RESEARCH ARTICLE

Design Innovations and Baseline Findings in a Long-Term Parkinson's Trial: the National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease Long-Term Study–1

Jordan J. Elm*[1], The NINDS NET-PD Investigators

ABSTRACT: Based on the preclinical data and the results of a phase II futility study, creatine was selected for an efficacy trial in Parkinson's disease (PD). We present the design rationale and a description of the study cohort at baseline. A randomized, multicenter, double-blind, parallel-group, placebo-controlled phase III study of creatine (10 g daily) in participants with early, treated PD, the Long-term Study–1 (LS-1), is being conducted by the National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease network. The study utilizes a global statistical test (GST) encompassing five clinical rating scales to provide a multidimensional assessment of disease progression. A total of 1,741 PD participants from 45 sites in the United States and Canada were randomized 1:1 to either 10 g of creatine/day or matching placebo. Participants are being evaluated for a minimum of 5 years. The LS-1 baseline cohort includes participants treated with dopaminergic therapy and generally mild PD. LS-1 represents the largest cohort of patients with early treated PD ever enrolled in a clinical trial. The GST approach should provide high power to test the hypothesis that daily administration of creatine (10 g/day) is more effective than placebo in slowing clinical decline in PD between baseline and the 5-year follow-up visit against the background of dopaminergic therapy and best PD care.

Key Words: neuroprotection; Parkinson's disease; clinical trial; creatine; global statistical test

Clinical trials in Parkinson's disease (PD) face several challenges that have limited their ability to detect meaningful clinical slowing of disease progression. Two specific obstacles, the lack of an agreed-upon, appropriate outcome measure of disease progression and the confounding effect of robust symptomatic benefits of current PD treatments, hamper current trial design and interpretation of results. The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease (NINDS NET-PD) network developed the Long-term Study–1 (LS-1) in response to these challenges. The LS-1 trial is a multicenter, double-blind, parallel-group, placebo-controlled, randomized phase III study of creatine in participants with PD receiving dopaminergic therapy per standard of care and is conducted by the NINDS NET-PD network (Clinical Trials.gov identifier: NCT00449865).

Scientific Rationale

Using an innovative, evidence-based process for the identification and evaluation of potential therapies for the slowing of PD progression, a multidisciplinary panel conducted a systematic review to identify key potential compounds. This was based on the strength of evidence from the preclinical and clinical data (i.e., scientific rationale, efficacy in animal models, safety and tolerability, and blood-brain barrier penetration).[1] The NET-PD program conducted two clinical trials of four selected potential therapies (creatine, minocycline, coenzyme Q10 [CoQ10], and GPI-1485).[2,3] These selected potential therapies were evaluated using a futility study design. Therapies not found to be futile

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Dr. Jordan J. Elm, Division of Biostatistics and Epidemiology, Medical University of South Carolina, 135 Cannon Street, Suite 303, P.O. Box 250835, Charleston, SC 29425, USA; elmj@musc.edu

Funding agencies: This study was sponsored by the National Institutes of Health, National Institute of Neurological Disorders and Stroke.

Relevant conflicts of interest/financial disclosure: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 14 February 2012; **Revised:** 19 June 2012; **Accepted:** 31 July 2012
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/mds.25175

would be recommended for further study in a large, simple trial for efficacy. The results of both futility trials and the extension study consistently supported the further study of creatine, whereas evidence was inconsistent for minocycline, GPI-1485, or CoQ10.[2–4]

Although the etiology of PD is incompletely understood, evidence suggests roles for oxidative stress and mitochondrial dysfunction.[5–7] Preclinical studies indicated that creatine exerts antioxidative properties, affects mitochondrial energy production, and protects against MPTP-induced dopamine (DA) depletion.[7–9] In this context, creatine mechanisms of action might be effective at directly or indirectly slowing this process of clinical decline. Creatine could support or augment mitochondrial function by acting as an energy buffer, by acting indirectly as an antioxidant, and by antagonizing mitochondrial permeability.[8] Creatine is a natural derivative of the amino acids, arginine and glycine. Cells primarily use creatine in the intermediate form of phosphocreatine, which serves as a phosphate donor to generate adenosine triphosphate from adenosine diphosphate. Creatine supplementation has most commonly been used by athletes to improve performance. Oral supplementation of creatine leads to increased plasma free creatine, increased muscle and brain creatine and phosphocreatine, and may lead to enhanced athletic performance.[10–13]

Study Objective

The primary aim of the study was to test the hypothesis that daily administration of creatine (10 g/day) is more effective than placebo in slowing clinical decline in PD between baseline and the 5-year follow-up visit against the background of dopaminergic therapy and best PD care. Given that PD is a multifactorial disease that contributes to motor, cognitive, and behavioral disability, a global outcome measure of clinical decline was utilized to provide sensitivity in detecting overall changes in disease state. The study global outcome is comprised of five measures: Schwab and England (S & E) activities of daily living (ADL); Parkinson's Disease Quality of Life (PDQ-39); UPDRS questions related to ambulatory capacity; Symbol Digit Modalities (SDM); and Modified Rankin and is analyzed by a global statistical test (GST). The primary hypothesis is that clinical decline after 5 years of follow-up, as measured by the mean summed rank of the five primary measures (modified Rankin score, S & E, ambulatory capacity, PDQ-39 summary score, and SDM) in the creatine arm will be less than the mean summed rank of the five primary measures in the placebo arm.

