Enhancing Efficiency and Decision Quality in Parkinson Disease Drug Trials for LRRK2 Programs Using Item Response Modelling

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Background

- Owing to the slow and variable progression of Parkinson's disease (PD) symptoms, clinical trials aiming at identifying drug effects can be long and costly.

Objectives

- The aim of this work was to develop a framework enhancing efficiency in PD drug effect characterization, through prior evaluation of the study design, for trials in patients with the LRRK2 gene mutation, characterized by a slow disease progression.

Methods

- Data were obtained from PPMI[1] and included observations up to five years, from the Genetic PD, the Genetic Registry PD, and the DeNovo PD cohorts. Individual, longitudinal, item-level scores of Part I, Part II and Part III from the MDS-UPDRS[2], a PD assessment instrument, were extracted.
- An Item Response Theory (IRT) model was built in R package::Piraid and NONMEM, as shown in **Flowchart 1**.
- Covariate effects from factors like age, sex, time from diagnosis, and LRRK2 mutation status, were evaluated on the disease state model, using stepwise covariate model building procedure, while handling missingness in LRRK2 through a mixture probability.
- Series of 2-year delayed-start design trials[3] were simulated 500 times with 1000 early diagnosed virtual patients presenting the LRRK2 gene mutation.
- Hypothetical, clinically relevant, symptomatic and disease-modifying drug effects[4] were implemented in addition to a placebo effect at the beginning of each phase, after mapping parameters from item score scale to their corresponding LVs estimates[5], as shown in **Equations 1-2**.

$$Effect_{Symp} = -Symp * \left(1 - \frac{-\ln(2)}{e^{Symp_{on} * Time}}\right)$$

$$PL = -Plac * \frac{Pl_{on}}{Pl_{on} - Pl_{off}} * \; e^{-Pl_{on} * Time} \; - e^{-Pl_{off} * Time}$$

$$DS = PL_{phase\,1} + PL_{phase\,2} + Base + Slope * \left(1 - Effect_{Symp}\right) * Time \qquad \boldsymbol{Eq(1)}$$

$$DS = PL_{phase\,1} + PL_{phase\,2} + Base + Slope * \left(1 - Effect_{Modifying}\right) * Time \quad \boldsymbol{Eq(2)}$$

Where $Symp$ is the symptomatic effect of a mean 0.08 on DP, with 30% variability as an additive IIV, controlled by $Symp_{on}$ of 0.73/day with 20% variability; $Effect_{Modifying}$ is the slope-modifying effect, with a mean of 0.3 and variance of 0.0169; $Plac$ is the placebo effect of a mean 0.16 on disease progression, with 30% variability as an additive IIV; DS is the disease state.

Results

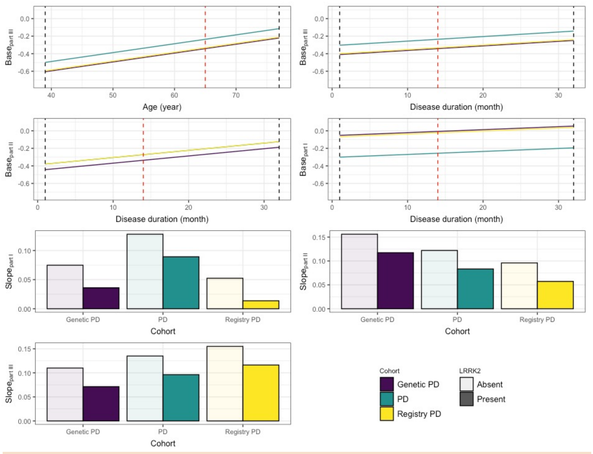


Fig 1. *Illustrations of the covariate effects on the affected parameters in the final IRT model, colored by study.*

- Transforming the non-tremor items in part III from left-side/right-side tests into best-side/worst-side tests resulted in a better description of the data.
- Identified predictors for the baselines were disease duration for all parts, and age for part III baseline. The factor found to affect the slopes of the three parts was LRRK2 gene mutation. These covariate effects are illustrated in **Fig 1**.
- The DP model described jointly the data from the three parts of the MDS-UPDRS scale in the three cohorts of the database, as summarized in **Fig 2**.

