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

Published online April 7, 2014.
Parkinson disease (PD) is a progressive neurodegenerative disease that leads to significant morbidity, disability, and institutionalization. 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. As part of the NET-PD, 2 futility drug studies (Futility Study 1 [FS-1]4 and Futility Study 2 [FS-TOO]5) 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 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 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 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 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 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 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 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 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 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 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 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 untreated PD.

Methods

Participants

Data from FS-1 and FS-TOO were used for this analysis. The 413 participants were men or women 40 years of age or older who received a diagnosis of PD (duration of diagnosis, ≤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 stroke surgery for PD were exclusion criteria. Women of childbearing 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. The following scales were administered as measures of disability: the UPDRS Part II, the mRS, the Schwab and England Independence Scale (which measures activities of daily living [ADL]), the Total Functional Capacity (TFC) scale, and the 39-item Parkinson’s Disease Questionnaire (PDQ-39) ADL subscale. The PDQ-39 summary index and the Medical Outcomes Study version 2 of the 12-item Short Form Health Survey (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 endpoint. 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, participants were randomized in a 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 of 3 areas: ambulation, ADL, or occupational status.

Statistical Design and Analyses

We conducted the analysis using the 2-stage model. 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 (Appendix 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: any variable associated with the time to ST at an α 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) 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 α > 0.05. Scaled Schoenfeld residuals were computed to assess the proportional hazards assumption. 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.

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. 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
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, 6 full-time employment, less smoking history, and left-sided onset. 17,18

A number of approaches have been tried to identify the best-suited measures of PD progression for use in clinical trials. 3 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. 4,5,13,18 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. 19 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 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, 8 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 2. Mean Baseline Variables Classified by Missing Values and Need for ST*

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

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

### Table 3. Final Cox Regression Model*

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

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

* All values are mean values, and standard deviations were omitted for clarity.
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.

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

<table>
<thead>
<tr>
<th>Predictive Value</th>
<th>Baseline</th>
<th>Rate of Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained</td>
<td>UPDRS Part III score(^a)</td>
<td>UPDRS Part III score</td>
</tr>
<tr>
<td>Retained</td>
<td>UPDRS Part II score, mRS score</td>
<td>UPDRS Part II score, mRS score</td>
</tr>
<tr>
<td>Retained</td>
<td>TFC scale, PDQ-39 ADL subscale, S&amp;E Independence Scale score</td>
<td>PDQ-39 SI, SF12 PS and MS</td>
</tr>
<tr>
<td>Did not retain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not retain</td>
<td>UPDRS Part III score</td>
<td>UPDRS Part III score, mRS score</td>
</tr>
<tr>
<td>Did not retain</td>
<td>TFC scale, PDQ-39 ADL subscale</td>
<td>PDQ-39 SI, SF12 PS and MS</td>
</tr>
</tbody>
</table>

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.

\(^{a}\) 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.

\(^{b}\) Baseline UPDRS III score lost its significance when rate of progression variables were included in the model.
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 Suchoworsky, MD, and Lorelei Derwent, RN, University of Calgary, Canada; Janyara Ran, MD, and Maureen Cook, RN, BSN: LSUiana State University Health Science Centers, New Orleans; Michael J. Aminoff, MD, DSc, Chad Christine, MD, and Jessie Roth, RN: University of California, San Francisco; Maureen Leehey, MD, and Jaci Bannides, Andrew Felfugh, MD, and Margaret Marie Health Sciences Center, Aurora; G. Webster Ross, MD, and Stephanie Terasita, RN: Pacific Health Research Institute, Honolulu, Hawaii; Carlos Singer, MD, Mariana A. Perez, AA, and Anita Blenke, PA-C, MS: University of Miami, Florida; Brad Racette, MD, and Patricia Deppen, CHC: Washington University School of Medicine, St Louis, Missouri; Rodger Ebble, 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 Bridgid Hayward: University of Texas Southwestern Medical School, Dallas; Joseph Jankovic, MD, and Patricia Reppen: Washingon University School of Medicine. St Louis, Missouri; Robert Kingsley, 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 Glenside Rehabilitation Hospital, Edmonton, Canada; Joanne Wojciezek, MD, and Joann Beldin, 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 Debra 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; James W. Richardson, MD, PhD, and Caroline Vinet: Vanderbilt University, Nashville, Tennessee; 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 Gwynn Vernon, MSN, CRNP: Thomas Jefferson University/Lankenau Hospital, Wynnewood, Pennsylvania; Peter LeWitt, MD, and Marjory 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 Krestevska, MD, Marilyn Flevenell, and Sharon McCarthy: Henry Ford Health System, Detroit, Michigan; Ryan Uitti, MD, and Margaret Turk, RN: Mayo Clinic, Jacksonville, Florida; James Bower, MD, and Susan Torgimson, RN: Mayo Clinic, Rochester, Minnesota; Marwan Sabaah, 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; George Fernandes, MD, and Gordon Brown: University of Florida, Gainesville.

NET-PD statistical center: Jordan Elno, 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 Shiman, JD, Debbie Fraser, ASA, Alcrenich Brocht, BA, Susan Bennett, AAS, Chris Weaver, Debbie Baker, AAS, and Beverly Ols: University of Rochester, New York.

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

REFERENCES