Design Rationale

The trial was not designed to distinguish a disease-modifying effect from a symptomatic effect, but rather to determine whether long-term treatment group differences could be found, even as participants received individually optimized PD symptomatic therapy. Recent PD trials enrolling early, untreated patients have shown that nearly half of the participants will require symptomatic therapy within 1 year.[3] By requiring participants to be receiving dopaminergic therapy before randomization, we hoped to target participants who were at or near their maximum benefit from such therapy at the time of enrollment. Thus, we would avoid the dramatic, but variable, improvement that commonly occurs when patients first begin dopaminergic therapy.[14]

Model-based estimates suggest that maximum motor benefit is achieved approximately 6 months after initiation of dopaminergic therapy, and motor decline is steady after that point, even in the presence of dopaminergic dosage adjustments.[15] We sought participants who were early enough in the course of the disease that, if treated, they might reasonably be expected to benefit from therapy. At the same time, we sought to evaluate patients over a sufficiently long period of time, such that progression of those features causing clinical disability (i.e., motor signs, balance impairment, and cognitive decline) could be observed, despite optimal treatment with currently available therapies. Hence, we sought to determine whether the addition of creatine could provide long-term clinical benefit beyond that which can be achieved by optimal dopaminergic therapies, which is of relevance to its potential use in clinical practice. This definition of the target study population required fewer participants than enrolling participants at a more-advanced stage of PD who would be less likely to benefit from a disease-modifying therapy. Similarly, allowing enrollment to include a mixture of treated and untreated participants would have made the cohort less homogeneous and would require a larger sample size.[15]

Given that PD is a multifaceted disease, there is no single clinical measurement that reflects the full range of PD signs and symptoms. The gold standard rating scale, the UPDRS,[16] is focused on classic PD motor features and is less sensitive to "nonmotor" symptoms. A multiple endpoint approach using a GST is a useful, efficient method of combining information from a set of validated measures, and this approach may provide a broader assessment of clinical decline.[17,18] The GST has been widely used in clinical trials (including neurological applications, such as the NINDS rTPA stroke trial), and its usefulness in studying PD has been described in detail previously.[17,18]

Participant Eligibility Criteria

The target population was patients with early stage PD (within 5 years from diagnosis) who were receiving dopaminergic therapy for symptom control. To be

eligible, participants must have taken dopaminergic therapy (levodopa or a DA agonist [DAA]) for at least 90 days, but no more than 2 years (Supporting Table 1). After baseline evaluation and the initiation of study medication, participants could receive any available PD therapies, with changes permitted over time to allow individual optimization of therapy.

Data Collection

Participants will be followed until the last enrolled participant has completed 5 years of observation. Thus, many participants will have extended follow-up, to a maximum of 8 years (with the average length of follow-up expected to be 6.5 years). In-person evaluations are conducted at baseline, 3, 6, 12, and 18 months, and then annually beginning at 24 months with telephone calls every 6 months.

Outcome Measures

Five outcome measures representing simple, brief assessments in clinically relevant domains (i.e., ADL, cognitive function, ambulatory capacity, quality of life, and global disability) were chosen based on a consensus of the NET-PD Steering Committee (comprised of five physicians specializing in movement disorders, one study coordinator, and one biostatistician) after consultation with the participating NET-PD site investigators and the sponsor's oversight boards. These outcome measures are combined using a GST into a single primary outcome.

The following measures are included in the 5-year primary outcome: *change from baseline* in modified S & E[16,19] (ADL), SDM-verbal[20] (cognitive function), PDQ-39[21] (quality of life), and ambulatory capacity (sum of five UPDRS questions: Q13 falling, Q14 freezing, Q15 walking, Q29 gait, and Q30 postural stability) and *the 5-year measurement* of modified Rankin Scale (global disability).[22] Additional outcome measures are collected for secondary analyses, including UPDRS Parts I to IV,[16] Beck Depression Inventory II (BDI),[23] Total Functional Capacity (TFC),[24] Scales for Outcome of Parkinson's Disease-Cognition (SCOPA-COG),[25] and EuroQOL (EQ-5D).[26]

Statistical Analysis

The primary analysis will compare the observed mean summed ranks of the five efficacy measures listed above in the creatine arm to the placebo arm in a nonparametric GST, adjusted for site.[27,28] All measures are coded such that higher values are worse (reverse coding some measures). Next, the summed ranks for a participant will be computed by ranking each participant on each measure (across both treatment arms) and then summing the ranks for each participant. If the GST is statistically significant, univariate testing of the individual outcomes measures will be conducted at the two-sided nominal level of 0.05. This approach provides weak protection of the type I error rate. When the treatment effect is consistent across all the measurement domains, then the GST approach is more powerful than any single metric. However, if the treatment is beneficial for one outcome, but demonstrates no effect on (or worsens) other outcomes, the GST will lose power to detect a treatment difference, and the GST would likely fail to show a difference between groups.

In LS-1, participants have the option of stopping study drug, but continuing to be followed at regular study visits, thereby minimizing the amount of missing data. The primary analysis for LS-1 will be will be analyzed under the intent-to-treat (ITT) principle and will include all participants who were randomized, regardless of discontinuation of study medication, noncompliance, or protocol deviations. The primary analysis will incorporate missing data using a multiple imputation method, based on item response theory, that takes into account correlations among outcomes and is preferable to standard methods, such as last observation carried forward.[29] As a sensitivity analysis, we will also do an analysis of those for whom we have efficacy data at 5 years; those participants who die will be given the worst possible score.