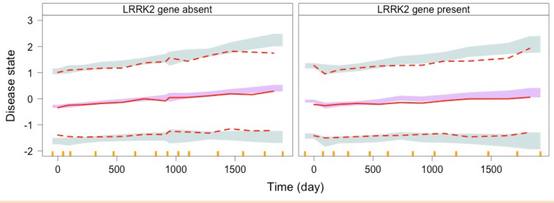


Fig 2. *Prediction-corrected visual predictive check of the disease state versus time since baseline visit based on 200 simulated data sets, using the final IRT model, stratified by LRRK2. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded purple and green areas represent the 95% CI of the median, 5th and 95th percentiles predicted by the model.*

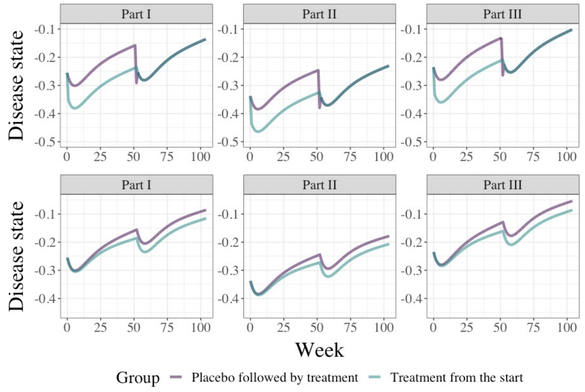


Fig 3. *Illustrations of the typical profiles of simulations with symptomatic drug effect (top row) and disease-modifying effect (bottom row).*

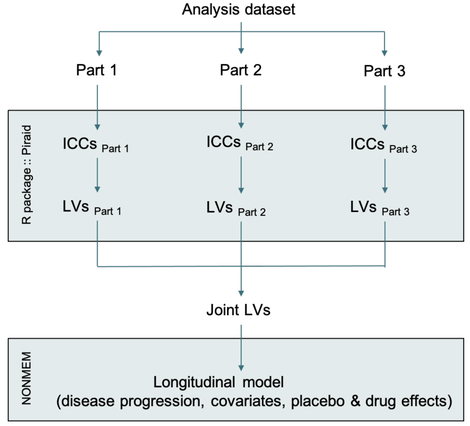
- Simulations included an initial reversible placebo effect in both arms at the beginning of each phase, with an alleviated disease progression in the early start arm in both phases and in the delayed start arm only in phase 2, as shown in **Fig 3**.
- Simulations of symptomatic drug effect showed that phase 1, of a duration of 1 year, was sufficient to distinguish the drug effect between the two arms, while this difference between the early and the delayed start arms was no longer visible after phase 2.
- However, simulations for the disease-modifying drug effect[4] was too small to be distinguished with the tested sample size and design.
- Results from the re-estimation of the simulations in terms of power and sample size are summarized in **Table 1**.

Parameter	Symptomatic drug effect		Disease-modifying drug effect	
	End of Phase 1	End of Phase 2	End of Phase 1	End of Phase 2
Proportion of trials detecting difference in effect (N=1000)	48%	6%	9%	7%
Sample size needed for 80% power at $X^2_{0.05}(3)$	2000	-	27000	35250

Table 1. *Results of 500 trials simulations and estimations.*

Conclusions

- We successfully developed a disease model for PD subjects with LRRK2 gene mutation.
- A novel design was simulated with hypothetical placebo and drug effects.
- This framework allows the estimation of the simulated scores with relevant analyses methods, with widespread applicability in evaluating the impact of different study design features, e.g., study duration, population, sample size, interim analyses, and assessment schedules.



Flowchart 1. *Schematic overview of IRT model building strategy, ICCs are the item characteristic curve parameters and LVs are the individual latent variables.*

References

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