, any significant therapeutic innovation in PD;)

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000334.jsp&mid=WC0b01ac05800ba1d9](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9)

*“Drug Development in Parkinson’s disease: The regulatory perspective, and how can we help coping with the bottlenecks”*

*Presented by: Pavel Balabanov, MD PhD  
Human Medicines Evaluation Division,  
Scientific and regulatory management department,  
CNS and ophthalmology*



## IN-PERSON ATTENDEES

- ITF coordinator, Science & Innovation Support
- Head of Science & Innovation Support
- Head of Scientific Advice
- Head of Central Nervous System & Ophthalmology
- Biostatistics & Methodology Support
- Evaluation Procedures Division

## REMOTE ATTENDEES

- Scientific Advice
- Central Nervous System & Ophthalmology
- Surveillance & Epidemiology
- Regulatory Affairs
- Clinical, Immunological/Biologicals, Pharmacovigilance and Risk Management Medicines and Medical Devices Agency, Austria



- Complimentary of the concept of coming to regulators early with a consortium approach focused on a defined prospective study
- Looking at motor, non-motor, and mood-related symptoms is critical
- Recommendation to assess the patient's perspective of how they function and feel through interviews and quality-of-life measures
- Establishment of normative databases from metrics that will be collected with wearables is very important
- Suggestion that it may be beneficial to enroll subjects at the earliest point possible in their disease progression to identify sensitive measures that are uniquely applicable to early PD



- Questions around at-home data collection (issues with patient adherence with the proposed hardware and potential environmental factors)
- Concerns around data quality (e.g., importance of raw data, software/firmware updates, dealing with missing data, transparency of algorithms)
- Data analysis, including comparators and assessment of novel measures, and the importance of context in home-based monitoring



- WATCH-PD study sponsors have integrated feedback into plans going forward
- Other members have seen value in learning how to address regulatory concerns and expectations in ongoing and planned studies employing digital devices
- Sponsors of WATCHPD have now initiated a new Normative sub-study based on regulatory advice
- Data sharing is now a reality: Those who participate in 3DT will be able to access raw data from both normative and WATCHPD subjects
- CPP 3DT project has been highlighted at FDA Workshops



## Session IV: Pulling It All Together – An Example Across Guidances

**Objective:** Explore an example –Information from this panel session will inform the development of a case study of developing a COA illustrating important concepts for consideration.

### Introduction

- **Moderator:** Ebony Dashiell-Aje, OND, CDER, FDA



### Moderated Panel Discussion

- Bill Byrom, Vice President of Product Strategy and Innovation, Signant Health
- Michelle Campbell, CDER, OND, FDA
- Andrea Coravos, Co-founder and Chief Executive Officer, Elektra Labs
- Matthew Diamond, OST, CDRH, FDA
- Mark Frasier, Senior Vice President, Research Programs, The Michael J. Fox Foundation for Parkinson's Research
- Abigail Luo, OBE, CBER, FDA
- Andrew Potter, OTS, CDER, FDA
- Diane Stephenson, Executive Director, Critical Path for Parkinson's Consortium, Critical Path Institute

### Audience Question and Answer





**EMA:** Innovative Task Force suggested taking a stepwise approach. Identify a small, well-defined meaningful measure and come back to them with a focused data-driven path for a future Scientific Advice and potential for qualification.

**FDA:** The appropriate FDA review divisions will continue to have iterative, disease-specific discussions with CPP, including strategies for establishing meaningful clinical endpoints.



- Partner with Biogen/Takeda to implement open science:
  - - acquire, standardize and share data from WATCHPD with 3DT stage 2 members
- Collectively support normative substudy initiation and execution in parallel with WATCHPD
- Initiate device agnostic platform :
  - - Acquire patient level digital device data from up to four PD clinical studies (same target population, early motor PD)
- Define paths for digital device data optimization
  - - Sources of variability
  - - Metadata standards
- Engage in paths to optimize alignment with what is important to patients with Parkinson's



