Characterizing Disease Progression for Parkinson's Disease to implement efficient trial designs

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Introduction

A quantitative assessment of the patient characteristics and enrichment of clinical trials evaluating disease-modifying therapies for neurodegenerative disorders are critical to improve trial efficiency. CPP is pursuing regulatory qualification of prognostic enrichment biomarkers and characterize disease progression in early stage Parkinson's Disease (PD) to enable selection of the most appropriate patient population for evaluating new therapeutics in long-term clinical trials.

Objectives

The goal of the present work is to develop a disease progression model and identify relevant patient characteristics to inform trial design for Phase 2/3 trials that evaluate therapeutic candidates for early stage PD

Methods

C-Path assembled subject-level longitudinal data from 410 subjects with early-stage PD and dopamine transporter deficit from the PPMI study was used to build the disease progression model. Beta regression analyses, an extension of the generalized linear model, was used to characterize the time course of MDS-UPDRS Part II plus III due to its ability to evaluate bounded scores[1].

$$f(Score;a,b)=\frac{\Gamma(a+b)}{G(a)+G(b)}*Score^{(a-1)}*(1-Score)^{(b-1)}$$

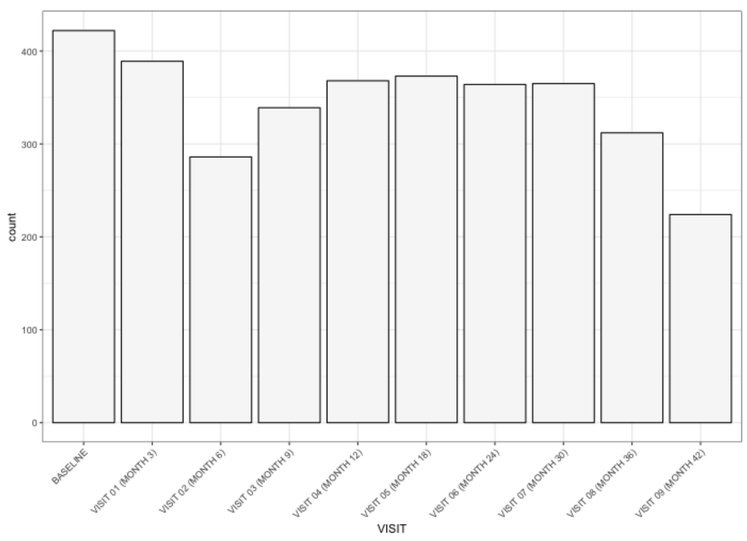
Where Γ(α) is the gamma function, that will be implemented in NONMEM using Neme approximation[2], α and β are shape parameters and Score [3] belongs to (0, 1) defined as

$$Score_1=\frac{Score-\min(Score)}{\max(Score)-\min(Score)} \quad (1)$$

$$Score_2=\frac{[Score_1*(n-1)+0.5]}{n} \quad (2)$$

With n is the sample size and $Score_2$ defined in (2) is the new dependent variable. Model selection was based on the Log-Likelihood Criterion, goodness of fit plots and scientific plausibility. Covariates, included demographic factors and genetic status (LRRK2 and GBA), were identified using automated SCM. The covariate was retained in the model during the forward addition step if there was a reduction in the objective value, i.e. OFV, of 6.63 or more ($P < 0.01$, degree of freedom [df] = 1). In the subsequent backward deletion step, an OFV increase greater than 10.83 ($P \leq .001$, df = 1) was required for a covariate to be retained in the model. Reliability of the final model was checked with diagnostic plots, visual predictive checks and bootstrap analysis. Simulation were performed to assess the impact of statistically selected covariates on disease progression rate

Figure 1: Distribution of subjects by visit



Results

Base model structure selection commenced with a linear model followed by non-linear models of increasing complexity [4].

