Critical Path for Parkinson's I: Data Sharing and Regulatory Science in Catalyzing Innovation for Parkinson's Disease

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Background and Objectives

Critical Path for Parkinson's (CPP) is a new precompetitive consortium funded by Parkinson's UK and the pharmaceutical industry, and led by the Critical Path Institute (C-Path). This presentation highlights the planned strategy for development of regulatory agency-endorsed biomarkers and quantitative drug development platforms that will improve the quality and efficiency of clinical trials in Parkinson's disease (PD) (**Figure 1**). The focus is on early stages of PD with the goal of advancing treatments that hold potential to delay disease progression.

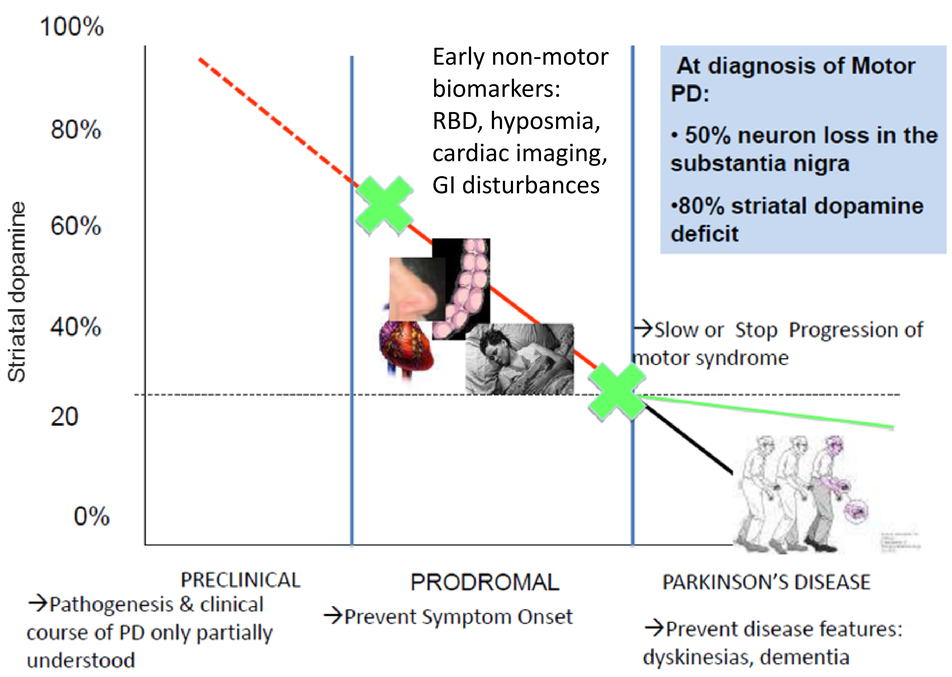

Figure 1 **Graphical construct for the Parkinson's disease continuum, and the need to understand early motor progression**

Methods

Regulatory agencies have identified quantitative disease models as valuable drug development platforms to accelerate drug development. The CPP coalition of industry members, regulatory agencies, academic experts and patient advocacy groups collectively aim to integrate data from international observational cohorts (e.g., CamPaIGN, OxfordDC, PRoBaND, ICICLE, and PPMI) and randomized controlled clinical trials (e.g., ADAGIO and PRECEPT) into a unified database (**Ref 1**), as shown in **Figure 2** and described in **Table 1**. These studies have been selected based on the longitudinal biomarker data available for patients recruited with early PD.

Results

CPP has designed a roadmap (**Figure 2**) to achieving the goal which is to qualify novel translational biomarkers and drug disease trial models for use in efficient clinical development programs designed to lead to the registration of new treatments for PD. C-Path in collaboration with NINDS and the Clinical Data Interchange Standards Consortium (CDISC), has successfully developed publically available global consensus clinical data standards for Parkinson's disease (**Ref 2**) which will be key to the data integration.