When 25% and 50% of participants have completed 5 years of follow-up, there will be formal interim analyses of the primary outcome to consider stopping the trial early for efficacy or for lack of power to show an effect. Before the first interim analysis, we assessed the variability of the outcomes used for the sample-size estimates for the placebo group, and we could not detect a difference from our hypothesized values, so the trial continued without a sample-size increase.

Sample Size

Using the previous NET-PD studies, available literature, and clinical trial data on patients similar to the LS-1 target population, mean and variance estimates of annual rates of change were obtained. With permission from the trial executive committees, patient-level data from previous PD clinical trials were used: CALM-PD (Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease) and DATATOP follow-on protocols PEP/PEPX (Primary Endpoint Protocol).[30,31] The first measurement, 3 to 6 months after initiation of dopaminergic therapy, was considered the baseline measurement to imitate the LS-1 inclusion criteria. For the modified Rankin scale of global disability and the SDM, no data were available for treated PD patients, and estimates from untreated PD patients and from healthy elders were used.[2,3,32–34] Although a GST is

the primary analysis, we powered the study such that there would be sufficient sample size to detect an effect, if one existed, for each univariate measure.

Minimum clinically meaningful difference was chosen to be a 1-year improvement in each measure, meaning that, at 5 years, the treatment arm progression is equivalent to progression in the placebo group at 4 years. Thus, progression (based on each measure) has been slowed by 1 year. With 549 per group, there is at least 85% power to detect a 1-year improvement in the treatment arm, compared to control, for change from baseline in S & E ADL, change from baseline in PDQ-39, and 5-year modified Rankin values. Likewise, this sample size provides 85% power to detect a ~1.5-year improvement in the treatment arm, compared to control, for the change from baseline in ambulatory capacity and change from baseline in SDM (in a two-sample *t* test assuming two-sided alpha of 0.05 and interim analyses). The 1-year difference in means (standard deviation; SD) are 2 (SD, 11), 3 (SD, 9), 0.2 (SD, 1), for S & E ADL change,[2,3,31] PDQ-39 change,[35] and 5-year modified Rankin values,[2,3,32] respectively[2,3,31,35] The 1.5-year difference in means (SD) are 0.383 (SD, 2.1) and 1.5 (SD, 8) for ambulatory capacity change[30,31] and SDM change,[33,34] respectively. Using the GST, this sample size (549 per group) will provide 99% power at the alternative global treatment effect (GTE) value of 0.1189, assuming the maximum correlation among outcomes is 0.50.[18,36] The GTE is estimated from the means and SD given above for each measure and has been previously described.[28] The power of the GST assumes a common treatment effect across all outcomes and will be less powerful if this assumption is not true. Total sample size was inflated from 1,098 to 1,720 (860/treatment group) to account for an expected drop-out or nonadherence rate of 20% over 5 years in the ITT sample[37] (where the inflation factor is equal to $1/[1–0.20]^2$).

Enrollment Process

Between March 13, 2007 and May 28, 2010, a total of 1,741 PD participants from 45 sites in the United States and Canada were randomized 1:1 to either 10 g of creatine/day or matching placebo. Each participant gave written informed consent. The protocol and consent forms were approved by the institutional review boards of each of the participating sites. Recruitment was completed in just over 3 years, slower than the targeted recruitment period of 2 years, in part because of delays in drug supply. In September 2008, the independent data safety monitoring board reviewed the LS-1 safety data and recommended modifications to the protocol to address elevated creatinine levels in some participants. Participants already enrolled were allowed to remain in the study, but discontinued study drug if they met alert criteria for creatinine or estimated glomerular filtration rate (eGFR). Participants with reduced renal function (eGFR <50 mL/min/1.73m^2 at baseline) who were randomized after September 16, 2008 were discontinued from study drug immediately. These participants were asked to return for a single premature withdrawal visit (n = 15). The primary analysis will include all 1,741 participants enrolled, but follow-up data will be imputed for these 15 individuals.

TABLE 1. Demographic characteristics (N = 1,741)

Characteristics	Frequency	Percent
Male gender	1,123	64.5
Non-Hispanic whites	1,571	90.2
Education		
<High school	83	4.8
High school/GED	223	12.8
Some college/associate	417	24.0
Bachelors	477	27.4
Graduate/professional	541	31
Right handed	1,540	88.5
Care level		
Chronic care/Full-time skilled nursing	19	1.1
Home	1,722	98.9
Current employment activities		
Working full time	669	38.5
Retired	658	37.8
Working part-time	232	13.3
Not working, on disability pay	72	4.1
Homemaker	61	3.5
Unemployed and looking for work	24	1.4
Other	22	1.3
Student	2	0.1
Primary occupation (most of career)		
Management/professional	1,100	63.2
Service	223	12.8
Sales/office	207	11.9
Farming/fishing/forestry	24	1.4
Construction/extraction/maintenance	89	5.1
Production/transportation/ material moving	54	3.1
Not in labor force	44	2.5

