

## Original Investigation

# Measuring Disease Progression in Early Parkinson Disease

## The National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD) Experience

Sotirios A. Parashos, MD, PhD; Sheng Luo, MS; Kevin M. Biglan, MD, MPH; Ivan Bodis-Wollner, MD, DSc; Bo He, MS; Grace S. Liang, MD; G. Webster Ross, MD; Barbara C. Tilley, PhD; Lisa M. Shulman, MD; for the NET-PD Investigators

**IMPORTANCE** Optimizing assessments of rate of progression in Parkinson disease (PD) is important in designing clinical trials, especially of potential disease-modifying agents.

**OBJECTIVE** To examine the value of measures of impairment, disability, and quality of life in assessing progression in early PD.

**DESIGN, SETTING, AND PARTICIPANTS** Inception cohort analysis of data from 413 patients with early, untreated PD who were enrolled in 2 multicenter, randomized, double-blind clinical trials.

**INTERVENTIONS** Participants were randomly assigned to 1 of 5 treatments (67 received creatine, 66 received minocycline, 71 received coenzyme Q10, 71 received GPI-1485, and 138 received placebo). We assessed the association between the rates of change in measures of impairment, disability, and quality of life and time to initiation of symptomatic treatment.


**MAIN OUTCOMES AND MEASURES** Time between baseline assessment and need for the initiation of symptomatic pharmaceutical treatment for PD was the primary indicator of disease progression.

**RESULTS** After adjusting for baseline confounding variables with regard to the Unified Parkinson's Disease Rating Scale (UPDRS) Part II score, the UPDRS Part III score, the modified Rankin Scale score, level of education, and treatment group, we assessed the rate of change for the following measurements: the UPDRS Part II score; the UPDRS Part III score; the Schwab and England Independence Scale score (which measures activities of daily living); the Total Functional Capacity scale; the 39-item Parkinson's Disease Questionnaire, summary index, and activities of daily living subscale; and version 2 of the 12-item Short Form Health Survey Physical Summary and Mental Summary. Variables reaching the statistical threshold in univariate analysis were entered into a multivariable Cox proportional hazards model using time to symptomatic treatment as the dependent variable. More rapid change (ie, worsening) in the UPDRS Part II score (hazard ratio, 1.15 [95% CI, 1.08-1.22] for 1 scale unit change per 6 months), the UPDRS Part III score (hazard ratio, 1.09 [95% CI, 1.06-1.13] for 1 scale unit change per 6 months), and the Schwab and England Independence Scale score (hazard ratio, 1.29 [95% CI, 1.12-1.48] for 5 percentage point change per 6 months) was associated with earlier need for symptomatic therapy.

**CONCLUSIONS AND RELEVANCE** In early PD, the UPDRS Part II score and Part III score and the Schwab and England Independence Scale score can be used to measure disease progression, whereas the 39-item Parkinson's Disease Questionnaire and summary index, Total Functional Capacity scale, and the 12-item Short Form Health Survey Physical Summary and Mental Summary are not sensitive to change.

**TRIAL REGISTRATION** clinicaltrials.gov Identifiers: NCT00063193 and NCT00076492

*JAMA Neurol.* doi:10.1001/jamaneurol.2014.391  
Published online April 7, 2014.

 Supplemental content at  
jamaneurology.com

**Author Affiliations:** Struthers Parkinson's Center, Golden Valley, Minnesota (Parashos); Division of Biostatistics, University of Texas at Houston (Luo, He, Tilley); Department of Neurology, University of Rochester, Rochester, New York (Biglan); State University of New York, Downstate Medical Center, Brooklyn (Bodis-Wollner); The Parkinson's Institute and Clinical Center, Sunnyvale, California (Liang); VA Pacific Islands Health Care System, Honolulu, Hawaii (Ross); Department of Neurology, University of Maryland School of Medicine, Baltimore (Shulman).

**Group Information:** The NET-PD Investigators are listed at the end of this article.

**Corresponding Author:** Sotirios A. Parashos, MD, PhD, Struthers Parkinson's Center, 6701 Country Club Dr, Golden Valley, MN 55427 (sotirios.parashos@mpls-clinic.com).

**P**arkinson disease (PD) is a progressive neurodegenerative disease that leads to significant morbidity, disability, and institutionalization.<sup>1,2</sup> Measuring disease progression in PD is challenging, and a variety of instruments have been used for this purpose, including measures of impairment, disability, and quality of life. Yet, a consistently reliable, easy-to-use measure of disease progression remains elusive.<sup>3</sup> As part of the NET-PD, 2 futility drug studies (Futility Study 1 [FS-1]<sup>4</sup> and Futility Study 2 [FS-TOO]<sup>5</sup>) explored the potential of 4 compounds as disease-modifying agents in early, untreated PD. The primary outcome measure of these studies was the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score (Parts II and III) between baseline and the time at which there was sufficient disability to warrant symptomatic treatment (ST). Participants in these 2 studies<sup>4,5</sup> were assessed using a number of impairment, disability, and quality-of-life measures at baseline, at predetermined intervals throughout the study, and at the end point. In a previously published analysis of the FS-1 and FS-TOO populations, we determined that, at baseline, the UPDRS Part III score, the UPDRS Part II score, and the modified Rankin Scale (mRS) score were independently associated with earlier need for ST.<sup>6</sup> In the present study, we examine the predictive value of the observed rate of change in the various assessment instruments used in FS-1 and FS-TOO, with regard to the time to ST. Our hypothesis was that, although some instruments may be of greater value as baseline predictors, different instruments might prove more useful in monitoring disease progression in early PD.

