DEVELOPMENT OF A STATISTICAL MODEL TO PREDICT EUROQOL FIVE DIMENSIONS (EQ-5D) UTILITIES IN PARKINSON'S DISEASE

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1

Background

Parkinson's Disease

- Parkinson's disease (PD) is a progressive neurological disorder characterized by numerous motor (e.g., postural instability) and non-motor symptoms (e.g., depression, cognitive impairment)
- The severity of PD is commonly measured using the Unified Parkinson's Disease Rating (UPDRS) Scale (1987)
  - Measures both motor and non-motor symptoms and is composed of four distinct parts

Health Utilities

- In a health economic model, utility is a measure of preference used to indicate patients' quality of life (i.e., cost-utility analysis)
  - Utilities may range from 0 to 1, where 0 indicates death, while 1 indicates perfect health
- A common method of utility measurement is using generic, preference-based instruments
  - EuroQol five dimensions (EQ-5D) is frequently used in practice and is the preferred method of NICE

2

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2

Goals and Objectives

Goals:

- The aim was to develop a predictive equation for utilities, suitable for use in an economic model to conduct cost-utility analysis (CUA)

Objectives:

- To develop a statistical model to predict utilities derived from the 3-level version of the EQ-5D (EQ-5D-3L) as a function of patient demographics and PD severity, as measured by the UPDRS subscales

Data Source

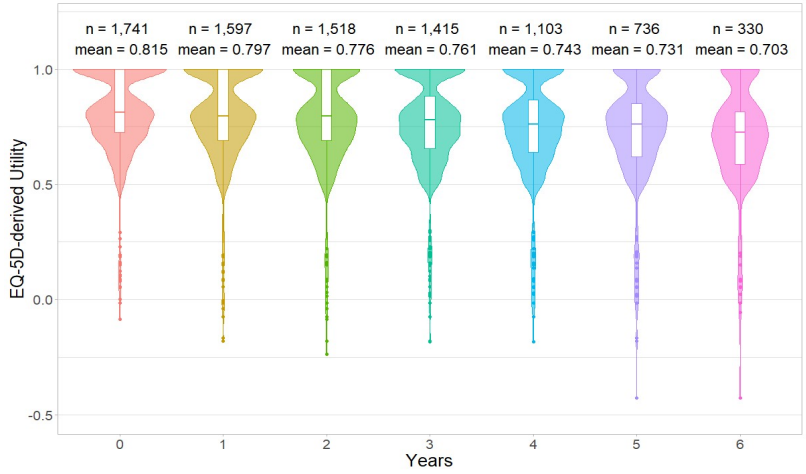
- Patient-level data were obtained from the National Institute of Neurological Disorders and Stroke (NINDS) Exploratory Trials in PD Long-Term Study 1 (NET-PD LS-1)[1]
  - A multicenter, placebo-controlled, phase 3 study of creatine in patients on dopaminergic therapy within 5 years of diagnosis (**N=1,741; 6 years follow-up**)
  - Participants recruited from **50 study locations** in the United States and Canada
  - Participants were enrolled from March 2007 to May 2010 and followed up until September 2013

Baseline Characteristics of LS-1 Participants

Baseline Characteristics	Mean	Standard Deviation
Age (years)	61.8	9.6
% Male	64.5%	--
EQ-5D-3L Utility Value	0.8	0.2
UPDRS I	1.3	1.4
UPDRS II	7.2	4.0
UPDRS III	17.8	8.4
UPDRS IV	1.3	1.6

Distributions of EQ-5D-3L Utilities

- Observed EQ-5D-3L-derived utilities have vast variability at each annual visit, approximately bimodal distributions, and gradual decline in average values over time



5

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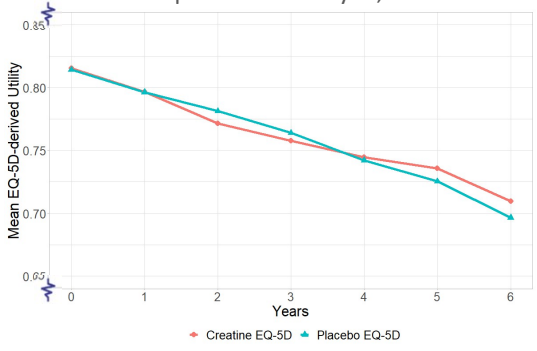
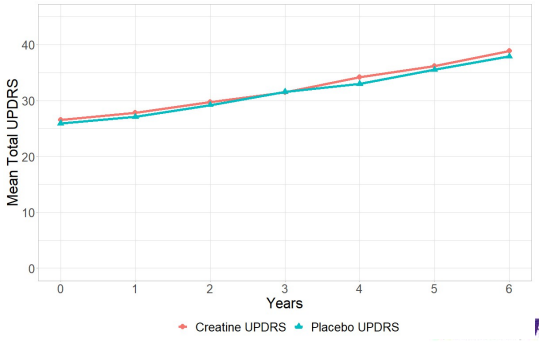
5