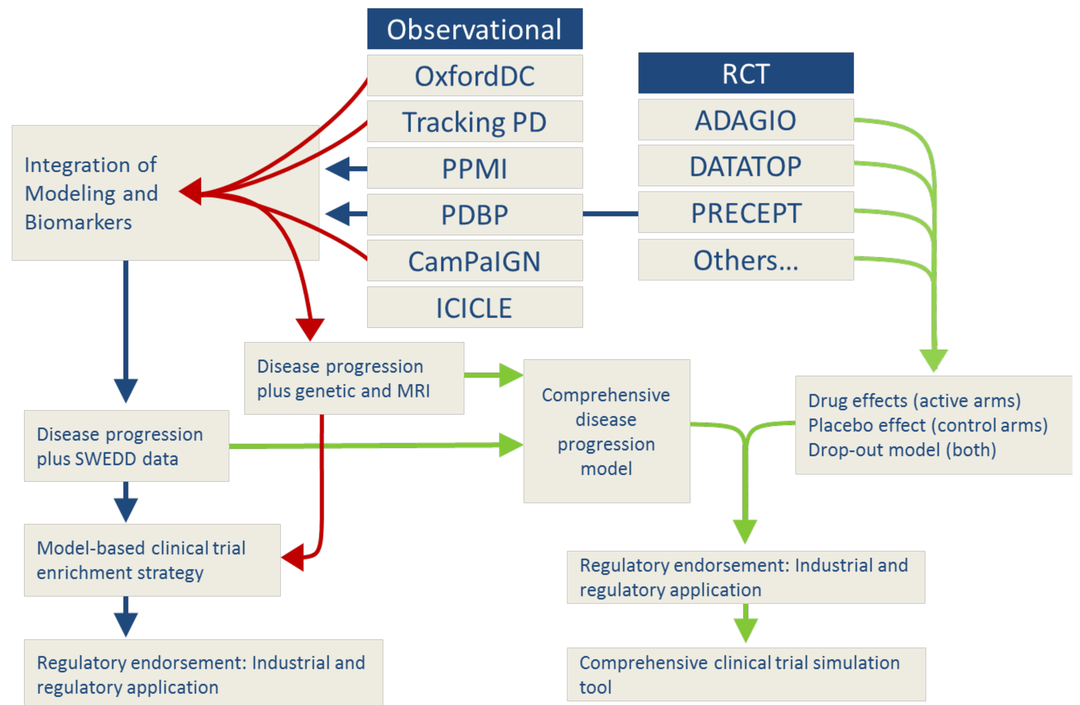

Figure 2 **Conceptual roadmap for CPP** *Adopted from **Ref 1***

Conclusions

CPP's focus is to integrate global clinical cohorts to create new tools and methods that can be applied during the development process of new treatments for PD. The precedent for CPP's vision is based on the success of C-Path's Coalition Against Major Diseases (CAMD) in achieving the first-ever regulatory endorsement by the FDA and EMA for an Alzheimer's disease (AD) clinical trial simulation tool (**Ref 3**). The clinical trial platform is publically available, and represents a milestone that serves to encourage the advancement of drug-disease-trial models, promising to increase the probability of success in future AD therapeutic trials. The development of clinical data standards for PD and the roadmap for data sharing, integration and modeling are designed to accelerate drug development for PD.

