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Enabling efficient use of digital health technologies to support Parkinson's disease drug development through precompetitive collaboration

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Background

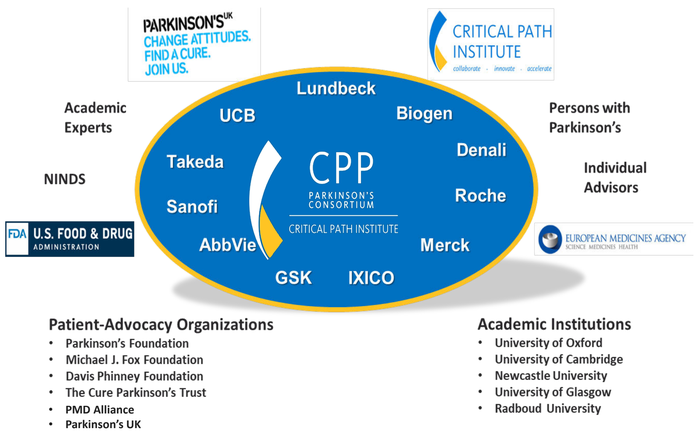
One major challenge to developing therapies that slow or halt Parkinson's disease (PD) progression is the paucity of sensitive, clinically interpretable tools that can capture clinically meaningful aspects of the disease in its earliest stages. Digital health technologies have the potential to enable measurement of PD signs and symptoms objectively, remotely, and frequently in natural environments during activities that are meaningful to patients' daily lives. Several PD clinical trials are already implementing digital technologies [1-3]. For these technologies to have widespread drug development impact, a regulatory-aligned consensus is required on best practice in selecting appropriate technologies and in collecting and processing digital data aimed at monitoring disease progression.

Objectives: To describe the Critical Path for Parkinson's (CPP) consortium approach to advance the field of digital technologies in clinical drug development for PD. To seek regulatory Agency feedback on the most efficient way to optimize a prospective observational study as a case study that may inform future PD clinical studies employing digital health technologies.

Results

CRITICAL PATH FOR PARKINSON'S

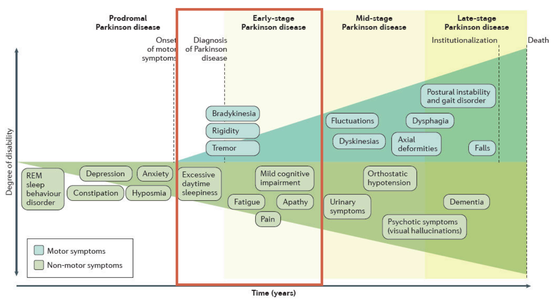
CPP is a global public-private partnership whose mission is to enhance the efficiency of clinical trials targeting early stages of PD.



- CPP was launched in 2015 with a major goal to develop tools to quantify disease progression
- Successfully acquired and integrated patient-level data from >8100 PD patients
- Qualification of imaging biomarker for enrichment of trials in early PD [4]
- Current CPP focus is regulatory endorsement of a PD drug disease trial model

The Digital Drug Development Tools (3DT) team was launched in 2018 with the goal of advancing regulatory readiness of digital health technologies in PD trials (Biogen, Takeda, GSK, Lundbeck, UCB, Merck, Roche, Michael J Fox Foundation, Parkinson's UK, and academic experts from University of Rochester, Rush University), with a focus on early motor PD.

Stages of PD and aspects amenable to quantitation using digital health technologies



Adapted from Poewe W, *et al*. Parkinson disease. Nat Rev Dis Primers. 017 Mar 23;3:17013

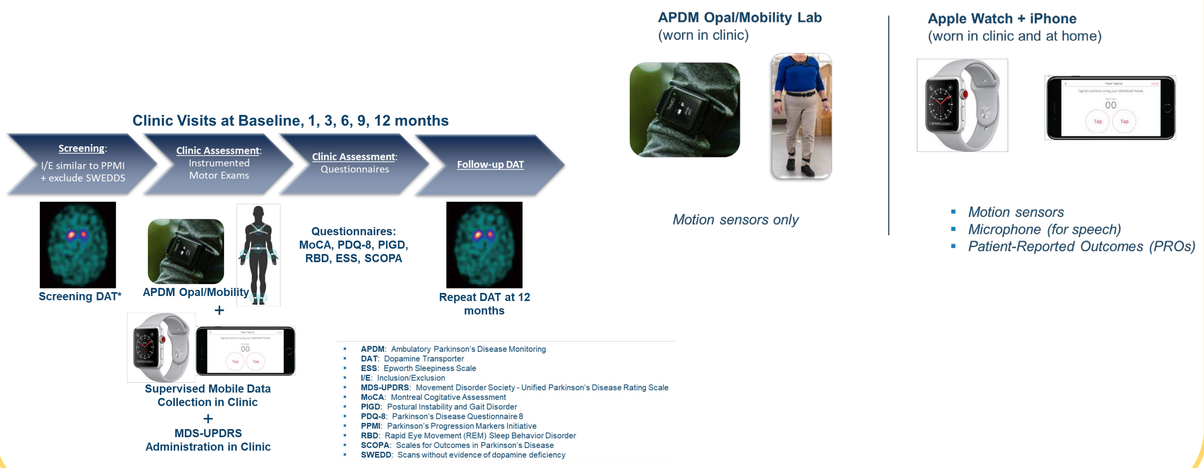
CASE STUDY TO ENGAGE REGULATORY AGENCIES

The CPP 3DT team is leveraging a prospective study called **WATCH-PD (Wearable Assessments in The Clinic and Home in PD)** as a case study to support discussions with regulatory agencies. WATCH-PD is a 12-month multi-center, longitudinal, digital assessment study of progression in subjects with early, untreated PD.