## Methods

### Participants

Data from FS-1<sup>4</sup> and FS-TOO<sup>5</sup> were used for this analysis. The 413 participants were men or women 30 years of age or older who received a diagnosis of PD (duration of diagnosis,  $\leq 5$  years) and who, at the time of study entry, did not require ST for PD. Two of the 3 classic clinical signs of PD (tremor, rigidity, or bradykinesia) were required for the diagnosis, and these had to be asymmetric signs. The presence of parkinsonism and prior brain surgery for PD were exclusion criteria. Women of child-bearing potential had to have had a negative pregnancy test result at baseline and were required to use adequate birth control for the duration of the studies. All participants gave written informed consent. The protocols and consents for the drug trials were approved by the National Institute of Neurological Disorders and Stroke oversight board, by an independent data safety monitoring board, and by the institutional review boards of the participating sites. Both studies were designed as multicenter, randomized, double-blind trials powered to assess the futility of candidate drugs as disease-modifying agents in early, untreated PD.

### Baseline and Follow-up Assessments

At the baseline visit of each participant, we collected data on sex, age, level of education, race/ethnicity, and disease duration (from diagnosis). The UPDRS Part III was administered as a measure of impairment.<sup>7</sup> The following scales were admin-

istered as measures of disability: the UPDRS Part II,<sup>7</sup> the mRS,<sup>8</sup> the Schwab and England Independence Scale (which measures activities of daily living [ADL]),<sup>9</sup> the Total Functional Capacity (TFC) scale,<sup>10</sup> and the 39-item Parkinson's Disease Questionnaire (PDQ-39) ADL subscale.<sup>11</sup> The PDQ-39 summary index and the Medical Outcomes Study version 2 of the 12-item Short Form Health Survey<sup>12</sup> (the Physical Summary and the Mental Summary) were administered as indicators of quality of life. The UPDRS Part II score and the UPDRS Part III score were obtained every 3 months during the study duration and at the end point. Besides at baseline, the mRS, the Schwab and England Independence Scale, the TFC scale, the PDQ-39, and the 12-item Short Form Health Survey were also administered at the end point or at 12 months.

### Treatments

In each of the futility studies,<sup>4,6</sup> participants were randomized in a 1:1:1 ratio to receive 1 of the 2 active experimental drugs or placebo. Of the 200 FS-1 participants, 67 received creatine, 66 received minocycline, and 67 received placebo. Of the 213 FS-TOO participants, 71 received coenzyme Q10, 71 received GPI-1485, and 71 received placebo.

### End-Point Determination

The primary end point for the analyses in the present study was time to initiation of ST. Symptomatic treatments included levodopa, dopamine agonists, amantadine, anticholinergics, and selegiline. Participants were censored at 12 months of follow-up, if they had not reached the end point by that time. Site investigators used their clinical judgment to determine when participants had reached a level of dysfunction sufficient to require ST in any 1 of 3 areas: ambulation, ADL, or occupational status.<sup>5,6,13</sup>

### Statistical Design and Analyses

We conducted the analysis using the 2-stage model.<sup>14</sup> First, a linear model was fit to each participant, using each measurement as the response variable and time in 10-day increments as the sole covariate. A participant-specific rate of change for each measurement was obtained for each participant. The participant-specific slopes indicated the rates of change of each covariate per 6 months. Because the mRS is a discrete ordinal scale, an mRS "rate of change" was not considered for further analysis (eAppendix in Supplement), although the baseline mRS score was included as a confounding variable. To reduce the number of covariates to be considered in the model, Cox proportional hazards models were used to test the association of each variable's rate of change separately with the primary end point according to the Hosmer and Lemeshow model development strategy<sup>15</sup>: any variable associated with the time to ST at an  $\alpha$  level of .15 was selected for inclusion in the second stage. Univariate models were subsequently adjusted for the 4 confounding baseline covariates previously identified (UPDRS Part II score, UPDRS Part III score, mRS score, and level of education)<sup>6</sup> and for treatment group assignment. Spearman rank correlations among all pairwise combinations of the selected variables were computed to assess potential collinearity prior to the second-stage analysis.

In the second stage, a multivariable Cox proportional hazards model with time to symptomatic therapy as the dependent variable was constructed using the selected variables, the 4 previously mentioned confounding baseline covariates, and the treatment group assignment. Backward variable selection was used to remove the variables meeting the exclusion criteria of  $\alpha > .05$ . Scaled Schoenfeld residuals were computed to assess the proportional hazards assumption.<sup>16</sup> The analysis was completed using R version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria).

There were 47 participants (25 in the ST group and 22 in the group not reaching the end point) whose baseline values on some of the variables were missing (eTable 1 in Supplement). After establishing that the participants with missing baseline values did not differ significantly from the rest of the participants at baseline in terms of the variables of interest, we applied multiple imputation techniques using the “mi” package in R while adjusting for each variable’s baseline value, the 4 previously mentioned confounding baseline covariates, and treatment assignment, to impute the missing values. A total of 62 participants had missing values that needed to be imputed. A total of 13 participants (3.1%) were excluded from the multivariable analysis because the amount of missing data precluded analysis.

In assessing the rate of change in PD, worsening corresponds to increases in UPDRS scores and the PDQ-39 ADL subscale and summary index and decreases in the Schwab and England Independence Scale score, the TFC scale, and the 12-item Short Form Health Survey subscales. Because these measures were expected to worsen, if anything, for most participants, we reversed the signs of the rates of changes for the Schwab and England Independence Scale, the TFC scale, and the 12-item Short Form Health Survey subscales so that all slopes would represent rates of worsening, for ease of interpretation. In addition, the measurements of the Schwab and England Independence Scale were percentages ranging from 0% to 100% in increments of 5; therefore, we divided these values by 5 before computing the rate of worsening.