Baseline Characteristics

On November 14, 2011, the LS-1 baseline database was frozen. Baseline demographics and clinical characteristics of this cohort are presented in Tables 1 to 5. The LS-1 baseline cohort includes participants with, on average, mild motor impairment, minimal cognitive impairment, at most, mild depressive symptomatology, no significant disability, and mild effect on quality of life. Compared with studies of prevalence and incidence of PD by age, gender, and ethnicity, the LS-1 cohort is similar in gender distribution to other reports,[38,39] but enrolled younger patients than expected (average age was 61.8 years [SD = 9.6], and most LS-1 patients were concentrated in the age range of 50–69)[40] (see Fig. 1). Despite extensive efforts to enroll diverse participants, the LS-1 trial enrolled more non-Hispanic whites than expected, based on

TABLE 2. Duration of PD and dopaminergic therapy use

	N Observations	Mean	SD
Years since PD symptom onset	1,741	3.3	2.2
Years since PD diagnosis	1,741	1.5	1.1
Length of time on dopaminergic therapy, years	1,741	0.82	0.7
L-dopa-equivalency total daily dose, mg[52]	1,740	380.3	232.9

PD therapy use, N = 1,741	Frequency	Percent
L-dopa alone	506	29.1
DAA alone	463	26.6
More than one PD medication[a]	772	44.3

[a]Includes use of L-dopa, DAA, or other PD medications for which there is an established L-dopa equivalency.[52]

population incidence rates by race/ethnicity, but this was similar or better than other clinical trial enrollment rates of minority participants.[39,41] Participants tended to be well educated and most were living at home without outside care and over half were working full (39%) or part time (13%). Sixty-three percent had a primary occupation that could be considered management or professional for most of their career (see Table 1).

Discussion

Several clinical trial designs have been used to differentiate symptomatic from disease-modifying effects. However, none has been entirely successful, as wash-in and wash-out of symptomatic effects may evolve over prolonged and uncertain periods of time and will vary based on the intervention.[42] An alternative approach is to determine whether a therapy provides long-term additional benefits over and above those that can be achieved with current therapies, regardless of the nature of the treatment effect. Past trials of disease-modifying drugs have been conducted in participants who were early in their disease course and not receiving symptomatic therapy. A considerable number of participants require dopaminergic therapy in the course of such studies, thus limiting the value of the data collected from the long-term follow-up.

The LS-1 design rationale was to target participants still early enough to benefit from a disease-modifying drug and to follow them for long enough to demonstrate such benefit. To minimize potential confounding resulting from the initiation of concomitant, symptomatic PD drugs, the LS-1 design enrolled participants with early PD, who were already treated with dopaminergic therapy for a common exposure period. Considering increased use of dopaminergic therapy as a

TABLE 3. Clinical rating scales: motor, ADL, and function

	N Observations	Mean	SD
Ambulatory capacity	1,739	1.7	1.5
S & E ADL	1,740	91.1	6.8
UPDRS total	1,732	26.2	11.4
UPDRS motor	1,733	17.8	8.4
UPDRS ADL	1,740	7.2	4.0
UPDRS motor+ADL	1,732	24.9	11.0
TFC	1,739	12.0	1.4

Modified Rankin scale*	Frequency	Percent
0 (no symptoms at all)	23	1
1 (no significant disability despite symptoms)	1,344	77
2 (slight disability)	345	20
3 (moderate disability)	29	2
4+ (moderately severe disability/severe disability)	0	0

*During training, investigators were instructed to only consider symptoms related to PD in scoring the modified Rankin scale. All baseline data were scored in this way. In January 2012, before the collection of any 5-year outcome data, the administration of the modified Rankin instrument was changed to indicate that the instrument should be scored as designed, as a global score of disability.

TABLE 4. Quality of life

	N Observations	Mean	SD
PDQ-39 summary index	1,738	13.2	10.6
0 (no problem) to 100 (maximum)			
Discomfort	1,740	20.8	19.1
ADL	1,741	15.0	15.6
Cognition	1,741	15.0	15.1
Emotional	1,741	14.1	14.9
Stigma	1,741	12.9	16.4
Mobility	1,739	11.5	16.2
Communication	1,741	11.3	14.6
Social	1,741	5.3	11.6
EuroQol (generic instrument)			
EQ5D utility score (1 = perfect health)	1,741	0.8	0.2
Visual analog scale (100 = best imaginable state)	1,739	81.3	13.8

TABLE 5. Cognition and mood

	Best Possible Score	N Observations	Mean	SD
SDM[a] (total correct responses)	110	1,736	44.4	11.7
UPDRS mental	0	1,741	1.3	1.4
SCOPA-COG total[a]	43	1,731	30.3	5.4

	N Observations	Mean	SD
BDI	1,736	6.9	5.5

	Frequency	Percent
BDI >17	83	4.8

[a]Higher scores are "better."

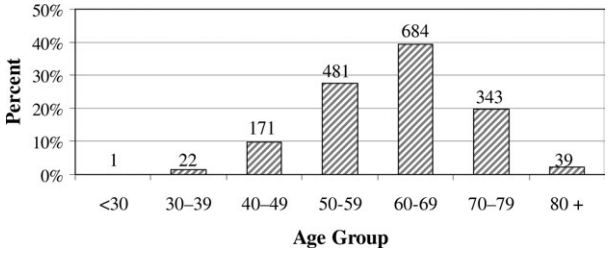

FIG. 1. Frequency of Age Groups Enrolled.

negative outcome, a secondary analysis will compare the total cumulative L-dopa dose equivalency over 5 years in the creatine group versus the placebo group. Allowing participants to be individually, appropriately treated reflects real-world practice, appeals to participants and families, and may help to retain participants for long-term follow-up.