WATCH-PD study goals:

Primary goal: To **generate a set of candidate objective digital measures** to complement standard clinical assessments in measuring the progression of early-stage PD and response to standard of care treatment

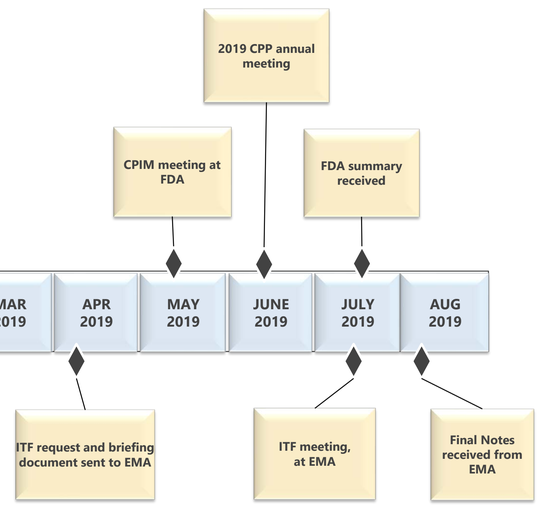
Secondary goal: To understand the relationship between standard clinical assessments, research-grade digital tools used in a clinic setting, and more user-friendly consumer digital platforms to **develop a scalable approach for objective, sensitive, and frequent collection of motor and non-motor data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



REGULATORY AGENCY FORUMS FOR ENGAGEMENT AND FEEDBACK

- ***FDA Critical Path Innovation Meeting (CPIM):*** A forum to meet with the FDA to receive cross-Agency feedback on how novel methodologies might enhance drug development
- ***EMA Innovative Task Force (ITF):*** A discussion platform for early dialogue with the Agency to proactively identify scientific, legal, and regulatory issues of emerging therapies and technologies

TIMELINE OF 3DT TEAM PROGRESS



SUMMARY OF REGULATORY FEEDBACK

- Recognize the importance of seeking guidance in the early stage of digital health technology and study planning
- Evaluation of motor, non-motor, and mood-related endpoints is important
- Incorporate the patients' perspective of how they function and feel by performing interviews and conducting quality-of-life surveys to compare to digital measures
- Both Agencies noted the importance of collecting normative digital health data from healthy individuals
- It may be beneficial to enroll subjects at the earliest point possible in their disease progression

TECHNICAL CONSIDERATIONS

- Patient factors: Adherence with home data collection and effect of differences in patients' environments and lifestyle on variability of measurements
- Data quality: Access to raw data, effect of software/firmware updates, dealing with missing data, transparency of algorithms
- Data analysis methods: Comparators for evaluation of novel measures

REGULATORY ADVICE: NEXT STEPS

- ***FDA*:** The review division will continue to have iterative, disease-specific discussions with CPP, including strategies for establishing meaningful clinical endpoint
- ***EMA:*** Identify a small, well-defined digital measure and return to EMA for scientific advice with a focused, data-driven development path

CPP FUTURE STRATEGY

Align on data-driven path for acquiring digital device data from relevant PD studies to inform future clinical trials

Next Steps: CPP is reaching out to stakeholders to prepare a **comprehensive digital data inventory** of PD clinical studies and a **Voice-of-the-Patient inventory** to capture what is bothersome to people living with PD. Such data is key to informing the near- and long-term future paths.

Conclusions

- 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 in precompetitive forums** 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 technologies in future clinical trials
- CPP aims to encourage the **sharing of positive and negative experiences with digital health technologies** in PD and align with regulators early and often to maximize knowledge and minimize duplication of efforts across sponsors, drug development programs, and geographies
- The 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

References

1) Silva de Lima AL, Hahn T, Evers LJW, de Vries NM, Cohen E, Afek M, et al. (2017). PLoS ONE 12(12):e0189161.
2) Lipsmeier, F. et al. Movement Disorders (2018).33(8): 1287-1297
3) Boroojerdi, B., Parkinsonism and Related Disorders, 2019: 61: 70-76
4) Stephenson et al., J Parkinsons Dis. (2019); 9(3):553-563

Acknowledgements

The Critical Path Institute's CPP Consortium is funded by Parkinson's UK and the following industry members: AbbVie, Biogen, Denali, GSK, H. Lundbeck A/S, Merck Sharp and Dohme, F. Hoffmann La Roche, IXICO, Sanofi Genzyme, Takeda and UCB. We also acknowledge additional CPP member organizations, including The Cure Parkinson's Trust, Davis Phinney Foundation, Michael J. Fox Foundation, Newcastle University, Parkinson's Foundation, Radboud University, University of Cambridge, University of Glasgow, University of Oxford, NINDS, FDA, and EMA. CPP acknowledges the strong support from FDA colleagues Dr. Billy Dunn and Dr. Gerald Podskalny, and EMA colleagues Prof. Maria Tome, Prof. Pavel Balabanov and Prof. Corrine de Vries. CPP acknowledges the leadership of Marjan Meinders and John Hall for their outreach on behalf of their role in helping to lead the CPP digital data inventory taskforce.