## Results

### Baseline Demographics and Disease Characteristics

**Table 1** summarizes the baseline demographics of the patient population, along with baseline impairment, disability, and quality-of-life measures. Of 413 participants, 200 (48.4%) started ST within 12 months from baseline.

**Table 2** indicates that, among the participants who needed ST, those with missing values had similar ST-free survival times as those without missing values, and there was no difference in baseline parameters between participants with missing values and participants without missing values within the 2 subgroups. The rates of worsening with regard to the Schwab and England Independence Scale, the TFC scale, the PDQ-39 ADL subscale and summary index, and the 12-item Short Form Health Survey Physical Summary and Mental Summary were computed for the participants without missing values and were imputed for the participants with missing values.

**Table 1. Baseline Characteristics of 413 Study Participants**

| Variable                                    | Value, Mean (SD) |
|---|------------------|
| Age, y                                      | 61.7 (10.4)      |
| Education, y                                | 15.2 (3.2)       |
| Duration of PD diagnosis, y                 | 0.66 (0.84)      |
| Male sex, % of participants                 | 64.2             |
| Non-Latino white, % of participants         | 91.0             |
| Unified Parkinson’s Disease Rating Scale    |                  |
| Part II score                               | 5.99 (3.26)      |
| Part III score                              | 15.89 (6.74)     |
| 12-Item Short Form Health Survey            |                  |
| Physical Summary                            | 50.02 (7.63)     |
| Mental Summary                              | 51.40 (9.09)     |
| mRS score >1, % of participants             | 12.0             |
| Schwab and England Independence Scale score | 93.05 (5.31)     |
| TFC scale                                   | 12.37 (1.27)     |
| PDQ-39                                      |                  |
| ADL   | 15.94 (15.22)    |
| Summary index                               | 15.78 (11.73)    |

Abbreviations: ADL, activities of daily living; mRS, modified Rankin Scale; PD, Parkinson disease; PDQ-39, 39-item Parkinson’s Disease Questionnaire; TFC, Total Functional Capacity.

The rates of worsening of all the variables met the criteria for inclusion in the multivariate Cox proportional hazards model based on univariate models both unadjusted and adjusted for baseline confounding variables (eTable 2 in Supplement). The correlation between the rates of worsening of the different variables was not strong (the maximum correlation coefficient being 0.68). The final selected model retained rate of worsening in the following variables after adjusting for treatment assignment and the 4 confounding baseline variables: UPDRS Part II score, UPDRS Part III score, and Schwab and England Independence Scale score (**Table 3**). As seen in the final model, the effect of treatment assignment was not statistically significant. The proportional hazards assumption was satisfied for the final model. Rates of worsening of the UPDRS Part II score, the UPDRS Part III score, and the Schwab and England Independence Scale score were associated with earlier need for ST. Rates of worsening of the TFC scale, the PDQ-39 ADL subscale and summary index, and the 12-item Short Form Health Survey Physical Summary and Mental Summary did not retain a statistically significant association with the end point in the multivariable model.

## Discussion

This analysis complements our previous study of the value of measures of impairment, disability, and quality of life as indicators of disease progression in early PD.<sup>6</sup> We concluded that the rates of worsening of UPDRS Part II score, UPDRS Part III score, and Schwab and England Independence Scale score predicted an earlier need for ST. Interestingly, when the rates of worsening of these variables were included in the model, the

Table 2. Mean Baseline Variables Classified by Missing Values and Need for ST<sup>a</sup>

| Variable                        | Need for ST                 |                         |         | No Need for ST              |                         |         |
|---------------------------------|-----------------------------|-------------------------|---------|-----------------------------|-------------------------|---------|
|                                 | No Missing Values (n = 175) | Missing Values (n = 25) | P Value | No Missing Values (n = 191) | Missing Values (n = 22) | P Value |
| UPDRS                           |                             |                         |         |                             |                         |         |
| Part II score                   | 6.93                        | 6.88                    | .94     | 5.23                        | 4.18                    | .12     |
| Part III score                  | 17.53                       | 18.40                   | .54     | 14.45                       | 12.55                   | .17     |
| Education, y                    | 15.63                       | 15.80                   | .78     | 14.70                       | 15.27                   | .44     |
| mRS score >1, % of participants | 17.7                        | 12.0                    | .67     | 6.3                         | 9.1                     | .96     |
| ST-free survival time, d        | 224.70                      | 195.16                  | .14     | NA                          | NA                      |         |

Abbreviations: mRS, modified Rankin Scale; NA, not applicable; ST; symptomatic treatment; UPDRS, Unified Parkinson's Disease Rating Scale.

<sup>a</sup> All values are mean values, and standard deviations were omitted for clarity.

baseline UPDRS Part III score was no longer statistically significant, while the baseline UPDRS Part II score and the baseline mRS score retained their previously reported associations. The combined findings of the 2 analyses are summarized in Table 4.

Motor impairment and disability are the most consistent baseline predictors of an earlier need for symptomatic pharmacotherapy. Other important predictors include higher level of education,<sup>6</sup> full-time employment, less smoking history, and left-sided onset.<sup>17,18</sup>

A number of approaches have been tried to identify the best-suited measures of PD progression for use in clinical trials.<sup>3</sup> The task is even more daunting when assessing patients in the earliest stages of the disease, when symptoms are generally mild and when impairment and disability can be minimal. Using the time between baseline and the need for ST as an end point has been a common characteristic of many studies in early PD, particularly clinical trials of agents with disease-modifying potential.<sup>4,5,13,18</sup> Our analysis now identifies the measures that are most likely to reflect the progression of impairment and disability that leads to the decision to treat.