Although there is no other study that is directly comparable to LS-1, the cohort's PD characteristics appear to be close to what might be anticipated with the study inclusion criteria. One recent study compared treatment with carbidopa/L-dopa/entacapone (C/L/E) to carbidopa/L-dopa (C/L) at a dose of 300 mg/day for 39 weeks in early untreated patients who required L-dopa therapy. At the end of the study, mean duration since PD diagnosis was 1.9 years, and total UPDRS (I–III) was approximately 25.9 (C/L/E) or 27.4 (C/L).[43] This is similar to the LS-1 population in which mean duration since PD diagnosis was 1.5 years, mean total daily L-dopa dose equivalent at baseline was 380 mg, and mean total UPDRS (I–III) was 26.2. However, subjects in the C/L/E versus C/L study were older (64.8 years) than those in the LS-1 study (mean age: 61.8), possibly because the former study excluded subjects on DAAs. Compared with recent trials enrolling early untreated patients, the LS-1 patients are comparable in age, but have had the disease for slightly longer than patients in the TEMPO, ADAGIO, and ELLDOPA trials (1.5 versus less than 1 year).[44–46] The clinical rating scales of LS-1 patients are similar to the untreated UPDRS and S & E ADL scores in TEMPO and ELLDOPA patients, suggesting that the LS-1 patients are indeed appropriately treated with dopaminergic therapy and represent the desired population.

Lessons to be Learned

Historically, long-term clinical trials of PD patients have considerable attrition, in many cases more than 30%.[30,48–51] In planning LS-1, a 20% rate of dropouts or study drug nonadherence was assumed. Although LS-1 participants are encouraged to continue follow-up even after discontinuation of study drug, participants who discontinue medication or who are only partially compliant still represent an obstacle to identifying an effect of study treatment, if such an effect occurs. The sample-size inflation factor used assumed that the average proportion of assigned treatment that is actually received over 5 years will be 80%. Although the dropouts or study drug nonadherence rate may be optimistic, the GST was highly overpowered at greater than 99%; thus, even if the dropouts or study drug nonadherence rate is 30%, the GST has power of at least 95% to detect the specified effect. Currently, innovative approaches to reducing the dropouts or study drug nonadherence rate are being used, including teleconferences with trial participants to discuss the importance of continued participation and to address any questions. Efforts are being made to increase the flexibility of clinic hours and to address other barriers to participation.

A substudy attempted to increase minority recruitment, but was not successful.[47] Focused efforts with substantial resources will be needed to understand and overcome the barriers to minority participation in PD research.

Conclusions

In conclusion, LS1 represents the largest cohort of patients with early treated PD ever enrolled in a clinical trial. Although the cohort includes more younger patients and more non-Hispanic whites than expected, based on epidemiological studies, the size of the cohort, broad inclusion and limited exclusion criteria, flexible dosing of symptomatic medications optimized by the treating physician, the large number of clinical sites involved in the United States and Canada, and the similarities with other clinical trials suggest the findings of this baseline cohort may be generalizable to an early PD clinical population already receiving symptomatic treatment in the United States and Canada. Although some of the clinical rating scales collected at baseline were validated in smaller samples, this study provides an opportunity to assess these scales in a larger cohort of early PD patients. In addition to the primary aim, the long-term follow-up of this homogeneous target population (dopaminergic treated patients beginning the trial early in their course of PD) will provide a rich database to learn more about many features of PD.

The study utilizes a GST, the individual components of which provide multidimensional assessment of disease related disability, and participants, receiving dopaminergic therapy and best PD care, are followed for an extended period of time. Even in the face of a higher than expected percentage of dropouts or study drug nonadherence, the novel GST approach should provide high power to detect an effect of creatine on clinical decline in PD, if one exists. Although the size and duration of the trial is daunting, the recruitment and retention of research subjects and investigative

sites appears feasible. The longitudinal data will be useful in determining whether future studies in this population can possibly be smaller and shorter, yet still be able to detect meaningful differences in clinical decline. ■

Acknowledgments: The authors acknowledge the following participants, committees, investigators and coordinators, consultants, boards, and institutions.

LS1 participants: The authors thank the patients and families who participate in the LS-1 study.

NET-PD steering committee: Karl Kieburtz, MD, MPH (principal investigator [PI], coordination center), University of Rochester, Rochester, NY; Barbara Tilley, PhD (PI, statistical center), University of Texas, Houston, TX; Debra Babcock, PhD, MD, Wendy Galpern, MD, PhD, National Institutes of Health, Bethesda, MD; Robert Hauser, MD, University of South Florida, Tampa, FL; Connie Kawai, RN, BSN, CCRC, University of Southern California, Los Angeles, CA; Brad A. Racette, MD, Washington University School of Medicine, St. Louis, MO; Bernard Ravina, MD, MSCE, Biogen Idec, Cambridge, MA; Sue Reichwein, CCRC, University of Pennsylvania, Philadelphia, PA; G. Webster Ross, MD, Pacific Health Research and Education Institute, Honolulu, HI; Kathleen M. Shannon, MD, Rush University Medical Center, Chicago, IL; Oksana Suchowersky, MD, University of Calgary, Alberta, Canada; Caroline M. Tanner MD, PhD, The Parkinson's Institute, Sunnyvale, CA; Jessie Tatsuno Roth, RN, BSN, University of California San Francisco, San Francisco, CA.