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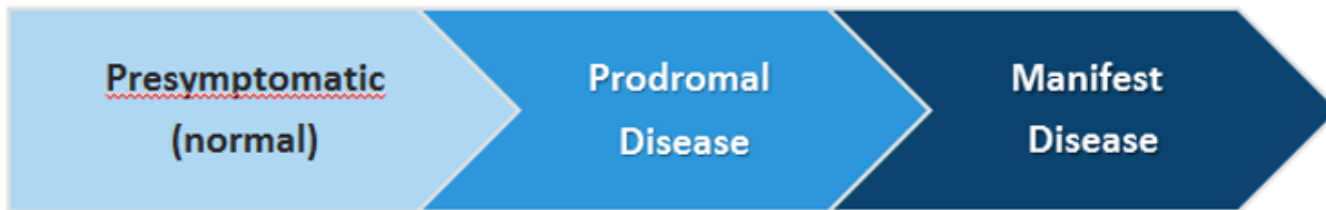
- Forum for industry members actively engaged in PD to **share drug development knowledge and experience using digital measures** in a pre-competitive setting
  - 3DT members will be able to access data from distinct digital device studies all focused on early motor PD as the target population
  - Participate actively to engage in the latest thinking on PD shared through CPP's advisors and collaborators throughout US and EU
    - CPP has over **25 world leading experts in PD signed on as scientific advisors**
  - CPP provides a **venue to communicate with regulators and solicit feedback**
    - Regulators will continue to provide informal engagement with 3DT members in 3DT future stages and help participants better understand how to optimize the use of DHTs in clinical trials
  - **Regulators encourage the consortium approach** to discuss and develop new measures and digital technologies to support PD clinical trials
-



- Embark on an iterative, **data driven path under the advisement of worldwide regulatory agencies** to optimize the use of DHTs in a device agnostic way for use in clinical trials for Parkinson's disease
- The specific applications for decision making in PD trials will be guided by the data itself, relevance to patients with Parkinson's and the specific *context of use* applications
  - Examples include patient stratification/subject selection, phase 1 dose selection, decision making/proof of concept in early phase clinical trials and endpoints to monitor disease progression
- Advance DHTs as quantitative tools to aid in measurement of PD disease progression throughout all stages of the PD continuum and enhance decision making in drug development



## The Progression of Chronic CNS Diseases



**We need to be here  
to treat the earliest stages of disease detected by  
more sensitive biomarkers**



Current biomarkers,  
existing COAs &  
approved treatments

\*COA = clinical outcome assessments

*Stephenson and Arneric,  
Translational Medicine in CNS Drug Development  
V29, Chapter 20 (Elsevier, Feltner and Nomikos Eds), 2019*



- CPP's 3DT effort has made significant progress on the goal of reaching a shared understanding of the open regulatory and scientific issues in the use of digital health technologies as endpoints in PD clinical trials, using the WATCH-PD study as a case example
- By seeking regulatory agency feedback on how to maximize the value of the WATCH-PD pilot study in advancing the regulatory maturity of these digital technologies, multiple sponsors have been informed on issues to attend to for optimizing the use of digital health technologies in future clinical trials.
- CPP consortium model including alignment with regulatory agencies and data core competencies is well placed to fill gaps to enable efficiencies in the use of digital health technologies as drug development tools in PD
- Future 3DT strategies are underway to respond to regulatory feedback and advance multistakeholder engagement, data sharing and regulatory acceptance



### ■ Critical Path Institute Staff:

Klaus Romero, Mike Minchik, Jackson Burton, Bob Stafford, Kristen Swingle, Rick Liwski, Sakshi Sardar, Varun Aggarwal, John Maciejewski, Roopal Bhatnagar, Joseph Scheeren

### ■ Critical Path for Parkinson's Consortium Members

### ■ Parkinson's UK, CPP advisors

### ■ Food and Drug Administration, CDER

Dr. Billy Dunn, Dr. Michelle Campbell, Dr. Eric Bastings, Dr. Gerald Podskalny,

### ■ European Medicines Agency

- Maria Tome, Corrine de Vries, Spiros Vamvakas

*If you have interest in joining CPP please reach out to Diane Stephenson ([dstephenson@c-path.org](mailto:dstephenson@c-path.org))*



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