Predictably, measures associated with physical impairment, such as the UPDRS Part II and Part III scores and the Schwab and England Independence Scale score, were retained in the final model. Among all the measures considered in this analysis, these are conceivably the measures most reflective of increasing physical impairment. Mobility impairment and difficulties with mobility-dependent ADL are indeed the most important determinants of emerging disability in progressing PD.<sup>19</sup> Table 4 shows that, among all the measures assessed in our analyses, the UPDRS Part II score was the most informative in determining both baseline disease activity and subsequent disease progression. Certainly, this strong association between the compromise of ADL (UPDRS Part II score) and the initiation of ST may simply reflect the fact that treating physicians use the decline in ADL as a trigger to discuss and recommend ST, and therefore may simply be the consequence of current standards in practice rather than an indication that this measure is the best way to assess disease progression.

Among the remaining measures of disability examined in our study, the mRS score demonstrated good predictive value at baseline; because it is an ordinal variable, it would be incorrect to calculate a "rate of change," and therefore we were

Table 3. Final Cox Regression Model<sup>a</sup>

| Parameter                                   | HR (95% CI)      | P Value |
|---|------------------|---------|
| Rate of worsening                           |                  |         |
| UPDRS Part II score                         | 1.15 (1.08-1.22) | <.001   |
| UPDRS Part III score                        | 1.09 (1.06-1.13) | <.001   |
| Schwab and England Independence Scale score | 1.29 (1.12-1.48) | <.001   |
| Baseline                                    |                  |         |
| UPDRS Part II score                         | 1.06 (1.01-1.12) | .03     |
| UPDRS Part III score                        | 1.02 (0.99-1.04) | .17     |
| mRS score                                   | 2.22 (1.43-3.42) | <.001   |
| Education (in 4-y increments)               | 1.32 (1.08-1.60) | .006    |
| Treatment                                   |                  |         |
| Creatine                                    | 0.78 (0.46-1.32) | .35     |
| Minocycline                                 | 0.69 (0.41-1.16) | .16     |
| GPI-1485                                    | 0.88 (0.53-1.47) | .64     |
| CoQ10                                       | 0.80 (0.48-1.33) | .39     |
| Placebo                                     | 0.84 (0.51-1.40) | .51     |

Abbreviations: CoQ10, coenzyme Q10; mRS, modified Rankin Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

<sup>a</sup> Data from 400 participants were used for the model; 13 participants were left out owing to missing values at baseline. Hazard ratios (HRs) for rates of worsening were calculated for increases of 1 unit per 6-month interval in the rate of worsening of the corresponding measure. For the Schwab and England Independence Scale score, 5 percentage points represented 1 unit.

not able to assess its sensitivity to change in this particular analysis scheme. It should be recalled that the mRS was developed to measure stroke outcomes,<sup>8</sup> and, as such, its sensitivity to change when applied to a chronic progressive neurologic disease, as opposed to a discrete insult to the nervous system, is unknown. With our analysis, we were unable to determine whether the mRS is a reliable measure of early PD progression. The TFC scale and the PDQ-39 ADL subscale did not stand out either as baseline predictors or as measures of progression.

The PDQ-39 summary index, a global PD-specific measure of health-related quality of life, and the 12-item Short Form Health Survey did not appear as responsive to disease progression in early PD. In the univariate models, these measures of health-related quality of life demonstrated sufficient correlation to disease progression to be included in multivariable modeling; however, the multivariable analysis would suggest that they do not reflect disease progression as robustly as

Table 4. Predictive Value of Measures of Impairment, Disability, and Quality of Life in Assessing Early PD Progression in the Final Multivariable Model

| Predictive Value | Baseline                          |  |                           | Rate of Progression  |   |                           |
|------------------|-----------------------------------|--|---------------------------|----------------------|---|---------------------------|
|                  | Impairment                        | Disability   | Quality of Life           | Impairment           | Disability <sup>a</sup>                           | Quality of Life           |
| Retained         | UPDRS Part III score <sup>b</sup> | UPDRS Part II score, mRS score                               |                           | UPDRS Part III score | UPDRS Part II score, S&E Independence Scale score |                           |
| Did not retain   |                                   | TFC scale, PDQ-39 ADL subscale, S&E Independence Scale score | PDQ-39 SI, SF12 PS and MS |                      | TFC scale, PDQ-39 ADL subscale                    | PDQ-39 SI, SF12 PS and MS |

Abbreviations: ADL, activities of daily living; mRS, modified Rankin Scale; PD, Parkinson disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; S&E, Schwab and England; SF12 PS and MS, 12-item Short Form Health Survey Physical Summary and Mental Summary; SI, summary index; TFC, Total Functional Capacity; UPDRS, Unified Parkinson's Disease Rating Scale.

<sup>a</sup> A "rate of change" could not be calculated for mRS score, and therefore its sensitivity to rate of progression could not be assessed in this analysis.

<sup>b</sup> Baseline UPDRS III score lost its significance when rate of progression variables were included in the model.

the measures that were retained in the final multivariable model. The implication may be either that changes in quality of life are not as potent a motive to initiate ST in early PD as progressive motor impairment or that the available instruments are not as sensitive to change in the early stage of the disease. In addition, ST as defined in the FS-1 and the FS-TOO referred to drug treatment of the motor symptoms of the disease, whereas these measures of global health may also be influenced by nonmotor symptoms, and their relationship to an end point so obviously tied to motor dysfunction may not be as robust.

