Critical Path for Parkinson's Consortium: Catalyzing Innovation for Parkinson's Clinical Trials through Data Sharing and Regulatory Science

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Background and Objectives

To highlight the progress of Critical Path for Parkinson's (CPP), a precompetitive consortium to advance drug development tools for early stages of Parkinson's disease (PD).

CPP is a public-private partnership, led by Critical Path Institute (C-Path), jointly funded by Parkinson's UK and pharmaceutical companies. CPP comprises a broad coalition of stakeholders, including industry, regulatory agencies, academic experts and patient-advocacy groups. By integrating diverse, multifaceted patient-level data into a standardized database, CPP seeks to generate solutions to bottlenecks in the drug development process for PD.

Methods

The CPP PD unified database's current sources include: *Parkinson's Progression Markers Initiative* (**PPMI**), *Cambridgeshire Parkinson's Incidence from GP to Neurologist* (**CamPaIGN**) cohort, *Oxford Parkinson's Disease Centre* (**OPDC**) Discovery Cohort, *Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation - PD* (**ICICLE-PD**) and *Tracking Parkinson's*. Clinical trial data include *Parkinson Research Examination of CEP-1347 Trial* (**PRECEPT**), *Deprenyl and tocopherol antioxidative therapy of Parkinsonism* (**DATATOP**), *Futility Study I* (**FS1**) *and Futility Study II* (**FSToo**), *Earlier versus Later Levodopa Therapy in Parkinson Disease* (**ELLDOPA**) and *Attenuation of Disease Progression with Azilect Given Once-daily* (**ADAGIO**), *Short Term Assessment of RO 19-6327* (short-acting MAOB-I) *Tolerability in Untreated PD* (**START UP**), *Multicentre, Phase III, 3-Arm Parallel Group, Placebo- and Ropinirole-Controlled Trials of the Efficacy and Safety of the Rotigotine Patch in Early-Stage Parkinson's Disease* (**SP512, SP513**), *Investigation of Cogane (PYM50028) in early stage Parkinson's disease* (**CONFIDENT-PD**), *SURE PD PhII* (**Inosine**) and *Study of Urate Elevation in PD* (**SURE-PD Ph2)** (**Table 1**). Further datasets are scheduled to be included in the near future.

CPP's data-driven goals include regulatory-accepted disease progression models, clinical trial simulators and model-informed biomarkers to optimize clinical trial design (**Figure 1**).

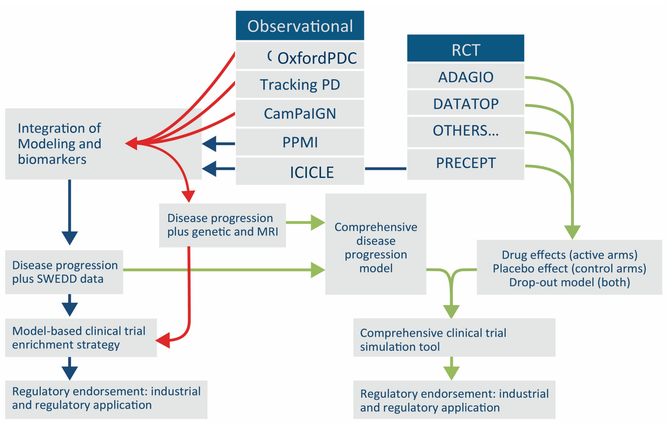


Figure 1. CPP roadmap: Regulatory impact based on precompetitive data sharing **[3]**

Results

Three years after launching, CPP has

1) Developed a worldwide PD patient-level database of **>8,100** individuals,
2) Achieved a model-based qualification opinion from the European Medicines Agency (EMA) for the use of Dopamine Transporter neuroimaging (DAT) as an enrichment biomarker for early motor clinical trials [**2,3**],
3) Released a user-friendly trial simulator based on the DAT model (**Figure 4**), and
4) Formally engaged both FDA and EMA for regulatory acceptance of a PD disease progression model.