Study	Type of study	Number of patients	Duration of study (if longitudinal)	Reason for cohort (drug trial/cohort study/other)	Study ongoing (yes/no)	Assessments	Tissue sample available (serum, plasma, CSF, etc.)	Genotyped	Scanning (MRI, PET, etc.)	Other
ICICLE	Longitudinal (predicting dementia)	160	8 years	Predicting dementia	Yes	UPDRS, motor, non-motor, cognitive decline	Serum, CSF, DNA, RNA	Yes	MRI baseline & 18mo & FDG PET in ~ 45	Gait & sleep data
CamPaIGN	Longitudinal (from time of diagnosis)	142 (diagnosed between 2000-2002)	13-15 years	Community-based incidence cohort	Yes	UPDRS, motor, non-motor, cognitive decline	No	Yes (n=129) (MAPT H1 vs H2, COMT val(158)met, SNCA, APOE, MAOA), DNA stored	No	Neuropsychologic, mood, function, quality of life
PICNICS	Longitudinal (from time of diagnosis)	286 (diagnosed Dec 2007 - June 2013)	2-7 years	Community-based cohort study	Yes	UPDRS, motor, non-motor, cognitive decline	Plasma and serum (n=98), CSF (n=11)	Yes (n=276) (MAPT H1 vs H2, COMT Val158Met, SNCA, BuChE, ApoE), DNA stored	Yes (n=48)	Neuropsychologic, mood, function, quality of life
Tracking Parkinson's	Longitudinal (from time of diagnosis for PD)	3000 (2000 patients within 3 years of diagnosis, 240 young onset and 760 relatives)	3-5 years	Community-based cohort study	Yes	UPDRS, motor, non-motor, cognitive decline	Serum	Yes, LRRK2 and GBA (all subjects) and Parkin and PINK1 (young onset)	Sub-study in 4-5 centers	Olfactory function, Sleep, Autonomic function, Quality of life, Environmental exposures
Oxford Discovery cohort	Longitudinal (within 3 years of diagnosis)	1630 (1086 PD patients within 3 years of diagnosis; 111 first degree PD relative; 133 PSG-confirmed RBD; 300 control)	10 years	Community-based cohort study	Yes	UPDRS I-IV, motor, non-motor, cognitive decline	Serum and DNA in all. Plasma, CSF, G.I biopsy tissue, nasal olfactory mucosa, skin in subgroup	Yes (n=900) SNP analysis, LRRK2 and GBA (all subjects) DNA stored. 250 whole exome analysis.	MRI (structural and functional) in 150 PD, 30 controls, 30 RBD subjects	Olfactory function, Objective motor testing (android phone app test, saccadometry, Gait analysis)
PRECEPT	Longitudinal	806 early PD	Terminated early (average of 21.4 months follow-up)	Clinical trial	No	UPDRS, cognition, depression, quality of life	No	No	Beta-CIT SPECT imaging	
ADAGIO	Longitudinal	1176 early PD	72 weeks	Delayed start clinical trial	No	UPDRS	No	No	Beta-CIT SPECT imaging	Rasagiline as a disease-modifying therapy in PD
PostCept (and LABS-PD)	Longitudinal	709 subjects from PRECEPT enrolled into PostCEPT and LABS-PD	Ongoing since 2008	Population-based study	Yes	UPDRS, quality of life, cognition	Serum, blood biomarkers (alpha-synuclein, proteomics)	Yes (DNA banking)	Beta-CIT SPECT imaging, DAT imaging	PostCEPT rolled into LABS-PD (see ref)
Parkinson Progression Marker Initiative (PPMI) Biomarker Study	Longitudinal (from time of diagnosis)	400 newly diagnosed PD, 200 controls, 64 SWEDD, 100 prodromal, 600 genetic registry participants	Ongoing since 2010	Community-based cohort study	Yes	UPDRS-III, motor, non-motor, cognitive decline MDS-UPDRS	DNA, RNA, serum, plasma, urine, CSF	Yes (ApoE and selected SNPs)	MRI, DAT, PET ([18F] florbetaben) CT (some sites)	
DATATOP	Longitudinal	800	8 years	Clinical trial	No	UPDRS, cognition, depression, quality of life	Serum, urine, CSF, DNA	Yes, by requesting for access to bio-specimen repository	No	Video repository
ELLDOPA	Longitudinal	361	42 - 44 weeks	Clinical trial	No	UPDRS, quality of life, MMSE, Hamilton depression	No	No	Beta-CIT Spect imaging (select subjects)	Video repository
The National Institute of Neurological Disorders and Stroke (NINDS) Parkinson's Disease Biomarker Program (PDBP)	581 Cross sectional, 880 Longitudinal (3-5 years)	839 PD, 515 control, 37 Multisystem Atrophy, 42 Progressive Supranuclear Palsy, 24 Essential Tremor, 4 Cortical Basal Degeneration	3-5 years	Community-based cohort study	Yes	MDS-UPDRS, motor, non-motor, cognitive decline, UPSIT, quality of life	CSF (320), plasma (8865), serum (736), RNA (1417), DNA (1,417) at baseline	Yes, NeuroX chip, whole genome analysis available in 2017	MRI (290), DTI (440), fMRI (150)	Gait (120), biosample QC (hemoglobin analysis for plasma, serum and CSF), urate, vitamin D,

Table 1 **Description of relevant aspects of the targeted data sources for CPP**

References

(1) Stephenson, D. T., *et al.* (2015) Precompetitive data sharing as a catalyst to addressing unmet needs in PD. Journal of Parkinson's Disease 5: 581-94.

(2) CDISC Parkinson's Disease Therapeutic Area User Guide v1; http://www.cdisc.org/parkinson%E2%80%99s-disease-therapeutic-area

(3) Romero, K., *et al.* (2015) The future is now: model-based clinical trial design for Alzheimer's disease. Clinical Pharmacology & Therapeutics, 97(3): 210-4.

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