A limitation of our analysis is that there were a relatively large number of participants with missing data. We do believe that the algorithm we applied optimized the use of available data by imputing missing data, while minimizing the potential of bias that may have resulted from excluding cases with missing data. For completeness, we repeated the analysis, but we restricted the analysis to participants without missing values (eTable 3 in Supplement) and arrived at essentially the same conclusions, with the only difference being that change (ie, worsening) in the 12-item Short Form Health Survey Physical Summary was now retained in the final model, whereas the baseline UPDRS Part II score was not. Because our data are derived from 2 clinical trials, the applicability of our conclusions to clinical practice may be questioned, as participants in clinical trials may exhibit somewhat different characteristics that may act as a "stealthy" source of bias, especially when it comes to instruments that are more dependent on subjective perceptions and attitudes. It is therefore conceivable that instruments that may be more sensitive to change in the general population are not so in a clinical trial population and vice versa. In any case, the conclusions of our study should be helpful in

designing similar clinical trials in early PD and may serve as a starting point for evaluating these and newer measures in the general population. Although we forced treatment assignment to remain through the final model in our regression analysis, and found it to be not statistically significant, we cannot fully exclude that 1 or more of the treatments may have had a differential effect on the responsiveness of the outcome measures, thereby indirectly influencing the final model. We were unable to perform treatment subgroup analyses owing to a lack of sufficient statistical power. Our results are based on a 12-month-long observation period, and although some outcomes were assessed repeatedly, others were only assessed twice; it is possible that more frequent assessments over a longer period of observation might have yielded different results. Finally, we should point out that our conclusions only apply to the outcome measures studied, and we cannot preclude the possibility that other, as yet not tested measures may prove more sensitive in the future.

## Conclusions

In summary, although all the measures of impairment, disability, and quality of life used in the FS-1 and the FS-TOO track well with PD progression, the UPDRS Part II and Part III scores seem to be the most reliable and responsive prognostic measures of disease activity at baseline and of disease progression in early, untreated PD. The baseline mRS score and longitudinal assessments with the Schwab and England Independence Scale are similarly useful in predicting disease progression. These conclusions need to take into account the fact that the end point used in this analysis was one heavily biased toward motor dysfunction.

### ARTICLE INFORMATION

**Accepted for Publication:** February 12, 2014.

**Published Online:** April 7, 2014.  
doi:10.1001/jamaneurol.2014.391

**Author Contributions:** Drs Parashos and Luo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Parashos, Luo, Shulman.  
**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Luo, He, Tilley.

**Administrative, technical, or material support:**

Parashos, Luo, He, Tilley, Shulman.

**Study supervision:** Parashos, Shulman.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This work was supported by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke.

**Role of the Sponsor:** The funding authority exerted oversight, but had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**The NET-PD Investigators:** The NET-PD Investigators consist of the following FS-1 investigators, advisors, and monitors:

Data safety monitoring board: Cynthia R. Gross, PhD (Chair): University of Minnesota, Minneapolis; Donna T. Chen, MD, MPH: University of Virginia Health

System, Charlottesville; David E. Levy, MD: Neurobiological Technologies, Inc, Mahwah, New Jersey; Karen Marder, MD, MPH: Columbia University, New York, New York; Robert L. Rodnitzky, MD: University of Iowa College of Medicine, Iowa City.

Oversight board: K. Michael Welch, MD (Chair): Rosalind Franklin University of Medicine and Science, North Chicago, Illinois; M. Flint Beal, MD: Weill Medical College of Cornell University, New York, New York; Jeffrey L. Cummings: David Geffen School of Medicine at the University of California, Los Angeles; Stanley Fahn, MD, and Bruce Levin, PhD: Columbia University, New York, New York; Russell G. Katz, MD: US Food and Drug Administration, Rockville, Maryland; Deborah B. Marin, MD, and C. Warren Olanow, MD: Mount Sinai School of Medicine, New York, New York; Jeffrey C. Martin, Esq: Shea & Gardner, Washington, DC; William McDonald: Emory University School of Medicine, Atlanta, Georgia; Diane Murphy, PhD: National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland; Steven Piantadosi, MD, PhD: Johns Hopkins University, Baltimore, Maryland; William J. Powers, MD: Washington University School of Medicine, St Louis, Missouri; Leon J. Thal, MD: University of California, San Diego; Alison Wichman, MD, and John Marler, MD: NIH, Bethesda, Maryland; Joanne Odenkirchen: National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland.

NET-PD steering committee: Bernard Ravina, MD, MSCE: National Institute of Neurological Disorders and Stroke, Bethesda, Maryland; Karl Kieburtz, MD, MPH (principal investigator, coordination center): University of Rochester, New York; Barbara Tilley, PhD (principal investigator, statistical center): Medical University of South Carolina, Charleston; Kathleen Shannon, MD: Rush University Medical Center, Chicago, Illinois; Caroline Tanner, MD, PhD: The Parkinson's Institute, Sunnyvale, California; G. Frederick Wooten, MD: University of Virginia, Charlottesville.

Participating investigators and coordinators: Brad Racette, MD, and Patricia Deppen: Washington University School of Medicine, St Louis, Missouri; Richard B. Dewey Jr, MD, and Brigid Hayward: University of Texas Southwestern Medical School, Dallas; Burton Scott, MD, and Joanne Field, BSN, RN: Duke University, Durham, North Carolina; Julie Carter, RN, MN, ANP, Matthew Brodsky, MD, and Pamela Andrews: Oregon Health and Science University, Portland; Bala Manyam, MD, and Jacqueline Whetteckey: Scott & White Healthcare/Texas A&M University, Temple; Jayaraman Rao, MD, and Maureen Cook, RN, BSN: Louisiana State University Health Sciences Center, New Orleans; Michael J. Aminoff, MD, FRCP, Chadwick Christine, MD, and Jessie Roth, RN: University of California, San Francisco; Martha Nance, MD, Sotirios Parashos, MD, and Susan Peterson, RN: Struthers Parkinson's Center, Golden Valley, Minnesota; Kathleen Shannon, MD, and Jeana Jaglin, RN, CCRC: Rush University Medical Center, Chicago, Illinois; Carlos Singer, MD, Marian A. Perez, AA, and Anita Blenke, PA-C, MS: University of Miami, Florida; Robert Hauser, MD, Theresa McClain, ARNP, and Summer Wolfrath, MSPH: University of South Florida, Tampa; Ted Dawson, MD, PhD, and Becky Dunlop, RN: Johns Hopkins University, Baltimore, Maryland; Rajesh Pahwa, MD, Kelly Lyons, PhD, and Amy Parsons, RN, BSN: University of Kansas Medical Center,