PD Observational Cohorts

STUDY NAME	CONTRIBUTOR	# OF SUBJECTS	REFERENCE
Parkinson Progression Marker Initiative (PPMI) Biomarker Study	Michael J. Fox Foundation	423 newly diagnosed PD, 196 controls, 64 SWEDD, 65 prodromal, 1,223 genetic registry participants	Prog Neurobio. 95: 629-35, 2011
CamPaIGN	University of Cambridge, UK	142 (diagnosed between 2000-2002)	JNNP 84: 1258-1264; 2013
ICICLE	Newcastle University , UK	160	Neurology 2014 82: 308-18
Tracking Parkinson's/PRoBaND study	University of Glasgow, UK	3,000 (2,000 patients within 3 years of diagnosis; 240 young onset and 760 relatives)	J Park Dis 2015 5: 947-59
OPDC Discovery cohort	University of Oxford, UK	1,630 (1,086 PD patients within 3 years of diagnosis; 111 first degree PD relative; 133 PSG-confirmed RBD; 300 control)	J Park Dis 2015 5: 269-79

PD Clinical Trials

STUDY NAME	CONTRIBUTOR	# OF SUBJECTS	REFERENCE
START UP	Roche	201 untreated PD	Annals of Neurol 1993, 33: 350-356
SP513: Ropinirole	UCB	561 early stage PD	Mov Dis 2007; 22(16):2398-404
SP512: Rotigotine	UCB	273 early stage PD	J Park Dis 2016, 6(2): 401-11.
SURE PD PhII (Inosine)	Michael J Fox Fdn/ MGH / M. Schwarzschild/ Indiana Univ	75	JAMA Neurol. 2014 71(2):141-50.
CONFIDENT-PD	Michael J Fox Fdn/Junaxo	425	NCT01060878 (CT.gov)
PRECEPT	Teva	806 early PD	Neurol 20:82: 1791-7; 2014
ADAGIO	Teva	1,176 early PD	Lancet Neurol 2011; 10: 415–23
DATATOP	NINDS	800 early PD	Neurol 1990; 40: 1529-34
FS-1	Univ Rochester/NINDS	200 early PD	Clin Neuropharmacol. 2008 31(3):141-50
FS-TOO	Univ Rochester/NINDS	213 early PD	JAMA Neurol. 2014 71(6): 710–716.
ELLDOPA	Univ Rochester/NINDS	361 early PD	N Engl J Med 2004; 351:2498-508.

Table 1. Description of data sources and data that are included in the CPP database

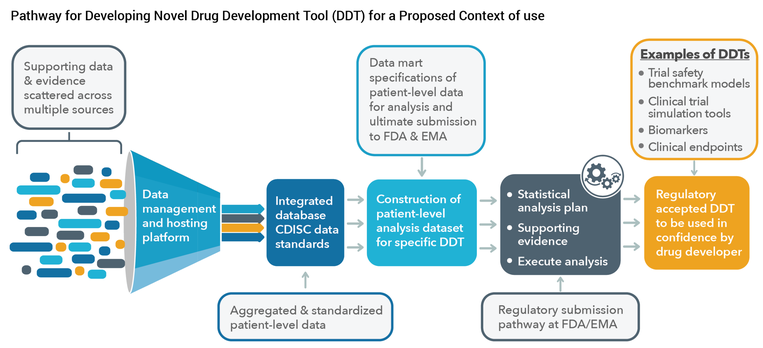


Figure 2. C-Path data-driven regulatory science

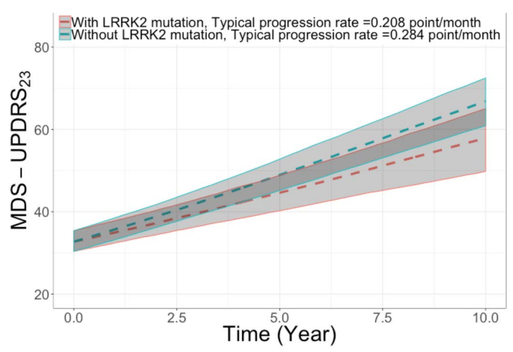


Figure 3. CPP Database use case: LRKK2 progression

A disease progression model characterizing the time course of MDS-UPDRS Part II and Part III was developed using an integrated dataset comprised of multiple observational studies (PPMI and ICICLE-PD). Monte Carlo simulations were performed to compare the statistical power by sample size in trials with and without enrichment using relevant covariates. From Reference [**4**].