Participating investigators and coordinators and associated grants: Ray L. Watts, MD, Harrison Walker, MD, Anthony Nicholas, MD, PhD, Natividad Stover, MD, Jeff Worrell, University of Alabama, Birmingham, AL (U10 NS044547); Robert Hauser, MD, Juan Sanchez-Ramos, MD, PhD, Theresa A. Zesiewicz, MD, Theresa McClain, RN, SN, ARNP, Deborah Burke, MD, Holly Delgado, RN, Summer Carter, MSPH, Gerry Piper, Patti Lowe, LPN, University of South Florida, Tampa, FL (U10 NS044425); Mark F. Lew, MD, Mickie Welsh, RN, DNS, Giselle Petzinger, MD, Daniel Togasaki, MD, PhD, Jennifer S. Hui, MD, Connie Kawai, RN, BSN, CCRC, Gina Barles, University of Southern California, Los Angeles, CA (U10 NS044462); Jorge L. Juncos, MD, Alan Freeman, MD, Mary Louise Musante Weeks, RN, Linda McGinn, RN, Rebecca McMurray, RN, BS, Gregg Everhart, RN, Lisa Miyatake, BS, Elaine Sperin, LPN, Cathy Wood-Siverio, MS, Emory University School of Medicine, Atlanta, GA (U10 NS053379); Julie Carter, RN, MN, ANP, Matthew Brodsky, MD, Pamela Andrews, Stephanie Crocker, BA, Andrea Jones, BS, Megan Murray, MA, Carolyn McCain, BS, CNA, April Wilson, BS, Karen Kerr, BS, Oregon Health & Science University, Portland, OR (U10 NS044483); Maureen Leehey, MD, Deborah Hall, MD, Jacquelyn Bainbridge, PharmD, Sarah Johnson, PharmD, Michael Egeberg, PharmD, Jeffery Clark, PharmD, University of Colorado (Denver), Anschutz Medical Campus, Aurora, CO (U10 NS044479); Zoltan Mari, MD, Ted Dawson, MD, PhD, Laura Marsh, MD, Joseph Savitt, MD, PhD, Becky Dunlop, RN, Melissa Gerstenhaber, RNC, MSN, Arita McCoy, RN, Johns Hopkins University, Baltimore, MI (U10 NS 044474); Richard B. Dewey, Jr., MD, Padraig O'suilleabhain, MD, Shilpa Chitnis, MD, Brigid Hayward, RN, Allison Johnson, BS, Amit Gode, MPH, Giselle Huet, MS, Peter Carreon, University of Texas Southwestern Medical Center, Dallas, TX (U10 NS 044545); Michael J. Aminoff, MD, FRCP, Chadwick W. Christine, MD, Jessie Tatsuno Roth, RN, BSN, Mariann DiMinno, RN, MA, CNS, University of California San Francisco, San Francisco, CA (U10 NS044460); Hubert Fernandez, MD, Ramon Rodriguez, MD, Irene Malaty, MD, Sonia Reback, BS, Gordon Brown, Kathryn Jemmott, MA, Margaret Neilson, JD, Anne Smith-Bova, Stacy Merritt, MA, Camille Swartz, BA, Kyle Rizer, Erin Hastings, PhD, University of Florida, Gainesville, FL (U10 NS053381); Burton Scott, MD, Mark Stacy, MD, Joanne Field, BSN, RN, Karen Grace, RN, Deborah Koltai Attix, PhD, Duke University, Durham, NC (U10 NS044453); Richard Zweig, MD, Robert N. Schwendimann, MD, Colette Hilliard, MS, Labrillia Johnson, LSU Health Science Center Shreveport, Shreveport, LA (U10 NS053370); John L. Goudreau, DO, PhD, Glen Ackerman, MD, Doozie Russell, Michigan State University, East Lansing, MI (U10 NS053380); Kathleen M. Shannon, MD, Jean A. Jaglin, RN, CCRC, Lucia M. Blasucci, RN, CCRC, Rush University Medical Center, Chicago, IL (U10 NS044475); Oksana Suchowersky, MD, Scott Kraft, MD, Lorelei Derwent, RN, Nancy Labelle, RN, BN, University of Calgary, Alberta, Canada (U10 NS044431); Martha Nance, MD, Sotirios Parashos, MD, Catherine Wielinski, MPH, John Worley, DO, Susan Peterson, RN, Patricia Ede, RN, Sarah Lenarz, CMA, Struthers Parkinson's Center, Golden Valley, MI (U10 NS044466); Andrew Siderowf, MD, Howard I. Hurtig, MD, Matthew Stern, MD, Amy Colcher, MD, Stacy Horn, DO, Sue Reichwein, CCRC, University of Pennsylvania, Philadelphia, PA (U10 NS044451); Caroline Tanner, MD, James Tetrud, MD, J. William Langston, MD, Melanie Brandabur, MD, Grace Liang, Neng C. Huang, MD, PhD, Tracy Stewart, RN, Katie Ersted, RN, Katharine Smith, RN, Cheryl Lawrence, BA, Julie Bergman, RN, Liza Reys, Anna Woods, RN, NP, Alice Brown, RN, NP, The Parkinson's Institute, Sunnyvale, CA (U10 NS044465); David K. Simon, MD, PhD, Daniel Tarsy, MD, Linda Paul, NP, Peggy Rose, RN, Althea Silver, MPH, BSN, RN, Shannon Donovan, BA, Chen Lim, BA, Jared Miller, BS, Lauren Kraics, BS, Beth Israel Deaconess Medical Center, Boston, MA (U10 NS044482); Andrew Feigin, MD, Michael Pourfar, MD, Barbara Shannon, RN, Margaret Marie Cox, RN, BSN, North Shore-LIJ Health System, Manhasset, NY (U10 NS044484); Rodger J. Elble, MD, PhD, Charlene Young, RN, MSN, CFNP, Dolly Kelley, RN, CCRC, Southern Illinois University, Springfield, IL (U10 NS044450); Kelvin Chou, MD, Roger Albin, MD, Kristine Wernette, RN, MS, University of Michigan, Ann Arbor, MI (U10 NS044504); Anne-Marie Wills, MD, Lewis Sudarsky, MD, Georgette Hage, MD, Sarah Pearl Aronow-Werner, BA, Brigham and Women's Hospital, Boston, MA (U10 NS053369); Carlos