Kansas City; Maureen Leehey, MD, and Jacci Bainbridge, PharmD: University of Colorado Health Sciences Center, Aurora; Lisa Shulman, MD, William Weiner, MD, and Katharine Pabst, CRNP, MS, MPH: University of Maryland, Baltimore; Rodger Elble, MD, PhD, and Charlene Young, RN, MSN, CFNP: Southern Illinois University, Springfield; Kapil Sethi, MD, and Buff Dill, BS, ED: Medical College of Georgia, Augusta; Wayne Martin, MD, and Germaine McInnes, RN: University of Alberta Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada; Vincent P. Calabrese, MD, and Peggy Roberge, RN: Hunter Holmes McGuire VA Medical Center, Richmond, Virginia; Robert Hamill, MD, and Clare Homan, MA: University of Vermont, Burlington; Ivan G. Bodis-Wollner, MD, and Elizabeth Hayes, RN: State University of New York Downstate Medical Center, Brooklyn; G. Webster Ross, MD, and Stephanie Terashita, RN: Pacific Health Research Institute, Honolulu, Hawaii; G. Frederick Wooten, MD, Joel Trugman, MD, and Margaret F. Keller, RN, MS, CCRC: University of Virginia, Charlottesville; Jacob I. Sage, MD, and Debbie Caputo, RN, MSN: University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick; John Fang, MD, and Dorothy Shearon, RN: Vanderbilt University Medical Center, Nashville, Tennessee; Danna Jennings, MD, and Tammie Kelsey, LPN: Institute for Neurodegenerative Disorders, New Haven, Connecticut; Joanne Wojcieszek, MD: Indiana University School of Medicine, Indianapolis; Andrew Feigin, MD: North Shore University Hospital, Manhasset, New York; Ray L. Watts, MD, Natividad Stover, MD, and Rebecca McMurray, RN, MSN: University of Alabama at Birmingham; Roger Albin, MD, and Kristine Wernette, RN, MS: University of Michigan, Ann Arbor; Andrew Siderowf, MD, and Sue Reichwein, CCRC: University of Pennsylvania, Philadelphia; David Simon, MD, Daniel Tarsy, MD, and Lisa Scollins, NP: Beth Israel Deaconess Medical Center, Boston, Massachusetts; Ron Tintner, MD, and Christine Hunter, RN, CCRC: Baylor College of Medicine, Houston, Texas; Peter LeWitt, MD, and Maryam DeAngelis, RN: William Beaumont Hospital, Southfield, Michigan; Richard S. Burns, MD, Holly Shill, MD, Jill Danielson, and Lynn Marlor, RN: Barrow Neurological Institute, Phoenix, Arizona; Charles Adler, MD, PhD, and Marlene Lind, RN: Mayo Clinic, Scottsdale, Arizona; Jay Gorell, MD, Shana Krstevska, MD, and Marilyn Flewelling, RN: Henry Ford Health System, Detroit, Michigan; Jay Schneider, MD, and Stephanie Sendek: Thomas Jefferson University, Philadelphia, Pennsylvania; Stephen Gollomp, MD, and Gwyn Vernon, MSN, CRNP: Thomas Jefferson University/Lankenau Hospital, Wynnewood, Pennsylvania; David Coffey, MD, and Pauline LeBlanc, BS: Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Mark F. Lew, MD, Allan Wu, MD, and Connie Kawai, RN, BSN, CCRC: University of Southern California, Los Angeles; Ryan Uitti, MD, and Margaret Turk, RN: Mayo Clinic, Jacksonville, Florida; James Bower, MD, and Susan Torgrimson, RN: Mayo Clinic, Rochester, Minnesota; Joseph Handler, MD, and Kathleen Greenbaum, RN: Neurology Associates PA, Wilmington, Delaware; Marwan Sabbagh, MD, and Zoran Obradov, CRC: Sun Health Research Institute, Sun City, Arizona.

NET-PD statistical center: Jordan Elm, MA, Paulo Guimaraes, PhD, Peng Huang, PhD, and Yuko Palesch, PhD: Medical University of South Carolina, Charleston.

NET-PD clinical trials coordination center staff: Cornelia Kamp, MBA, CCRC, Aileen Shinaman, JD, Debbie Johnsen, BS, Alicia Brocht, BA, Susan Bennett, AAS, and Chris Weaver: University of Rochester, New York.

NET-PD consultants: Christopher Goetz, MD, independent medical monitor: Rush University Medical Center, Chicago, Illinois; Susan Fagan, PharmD, BCPS, FCCP, pharmacologist: University of Georgia, Augusta.

The NET-PD Investigators also consist of the following FS-TOO investigators, advisors, and monitors:

Data safety monitoring board: Cynthia R. Gross, PhD (Chair): University of Minnesota, Minneapolis; Donna T. Chen, MD, MPH: University of Virginia Health System, Charlottesville; David E. Levy, MD: Neurobiological Technologies, Inc, Mahwah, New Jersey; Karen Marder, MD, MPH: Columbia University, New York, New York; Robert L. Rodnitzky, MD: University of Iowa College of Medicine, Iowa City.