Simulation scenario:
1. Generate 1000 virtual patients:
- 64 year old male
- Parkinson disease

With/without LRRK2 mutation
- Disease severity **for motor score**: 32
- Disease severity **for non-motor score**: 6

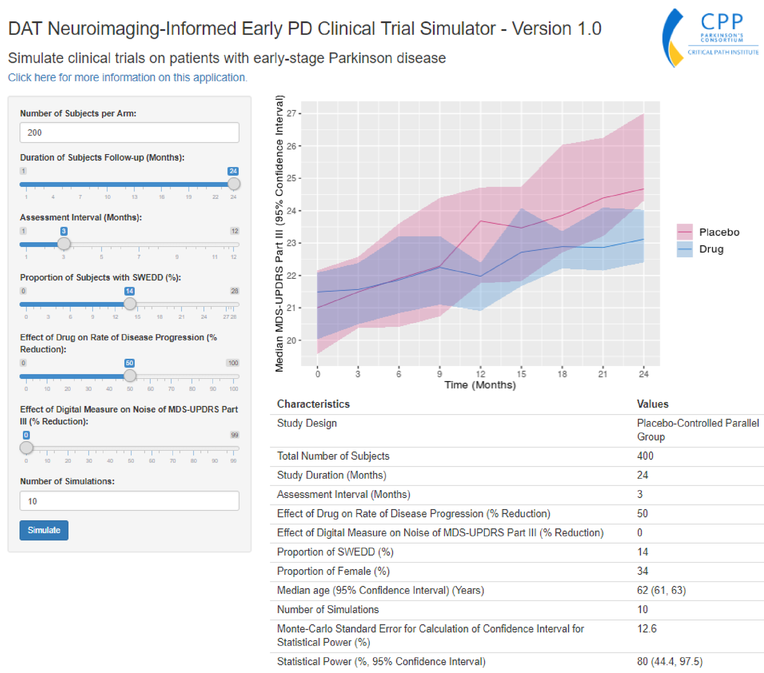
2. Simulate their progression for 10 years

DAT Graphical User Interface

CPP Website

Conclusions

CPP is a successful worldwide precompetitive consortium with a regulatory focus in advancing solutions for PD therapeutic development. The CPP global database represents a unique resource to further drug development tools, including biomarkers, disease progression models, and trial simulations, for use in Parkinson's clinical trials. Future strategies for the consortium are underway and include expanding the CPP database and evaluation of novel digital drug development tools for quantifying disease progression.



Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction)	0
Proportion of SWEDD (%)	14
Proportion of Female (%)	34
Median age (95% Confidence Interval) (Years)	62 (61, 63)
Number of Simulations	10
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	12.6
Statistical Power (%, 95% Confidence Interval)	80 (44.4, 97.5)

By Daniela Conrado (Model and App Developer) and Jackson Burton (App Developer) on behalf of the Critical Path for Parkinson's (CPP) consortium. E-mail DConrado@c-path.org with questions or comments.

Figure 4. Graphical user interface for the DAT early PD clinical trial simulator (based on integrated data from PPMI and PRECEPT)

References

(1) Romero K, Conrado D, Burton J, Nicholas T, Sinha V, Macha S, Ahamadi M, Cedarbaum J, Seibyl J, Marek K, Basseches P, Hill D, Somer E, Gallagher J, Dexter DT, Roach A, Stephenson D; Critical Path for Parkinson's (CPP) Consortium; Parkinson's Progression Markers Initiative (PPMI). Molecular Neuroimaging of the Dopamine Transporter (DAT) as a Patient Enrichment Biomarker for Clinical Trials for Early Parkinson Disease. Clin Transl Sci. 2019 Feb 1. [Epub ahead of print]

(2) Conrado DJ, Nicholas T, Tsai K, Macha S, Sinha V, Stone J, Corrigan B, Bani M, Muglia P, Watson IA, Kern VD, Sheveleva E, Marek K, Stephenson DT, Romero K; Critical Path for Parkinson's (CPP) Parkinson's Disease Modeling and Simulation Working Group. Dopamine Transporter Neuroimaging as an Enrichment Biomarker in Early Parkinson's Disease Clinical Trials: A Disease Progression Modeling Analysis. Clin Transl Sci. 2018;11(1):63-70.

(3) Stephenson D, Hu MT, Romero K, Breen K, Burn D, Ben-Shlomo Y, Bhattaram A, Isaac M, Venuto C, Kubota K, Little MA, Friend S, Lovestone S, Morris HR, Grosset D, Sutherland M, Gallagher J, Williams-Gray C, Bain LJ, Avilés E, Marek K, Toga AW, Stark Y, Gordon MF, Ford S. Precompetitive Data Sharing as a Catalyst to Address Unmet Needs in Parkinson's Disease. J Parkinson's Dis. 2015;5(3):581-94.

(4) Ahamadi M, Conrado DJ, Macha S, Sinha V, Stone J, Nicholas T, et al. Disease progression model platform to inform efficient clinical trial design for Parkinson's Disease. J Pharmacokinet Pharmacodyn. 2018 Oct;45(3–134):S73.

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