Singer, MD, Alicia Facca, MD, Bruno V. Gallo, MD, Cenk Sengun, MD, Fatta Nahab, MD, Marian A. Perez, AA, Monica Quesada, Anita Blenke, PA-C, MS, University of Miami, Miami, FL (U10 NS044437); Vanessa Hinson, MD, PhD, Kenneth Bergmann, MD, FAAN, Gonzolo Revuelta, DO, Vicky Salak, FNP, Jennifer Zimmerman, RN, Amy Delambo, RN, Medical University of South Carolina, Charleston, SC (U10 NS053372); G. Webster Ross, MD, Helen Petrovitch, MD, Stephanie Terashita, RN, Pacific Health Research and Education Institute, Honolulu, HI (U10 NS044448); Wayne Martin, MD, Richard Camicioli, MD, Germaine McInnes, RN, Ingrid Scott, RN, Pamela King, BScN, RN, Marguerite Wieler, MSc, University of Alberta, Edmonton, Alberta, Canada (U10 NS044426); Brad A. Racette, MD, Joel S. Perlmutter, MD, Samer Tabbal, MD, Susan Criswell, MD, Allison Wright, MD, Patricia Deppen, RN, BSN, MA, Melissa Ammel, Mary Pecoraro, RN, BSN, Kathleen Wharton, Washington University, St. Louis, MO (U10 NS044455); Lisa Shulman, MD, William Weiner, MD, Stephen Reich, MD, Paul Fishman, MD, Bradley Robottom, MD, Renzo Figari, Michelle Cines, RN, Nancy Zappala, RN, University of Maryland School of Medicine, Baltimore, MD (U10 NS044446); Robert Hamill, MD, James Boyd, MD, Jessy Gardner, BA, Shannon Lenox, BS, Christine A. Potter, BA, Jennifer Young, CCRP, Sharon Kenney, RN, Colette Oesterle, BA, Christopher Ingvoldstad, BA, Sarah Waterman, Shannon Lucy, BA, University of Vermont, Burlington, VT (U10 NS044501); Tanya Simuni, MD, Aleksandar Videnovic, MD, Onur Melen, MD, Cindy Zadikoff, MD, FRCPC, Karen Williams, Teresa Kuhta, BS, Elaina Ziehm, Northwestern University, Chicago, IL (U10 NS053377); Rajesh Pahwa, MD, Kelly Lyons, PhD, Amy Parsons, RN, BSN, Tamara Gales, LPN, Carey Mack, RN, Meghan Ehlinger, BS, University of Kansas Medical Center, Kansas City, KS (U10 NS044469); Franca Cambi, MD, John T. Slevin, MD, Renee Wagner, RN, CCRC, Chris Miara, MA, University of Kentucky, Lexington, KY (U10 NS053368); Stephen Gollomp, MD, Gwyn M. Vernon, MSN, CRNP, Sabreen Raza, Randi Gollomp, BS, RN, Judy Spahr, CCRP, CTR, Thomas Jefferson University/Lankenau Hospital, Wynnewood, PA; David J. Coffey, MD, Pauline R. LeBlanc, BS, Tracy Ostler, BS, Dartmouth Hitchcock Medical Center, Lebanon, NH; Jayaraman Rao, MD, Robert Felberg, MD, Frank Oser, MD, Maureen Cook, RN, BSN, Carol Marques, Patricia Schaefer, Marilyn Carleton, Ochsner Clinic Foundation, New Orleans, LA (U10 NS044471); Ivan G. Bodis-Wollner, MD, William Lytton, MD, Jean Daniel Francois, MD, Thomas Mayer, PsyD, Patricia Kavanagh, MD, Mohammedyusuf Hajee, MD, Elizabeth Hayes, EdD, RN, Zoe Kyle M. Moffitt, RN, MFA, Sofya Glazman, MD, SUNY Downstate Medical Center, Brooklyn, NY (U10 NS044454); Jay Schneider, MD, Tsao-Wei Liang, MD, Stephanie Sendek, Teresa Barron, RN, Christine Randazzo, RN, Thomas Jefferson University, Philadelphia, PA (U10 NS044481); Joohi Shahed, MD, Joseph Jankovic, MD, William Ondo, MD, Christopher John Kenney, MD, Octavian Adam, MD, Christine Hunter, RN, Baylor College of Medicine, Houston, TX (U10 NS044441); Kapil Sethi, MD, John C. Morgan, MD, PhD, Buff Farrow, BSEd, Georgia Health Sciences University, Augusta, GA (U10 NS044464); Danna Jennings, MD, Kenneth Marek, MD, David Russell, MD, PhD, Rowena Tabamo, MD, Barbara Fussell, RN, Tammie Kelsey, LPN, James Behan, RN, Pam Becker, RN, Laura Leary, BS, Institute for Neurodegenerative Disorders, New Haven, CT (U10 NS044505); Daniel D. Truong, MD, Mayank Pathak, MD, Karen Frei, MD, An Hao Tran, RN, Michelle Tran, BA, Jassie Sombai, The Parkinson's & Movement Disorder Institute, Fountain Valley, CA (U10 NS053387); G. Frederick Wooten, MD, James Bennett, MD, PhD, Joel Trugman, MD, Madaline B. Harrison, MD, Elke Rost-Ruffner, RN, BSN, Margaret F. Keller, RN, MS, CCRC, Robert B. Davis, NP, University of Virginia, Charlottesville, VA (U10 NS044427); John Fang, MD, Fenna Phibbs, MD, MPH, Dorothy Shearon, RN, Vanderbilt University Medical Center, Nashville, TN (U10 NS044555); Richard Burns, MD, Rohit Dhall, MD, MSPH, Anwar Ahmed, MD, Holly Shill, MD, Nicklesh Thakur, MD, Guillermo Moguel-Cobos, MD, Michal Gostkowski, DO, Lynn L. Marlor, BSN, MSHS, Diane Gates, RN, Edith Simpson, Barrow Neurological Institute, Phoenix, AZ (U10 NS044458); Jacob I. Sage, MD, Anette Nieves, MD, Debbie Caputo, RN, MSN, Emily Kosa, RN, UMDNJ Robert Wood Johnson Medical School, New Brunswick, NJ (U10 NS044415); Frank Skidmore, MD, Amy Coenen, MSN, ARNP, Helen Dunn, RN, MSN, Stacy McCombs, Shirley Roessner, LPN, Linda Sawka, RN, Malcolm Randall VA Medical Center,