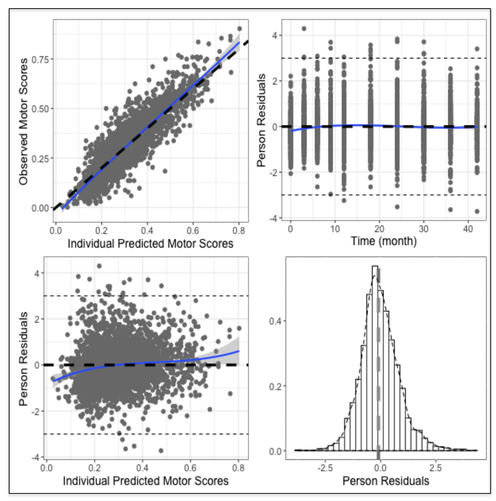
Table 1: Base Model development-

Base models	Disease progression rate	OBJV	*BIC
Linear (Normal distribution) $\frac{dScore}{dt}=r$	linear	18111.97	18152.43
Linear (Beta Distribution) $\frac{dScore}{dt}=r$	linear	-5930.941	-5890.484
Exponential model $\frac{dScore}{dt}=r*Score$	Non-linear	-6705.357 (Covariance Step could not evaluated)	-6664.901
Standard logistic model $\frac{dScore_i}{dt}=r_i*Score_i*\left[1-\frac{Score_i}{\max(Score_i)}\right]$	Non-linear , inflexion point=57	-6719.668	**-6679.211 (Final Base Model)**
Generalized logistic model $\frac{dScore_i}{dt}=r_i*Score_i*\left[\left(1-\frac{Score_i}{\max(Score_i)}\right)^{\beta}\right]$	Non-linear, Inflexion point =49.4	-6718.797	-6670.249 RSE (%) on: • r_i =148% • Beta=187%

* The Bayesian information criterion (BIC) was defined as **$OBJV+n_p*Ln(N)$**, where np is the total number of parameters in the model, and N is the number of data observations

Final model evaluation

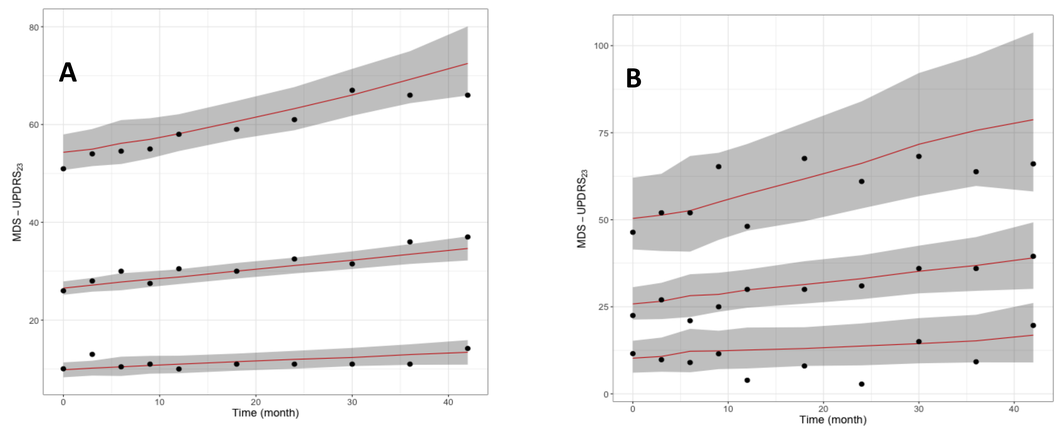
Parameter	Estimate		RSE (%)	
	Base Model	Final Model	Base Model	Final Model
Θ_{Score0} $\Theta_{AGE(centered\ at\ 62)}$	26.6	27.0 0.498	2.1	2.09 23.6
$\Theta_{Intrinsic\ rate\ (1/months)}$ Θ_{GBA} Θ_{female}	0.00593	0.00658 0.896 -0.36	10.9	11.3 41.1 21.4
T(Precision Parameter of Beta Distribution)	35	35.1	2..77	2.79
Random Effect				
IIV on Θ_{Score0}	0.149	0.142	8.06	7.97
IIV on $\Theta_{intrinsic\ rate\ (1/months)}$	0.887	0.832	14.6	15.4



- Final model based on standard logistic regression model
- AGE was identified as significant on the baseline of disease progression
- GBA mutation and gender were found significant on the disease progression rate
- Model adequately describe the data
- Pearson residual (Standardized ordinary residuals) based on the estimated mean and variance compared with the observations was used

