Development of a longitudinal Parkinson’s Disease Progression Model using Item-Response-Theory

Souvik Bhattacharya¹, Timothy Nicholas², Lawrence J. Lesko¹, Mirjam N. Trame¹

¹Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, FL; ²Global Clinical Pharmacology, Pfizer Inc, Groton, CT

Objectives: To evaluate and understand the natural history of early and long-term disease progression in Parkinson’s Disease (PD) by applying Item-Response-Theory (IRT) to analyze the longitudinal change of item-level data from the Unified Parkinson Disease Rating Scale (UPDRS).

Methods: Item-level UPDRS data from 317 patients followed over 15 months from a non-interventional NINDS trial (DATATOP) was used to develop a longitudinal IRT model. The model was developed in R 3.2.3 to predict patient-specific latent traits of individual subscores of the UPDRS at each study visit and estimate the change of each subscore for each individual over time in a Bayesian framework with normal prior distribution. A linear time-varying function was implemented, based on results from an initial Bootstrap clustering, in order to obtain a hierarchical structure of all UPDRS subscores and to determine the pattern of linkage between the UPDRS subscores over time. The Bayesian analyses were carried out using Markov Chain Monte Carlo simulations in the “brms” package in R which uses STAN. Estimation of inter-individual variability was allowed at each time point to describe the variability within the latent traits between the study population.

Results: The model was able to identify “Rigidity” and “Hand Movements” as the subscores being most influential for predicting the subscores higher in hierarchy, identified by the Bootstrap clustering analysis (e.g. “Handwriting” and “Preparing for Bed”). The simulated results using the developed model were utilized to simulate patient characteristics at specific time points from an external dataset. For each subject in the dataset, data from their respective visits were compared to the longitudinal simulations from the developed longitudinal IRT model, and were found to be in good agreement.

Conclusion: This approach is a promising tool being able to predict the overall disease progression in PD based on early disease progression information. The developed IRT model is embedded in a Shiny application.