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The Critical Path for Parkinson's Consortium: Understanding Motor Disease Progression through Quantitative Medicine

on behalf of the Critical Path for Parkinson's (CPP) Consortium

Klaus Romero[1], Daniela J. Conrado[1], Brian Corrigan[2] , Kuenhi Tsai[3], Malidi Ahamadi[3], Sreeraj Macha[4], Vikram Sinha[4], Ian Watson[5], Massimo Bani[6], Pierandrea Muglia[6], Volker D. Kern[1], Caroline H. Williams-Gray[7], Donald G. Grosset[8], Michele Hu[9], David Burn[10], Rachael Lawson[10], *Kenneth Marek[11], Arthur Roach[12], Diane Stephenson[1] and Timothy Nicholas[2]

[1]Critical Path Institute, [2]Pfizer Inc., [3]Merck & Co. Inc., North Wales, PA, [4]Merck & Co. Inc., Kenilworth, PA, [5]Lilly, [6]UCB Pharma, [7]University of Cambridge, [8]University of Glasgow, [9]University of Oxford, [10]Newcastle University, [11]Institute for Neurodegenerative Disorders, Molecular NeuroImaging LLC, [12]Parkinson's UK

Background

The Critical Path for Parkinson's (CPP) consortium (**Figure 1**) is based on the value of sharing patient-level data from cohorts and clinical trials in Parkinson disease (PD), and transforming those data into generalizable and applicable knowledge for PD therapeutics (**Figure 2**).

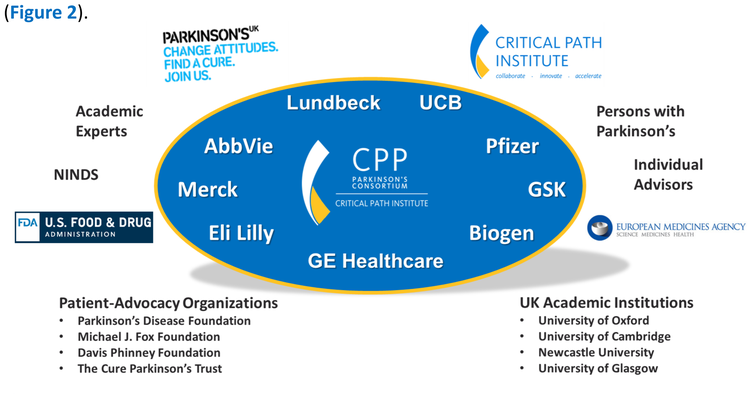

Figure 1
Critical Path for Parkinson's consortium members

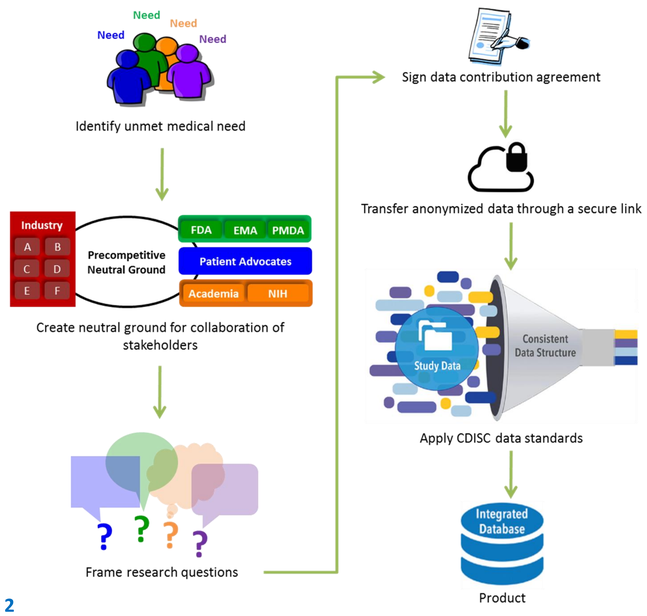

Figure 2
CPP as an expanded data sharing initiative (adapted from **Reference 1**)

Objective

- The goal herein is to develop and obtain regulatory endorsement of a computation tool for PD clinical trial enrichment.
- This tool will be based on a PD progression model and will inform entry criteria, enrichment strategies and stratification approaches.

Methods

Studies: Selected studies herein are the Parkinson's Progression Markers Initiative (**PPMI**), the Parkinson Research Examination of CEP-1347 Trial (**PRECEPT**), Oxford PD Centre (**OPDC**) Discovery Cohort; the Cambridgeshire Parkinson's Incidence from GP to Neurologist cohort (**CamPaIGN**); Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – PD (**ICICLE-PD**) and **Tracking Parkinson's** (the PRoBaND study) (**Figure 3**).

Data integration: The PD Clinical Data Interchange Standards Consortium (CDISC) standards will enable the integration of the studies in a unique database.

Model: The time course of the harmonized parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS) and MDS-UPDRS will be described using a non-linear mixed-effects regression.

Covariates: Subjects' demographic, genetic, biomarker and clinical characteristics to be tested as predictors of disease severity at baseline and/or intrinsic rate of disease progression are presented on **Figure 4**.