Oversight board: K. Michael Welch, MD (Chair): Rosalind Franklin University of Medicine and Science, North Chicago, Illinois; M. Flint Beal, MD: Weill Medical College of Cornell University, New York, New York; Stanley Fahn, MD, and Bruce Levin, PhD: Columbia University, New York, New York; Russell G. Katz, MD: US Food and Drug Administration, Rockville, Maryland; Deborah B. Marin, MD, and C. Warren Olanow, MD: Mount Sinai School of Medicine, New York, New York; Jeffrey C. Martin, Esq: Shea & Gardner, Washington, DC; Diane Murphy, PhD: National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland; Steven Piantadosi, MD, PhD: Johns Hopkins University, Baltimore, Maryland; William J. Powers, MD: Washington University School of Medicine, St Louis, Missouri; Leon J. Thal, MD: University of California, San Diego; Alison Wichman, MD, and John Marler, MD: NIH, Bethesda, MD; Joanne Odenkirchen: National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland.

Parkinson Study Group: Ira Shoulson, MD (Chair, executive committee); Cliff Shults, MD (deceased), principal investigator, QE2, for providing access to Parkinson Study Group databases (the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism trial, QE2, and the Parkinson Research Examination of CEP-1347 trial).

NET-PD steering committee: Karl Kieburtz, MD, MPH (principal investigator, coordination center): University of Rochester, New York; Bernard Ravina, MD, MSCE: NIH, Bethesda, Maryland (current affiliation: University of Rochester, New York); Wendy R. Galpern, MD, PhD: NIH, Bethesda, Maryland; Barbara Tilley, PhD (principal investigator, statistical center): Medical University of South Carolina, Charleston; Kathleen Shannon, MD: Rush University Medical Center, Chicago, Illinois; Caroline Tanner, MD, PhD: The Parkinson's Institute, Sunnyvale, California; G. Frederick Wooten, MD: University of Virginia, Charlottesville.

Participating investigators and coordinators: Robert Hamill, MD: University of Vermont, Burlington; Jacob I. Sage, MD, Emily Kosa: University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick; Ray L. Watts, MD, Natividad R. Stover, MD, and Rebecca McMurray, RN, MSN: University of Alabama at Birmingham; Mark F. Lew, MD, and Connie Kawai, RN, BSN, CCRC: University of

Southern California, Los Angeles; David Coffey, MD, and Pauline LeBlanc, BS: Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Julie Carter, RN, MN, ANP, Matthew Brodsky, MD, and Pamela Andrews: Oregon Health and Science University, Portland; Andrew Siderowf, MD, and Sue Reichwein, CCRC: University of Pennsylvania, Philadelphia; Lisa Shulman, MD, William J. Weiner, MD, and Katharine Pabst, CRNP, MS, MPH: University of Maryland, Baltimore; Kathleen Shannon, MD, and Jeana Jaglin, RN, CCRC: Rush University Medical Center, Chicago, Illinois; Robert Hauser, MD, Theresa McClain, ARNP, and Holly Delgado, RN: University of South Florida, Tampa; Oksana Suchowersky, MD, and Lorelei Derwent, RN: University of Calgary, Canada; Jayaraman Rao, MD, and Maureen Cook, RN, BSN: Louisiana State University Health Sciences Center, New Orleans; Michael J. Aminoff, MD, DSc, Chad Christine, MD, and Jessie Roth, RN: University of California, San Francisco; Maureen Leehey, MD, and Jacci Bainbridge, PharmD: University of Colorado Health Sciences Center, Aurora; G. Webster Ross, MD, and Stephanie Terashita, RN: Pacific Health Research Institute, Honolulu, Hawaii; Carlos Singer, MD, Marian A. Perez, AA, and Anita Blenke, PA-C, MS: University of Miami, Florida; Brad Racette, MD, and Patricia Deppen: Washington University School of Medicine, St Louis, Missouri; Rodger Elble, MD, PhD, and Charlene Young, RN, MSN, CFNP: Southern Illinois University, Springfield; Caroline Tanner, MD, and Tracy Stewart, RN: The Parkinson's Institute, Sunnyvale, California; Kapil Sethi, MD, and Buff Dill, BS, ED: Medical College of Georgia, Augusta; John Taylor, MD, and Peggy Roberge, RN: Hunter Holmes McGuire VA Medical Center, Richmond, Virginia; Richard B. Dewey Jr, MD, and Brigid Hayward: University of Texas Southwestern Medical School, Dallas; Joseph Jankovic, MD, and Christine Hunter, RN, CCRC: Baylor College of Medicine, Houston, Texas; Frederick Wooten, MD, and Margaret F. Keller, RN, MS, CCRC: University of Virginia, Charlottesville; Danna Jennings, MD, and Tammie Kelsey, LPN: Institute for Neurodegenerative Disorders, New Haven, Connecticut; Wayne Martin, MD, and Germaine McInnes, RN: University of Alberta Glenrose Rehabilitation Hospital, Edmonton, Canada; Joanne Wojcieszek, MD, and Joann Belden, RN: Indiana University School of Medicine, Indianapolis; Roger Albin, MD, and Kristine Wernette, RN, MS: University of Michigan, Ann Arbor; Joseph Savitt, MD, PhD, and Becky Dunlop, RN: Johns Hopkins University, Baltimore, Maryland; Rajesh Pahwa, MD, Kelly E. Lyons, PhD, and Amy Parsons, RN, BSN: University of Kansas Medical Center, Kansas City; John Fang, MD, and Dorothy Shearon, RN: Vanderbilt University Medical Center, Nashville, Tennessee; Andrew Feigin, MD, and Margaret Marie Cox, RN, BSN: North Shore University Hospital, Manhasset, New York; Charles Adler, MD, PhD, and Marlene Lind, RN: Mayo Clinic, Scottsdale, Arizona; Burton Scott, MD, and Joanne Field, BSN, RN: Duke University, Durham, North Carolina; Martha Nance, MD, and Susan Peterson, RN: Struthers Parkinson's Center, Golden Valley, Minnesota; Richard S. Burns, MD, and Lynn Marlor, RN: Barrow Neurologic Institute, Phoenix, Arizona; Ivan Bodis-Wollner, MD,