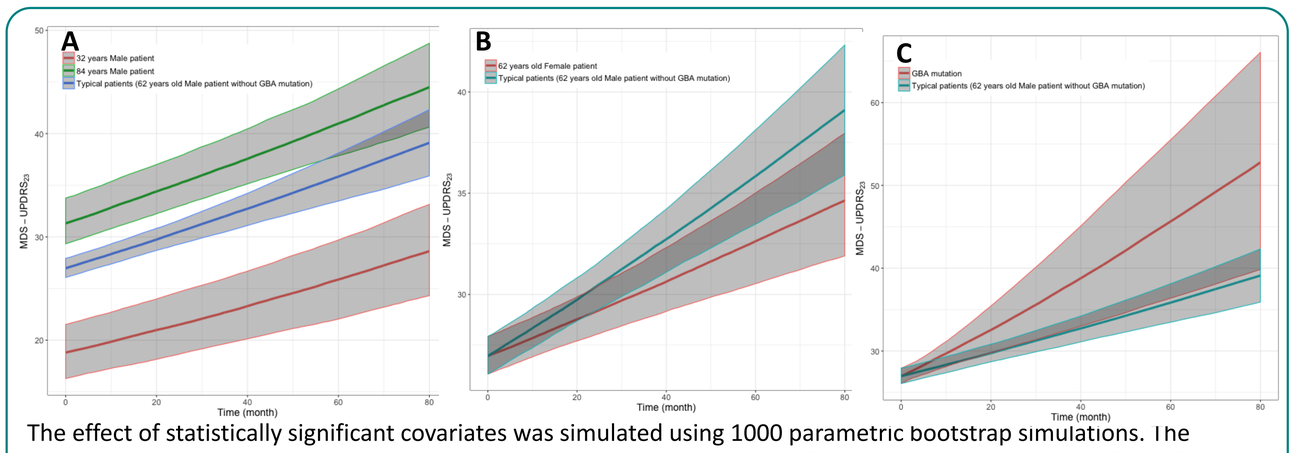
Model validation

Figure 2: Sample of Visual Predictive Check showing the robustness of the model



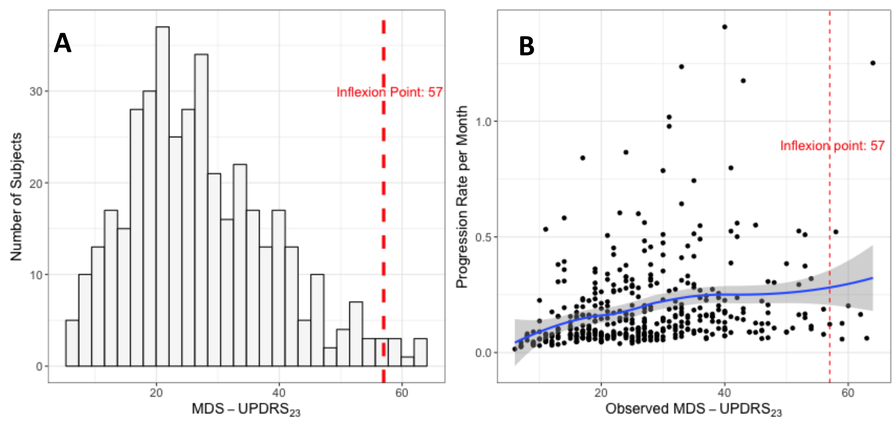
Visual Predictive Check (VPC) from N = 1000 Simulations. Solid and dashed black lines are observed median, 5th and 95th percentiles, and shaded areas are corresponding predicted intervals from the final model. A) full dataset, B) Stratified by GBA. Majority of the observations fall within the 90% prediction intervals suggesting the adequacy of the model to describe the individual temporal profiles.

Impact of selected covariates on disease progression



The effect of statistically significant covariates was simulated using 1000 parametric bootstrap simulations. The reference/typical patient is a 62 year old male without GBA mutation. A) Effect of AGE on baseline, B) Effect of Gender on disease progression rate; C) Effect of GBA mutation on disease progression rate.

Predicting inflection point



A) Distribution of observed MDS-$UPDRS_{23}$ with estimated inflection from the final model B)Estimated progression rate as function of observed MDS-$UPDRS_{23}$. High variability observed at high value of MDS-UPDRS23 due to lack of sufficient observed data that consisted of de Novo PD.

Conclusion

A logistic model describing the disease progression in early stage PD was successfully developed. The insights from this model represent valuable information for building a more robust disease progression model that will inform the entry criteria and enrichment strategies for long-term trials.

- A logistic (non-linear) model was chosen based on goodness-of-fit plots and BIC criteria.
- The progression rate increased with time until the inflection point and the maximum progression rate was estimated to be ~0.25 points/month.
- Preliminary covariate analysis indicated that age had a significant effect on baseline, and gender and GBA mutation had a significant effect on the slope of disease progression.

References

1. Daniela J. Conrado, et al, J Pharmacokinet Pharmacodyn (2014) 41:581–598
2. Xu Steven et al. J Pharmacokinet Pharmacodyn (2013) 40:537–544
3. Smithson M, et al. Psychol Methods 11:54–71. DOI:10.1037/1082-989X.11.1.54.
4. Venuto CS, et al.. Mov Disord 31:947-56. DOI: 10.1002/mds.26644

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