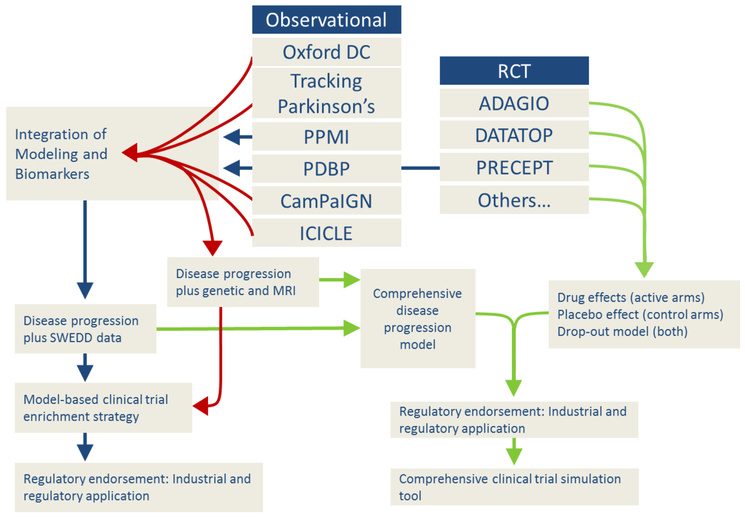

Figure 3
Overarching CPP Roadmap to Build Quantitative Drug Development Tools
Selected studies at the current stage are PPMI, PRECEPT, OPDC, CamPaIGN, ICICLE-PD, and Tracking Parkinson's (adapted from **Reference 2**)

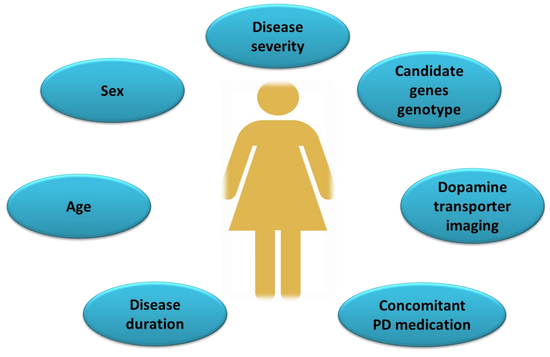

Figure 4
Examples of subject's characteristics to be tested as predictors of motor impairment in subjects with Parkinson

Results

- Up to this moment, patient-level data of PPMI, PRECEPT and CamPaIGN have been integrated using PD CDISC standard. Integration of ICICLE-PD, OPDC and the Tracking Parkinson's study will follow.
- The CPP integrated global database will result in a total of >6000 subjects into a unified database. Such database will expand the understanding of PD progression and allow a comprehensive investigation of subjects characteristics that predict of disease severity and/or rate of disease progression.
- An analysis of integrated subset – PRECEPT (n=191) and PPMI (n=481) – demonstrated that subjects defined as SWEDD (scans without evidence of dopamine transporter deficiency) have an average linear monthly progression in the harmonized motor scores that is 0.05 (90% CI: -0.04, 0.13) point/month or 0.13 point/month lower than that in subjects with dopamine transporter deficit (0.18 point/month; 90% CI: 0.14, 0.21) (**Figure 5**). The work herein will provide a comprehensive evaluation of the findings in the presence of additional studies and covariates, accounting for potential non-linearity in disease progression.

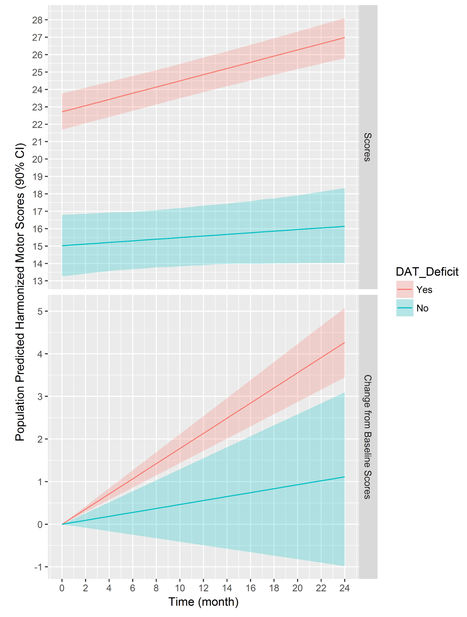

Figure 5
Population predicted harmonized motor scores of PD patients in PPMI and PRECEPT

Shaded area is the 90% confidence interval (CI). Predictions are for a PRECEPT-like study with average age of 60 years old.

Conclusion

Developing the quantitative drug development tools for PD through collaborative effort and regulatory review will enable optimized study design for trials targeting early stage PD.

References

(1) D.J. Conrado, M.O. Karlsson, K. Romero, C. Sarrc, J.J. Wilkins. Open Innovation: towards sharing of data, models and workflows. European Journal of Pharmaceutical Sciences (accepted for publication).

(2) D. Stephenson, M.T. Hu, K. Romero, K. Breen, D. Burn, et al. (2015) Precompetitive Data Sharing as a Catalyst to Address Unmet Needs in Parkinson's Disease. J. Parkinson's Dis., 5(3): 581-594.

Acknowledgments: The authors acknowledge the support of Parkinson's UK and the CPP member organizations. We also recognize Peggy Abbott for the skillful assistance in preparing this poster.