Background

- Parkinson's disease (PD) ranks among the most common late-life neurodegenerative diseases affecting 2% of people over 60 years of age.
- Disease progression is measured primarily using a single, 6-part composite Unified Parkinson Disease Rating Scale (UPDRS)[1] consisting of 4 sub-categories (sub-scores) under Part I, 13 under Part II, 27 under Part III and 11 under Part IV.
- Part I (Mentation, Behavior and Mood), Part II (Activities of Daily Living), Part III (Motor Examination), Part IV (Complications of therapy), Part V (Hoehn and Yahr (H&Y) Staging), Part VI (Schwab and England ADL scale).
- A limitation to the UPDRS scale is the inter-rater variability, especially for each of the subscale scores. This adduced variability affects the diagnosis and estimation of the progression of PD as well as differentiating between early and late disease stages.

Objective

- 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 UPDRS collected during NINDS trials.
- To predict the effect of Levodopa treatment of the longitudinal change of item-level data from the UPDRS using IRT.

Methods

1. Data and Subjects

- UPDRS data from 44 different sub-scores (Part I, Part II, Part III) obtained from the following NINDS trials were utilized:
  - DATATOP: 24 month study on 800 early untreated patients, H&Y stage <= 3
  - ELLDOPA: 15 month study on 360 subjects in early, mild PD, not requiring symptomatic medications, H&Y <= 2.5
  - PRESTO: 6 month study on 450 subjects with idiopathic PD who are experiencing motor fluctuations on levodopa therapy, H&Y Stages <= 4
  - OSE: 16 month study on 80 early PD patients not requiring treatment with levodopa or any other antiparkinsonian medication, H&Y Stage <= 3
  - RAPID-20: 24 weeks study on 300 PD patients with motor fluctuations on chronic LD/CD therapy, H&Y Stage <= 5
- Dataset for Placebo Effect and Drug Effect Model Development
  - ELLDOPA - Dataset with Placebo + Levodopa
    - Dose of Levodopa – Low (50mg), Medium (100mg), High (200mg)
    - No dose modifications in the subjects under study
  - IRT model[2] was developed in R 3.2.3 to predict patient specific latent scores using R package “mirt”.
  - Longitudinal Bayesian framework with random intercept was developed using “brms” package in R 3.2.3.
  - Logistic regression model was established using the “net” package from the CRAN directory.
  - Visual Predictive Check (VPC) plots were used to evaluate the developed model using R 3.2.3.

Model Adaptation Workflow

- Tree diagrams obtained from bootstrap algorithm[2], to provide a hierarchical structure to hypothesize the interlink between individual sub-scores of the UPDRS composite scale and to identify key drivers of sub-scales informing the overall diseases progression (Figure 1).

3. Development of Algorithm for Longitudinal PD Simulation Model

- Place subjects in HY Timeline

- Using the RAPID algorithm to obtain combined latent scores from UPDRS Part I–IV

- Visual Predictive Check (VPC) plots

- Obtain combined latent scores from observed HM/RA in up to 0 = IRT

- Identify the H&Y stage at time = 0

- Predict the approximate time duration

- Develop a function to predict HM/RA for future time points

- Longitudinal Bayesian Approach

- Each time point predicts all other sub-scores = Logistic Regression

Results

1. Development of longitudinal natural progression model of Hand and Rapid Movement

2. Development of longitudinal drug effect model for Hand and Rapid Movement

3. Estimated model parameters and its distribution

Conclusion

- The model identified “Hand Movement” (HM) and “Rapid/Alter Movement” (RAM) as the most influential and sensitive sub-scores within the UPDRS.
- The simulator needs only information of HM & RAM at baseline and the Hoehn & Yahr stage of the subject at baseline to predict disease progression in PD subjects and to predict the overall change and severity for all 44 sub-scores of UPDRS including motor and non-motor functions.
- Well defined placebo effect was not observed in the dataset.
- Drug effect was clearly identified by the parameter estimates.
- The simulator can be utilized for clinical trial simulations.

REFERENCES