Development of Predictive Equation

- Patient-level data obtained from the NET-PD LS-1 were analyzed to develop a predictive equation for EQ-5D-3L-derived utilities
- Candidate predictors were informed by a previous SLR conducted to identify published studies that reported the association between utilities and PD severity (Chandler et al., 2019[2])
- The mean utility values and UPDRS scores were comparable between treatment arms, and thus patient-level data were pooled for analysis, as the treatment effect was not statistically significant





6

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6

General Form of Predictive Equation (Mixed Linear Model)

- A mixed-effects linear model was used to analyze repeated measures (correlated) data
- Correlation between measurements from the same subjects were accounted for in the model by including a random intercept term
- The general form of the random intercepts model can be written as follows:

$$Y_{ij} = \beta_0 + \sum_{k=1}^{k=p}(\beta_k X_{ijk}) + \alpha_i + \epsilon_{ij}$$

Fixed part | Random part

Where Y_{ij} is the response for subject i, measurement j
β_0 is the fixed intercept
β_k is the fixed slope parameter for the k^{th} predictor
$\alpha_i \sim N(0, \sigma_\alpha^2)$ is the random intercept for subject i
$\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$ is the error term

- The subject-specific effect, α_i, quantifies how the mean response trajectory for subject i deviates from the population average[3]

Subject –Specific Mean Response	Population Mean Response
$E(Y_{ij}\|\alpha_i) = (\beta_0+\alpha_i) + \sum(\beta_k+X_{ijk})$	$E(Y_{ij}) = \beta_0 + \sum(\beta_k+X_{ijk})$

7

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7

Final Multivariate Model

- The EQ-5D-3L index scores were calculated using the **UK preference weights** and data were analyzed using a mixed-effects linear model
- Variables were tested individually to identify **significant predictors** and a multivariate model was then built from these and trimmed to retain only variables that remained significant
- **Age was excluded** from the multivariate model as it was not statistically significant after adjusting for UPDRS scores
  - Further, age had a positive coefficient in the multivariate model, flipped from the univariate analysis (i.e., multicollinearity)

Predictors	Included?
Male	Yes (+)
UPDRS I	Yes (-)
UPDRS II	Yes (-)
UPDRS III	Yes (-)
UPDRS IV	Yes (-)
Age	No
Treatment	No

Note, the positive and negative signs contained within the parentheses indicate the sign of the associated coefficient, as shown below.

$$Y = (\beta_0+\alpha) + \beta_1 Male - \beta_2 U1 - \beta_3 U2 - \beta_4 U3 - \beta_5 U4 + \epsilon$$

8

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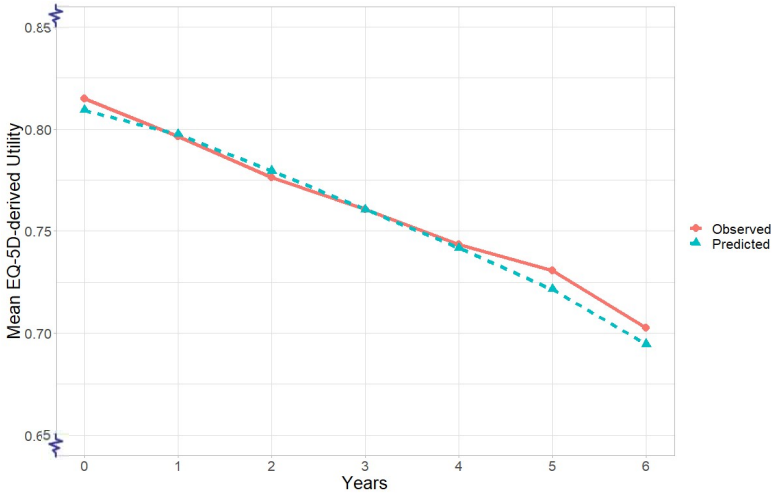
8

Validation of Predictive Equation

- The statistical model performed well in validation analyses—average predicted EQ-5D-3L utilities were compared with the average observed scores for each year post-baseline and were within **+/-0.009** at all visits



Conclusions

- The average decline in the observed EQ-5D-3L utilities was approximately constant over time (**-0.018 per year**)—that is, a negative linear relationship between years and EQ-5D-3L utility values was observed
- The model for utilities captures the impact of non-motor and motor-related aspects of the disease as all four UPDRS subscales were identified as significant predictors
- The model predictions were confirmed to be consistent with the observed EQ-5D-3L utilities in NET-PD LS-1; thus, this model is suitable to support CUA for a population similar to that of NET-PD LS-1

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11

References and Disclosures

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2. Chandler C, Alvarez P, Folse HJ, Ward A. PND125-The association between utilities and disease severity for Parkinson's Disease: A systematic literature review. Value in Health. 2018 Oct 1;21:S350.
3. Applied Longitudinal Analysis, 2nd Edition, by Garrett M. Fitzmaurice, Nan M. Laird, and James H. Ware, John Wiley & Sons, 2011.

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12