and Elizabeth Hayes, RN: State University of New York Downstate Medical Center, Brooklyn; Jay Schneider, PhD, and Stephanie Sendek: Thomas Jefferson University, Philadelphia, Pennsylvania; Stephen Gollomp, MD, and Gwyn Vernon, MSN, CRNP: Thomas Jefferson University/Lankenau Hospital, Wynnewood, Pennsylvania; Peter LeWitt, MD, and Maryan DeAngelis, RN, CCRC: William Beaumont Hospital, Southfield, Michigan; David Simon, MD, and Linda Paul, RN, NP: Beth Israel Deaconess Medical Center, Boston, Massachusetts; Jay Gorell, MD (deceased), Shana Krstevska, MD, Marilyn Flewelling, and Sharon McCarthy: Henry Ford Health System, Detroit, Michigan; Ryan Utti, MD, and Margaret Turk, RN: Mayo Clinic, Jacksonville, Florida; James Bower, MD, and Susan Torgrimson, RN: Mayo Clinic, Rochester, Minnesota; Marwan Sabbagh, MD, and Zoran Obradov, CRC: Sun Health Research Institute, Sun City, Arizona; Jorge Juncos, MD, and Mary Louise Musante Weeks, RN: Emory University School of Medicine, Atlanta, Georgia; Hubert Fernandez, MD, and Gordon Brown: University of Florida, Gainesville.

NET-PD statistical center: Jordan Elm, MA, Paulo Guimaraes, PhD, Peng Huang, PhD, and Yuko Palesch, PhD: Medical University of South Carolina, Charleston.

NET-PD clinical trials coordination center staff: Cornelia Kamp, MBA, Aileen Shinaman, JD, Debbie Fraser, BS, Alicia Brocht, BA, Susan Bennett, AAS, Chris Weaver, Debbie Baker, AAS, and Beverly Olsen, BA: University of Rochester, New York.

NET-PD consultants: Christopher Goetz, MD, independent medical monitor: Rush University Medical Center, Chicago, Illinois; Janis Miyasaki, MD, FRCP, independent medical monitor: Toronto Western Hospital, Canada; Susan Fagan, PharmD, BCPS, FCCP, pharmacist: University of Georgia, Augusta; Patrick Mauldin: Medical University of South Carolina, Charleston.

## REFERENCES

- Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ: Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66(7):968-975.
- Parashos SA, Maraganore DM, O'Brien PC, Rocca WA. Medical services utilization and prognosis in Parkinson disease: a population-based study. *Mayo Clin Proc*. 2002;77(9):918-925.
- Elm JJ, Goetz CG, Ravina B, et al; NET-PD Investigators. A responsive outcome for Parkinson's disease neuroprotection futility studies. *Ann Neurol*. 2005;57(2):197-203.
- NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology*. 2006;66(5):664-671.
- NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology*. 2007;68(1):20-28.

- Parashos SA, Swearingen CJ, Biglan KM, et al; NET-PD Investigators. Determinants of the timing of symptomatic treatment in early Parkinson disease: the National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD) Experience. *Arch Neurol*. 2009;66(9):1099-1104.
- Fahn S, Elton RL; Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CO, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Health Care Information; 1987:153-164.
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.
- Schwab RS, England ACJ. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. *Third Symposium on Parkinson's Disease, held at the Royal College of Surgeons of Edinburgh on 20, 21 and 22 May 1968*. Edinburgh, Scotland: E & S Livingstone; 1969:152-157.
- Shoulson I, Kurlan R, Rubin A, et al. Assessment of functional capacity in neurodegenerative disorders: Huntington's disease as a prototype. In: Munsat TL, ed. *Quantification of Neurologic Deficit*. Waltham, MA: Butterworth-Heinemann; 1989:285-309.
- Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*. 1997;26(5):353-357.
- Ware JE Jr, Kosinski M, Turner-Bowker DM, Gandek B. *How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1)*. Lincoln, RI: QualityMetric Inc; 2002.
- The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;321(20):1364-1371.
- Dafni UG, Tsiatis AA. Evaluating surrogate markers of clinical outcome when measured with error. *Biometrics*. 1998;54(4):1445-1462.
- Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: Wiley; 1989.
- Grambsch P, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515-526. doi:10.1093/biomet/81.3.515.
- McDermott MP, Jankovic J, Carter J, et al; The Parkinson Study Group. Factors predictive of the need for levodopa therapy in early, untreated Parkinson's disease. *Arch Neurol*. 1995;52(6):565-570.
- Marras C, McDermott MP, Marek K, et al; Parkinson Study Group DATATOP and PRECEPT investigators. Predictors of time to requiring dopaminergic treatment in 2 Parkinson's disease cohorts. *Mov Disord*. 2011;26(4):608-613.
- Shulman LM, Gruber-Baldini AL, Anderson KE, et al. The evolution of disability in Parkinson disease. *Mov Disord*. 2008;23(6):790-796.