Gainesville, FL; Zhigao Huang, MD, PhD, Lisa Smith, CRC, Rhonda Calhoun, RN, University of Florida Jacksonville, Jacksonville, FL; Joanne Wojcieszek, MD, Joann Belden, RN, Katie Price, Marsha Hughes-Gay, RN, Indiana University School of Medicine, Indianapolis, IN (U10 NS044472); Arif Dalvi, MD, Michael Rezak, MD, PhD, Susie Ro, MD, Kathy Kujawa, MD, PhD, Kevin Novak, PhD, Sandra Vergenz, RN, Gina Medalle, RN, BSN, Susan Silvio, RN, North Shore University Health System Research Institute, Glenview, IL.

NET-PD statistical center: Keith Burau, PhD, Rong Ye, MS, Sheng Luo, PhD, University of Texas Health Science Center at Houston, Houston, TX.

NET-PD clinical trials coordination center staff: Christine Weaver, CCRP, Gina Lau, BS, Ann Stoutenburg, CCRC, Renee Wilson, MA, David Shprecher, DO, Laith Khadim, MD, Debbie Frasier, BS, Debbie Baker, AAS, Beverly Olsen, BA, Susan Bennett, AAS, Jennifer Harman, PhD, CCRP, Irenita Gardiner, RN, CCRC, University of Rochester, Rochester, NY.

NET-PD consultants: Christopher Goetz, MD, Rush University Medical Center, Chicago, IL; David Ploth, MD, Medical University of South Carolina, Charleston, SC.

Data safety monitoring board: Cynthia R. Gross, PhD (chair), University of Minnesota, Minneapolis, MN; Karen L. Bell, MD, Columbia University, New York, NY; Donna T. Chen, MD, MPH, University of Virginia Health System, Charlottesville, VA; Robert Foley, MD, United States Renal Data System Coordinating Center, Minneapolis, MN; David E. Levy, MD, Neurobiological Technologies, Inc., Mahwah, NJ; Robert L. Rodnitzky, MD, University of Iowa College of Medicine, Iowa City, IA.

Oversight board: K. Michael Welch, MD (chair), Rosalind Franklin University of Medicine and Science, North Chicago, IL; M. Flint Beal, MD, Weill Medical College of Cornell University, New York, NY; Jeffrey L. Cummings, MD, UCLA Alzheimer Disease Center, Los Angeles, CA; David J. Edwards, PharmD, Wayne State University, Detroit, MI; Stanley Fahn, MD, Bruce Levin, PhD, Columbia University, New York, NY; Russell G. Katz, MD, U.S. Food and Drug Administration, Rockville, MD; Deborah B. Marin, MD, C. Warren Olanow, MD, Mount Sinai School of Medicine, New York, NY; Jeffrey C. Martin, Esq, Goodwin Proctor LLP, Rockville, MD; Diane DiEuliis, PhD, Health and Human Services, Washington, DC; Steven Piantadosi, MD, PhD, Cedars-Sinai Medical Center, Los Angeles, CA; William J. Powers, MD, University of North Carolina School of Medicine, Chapel Hill, NC; Alison Wichman, MD, National Institutes of Health, Bethesda, MD.

National Institutes of Health: Debra Babcock, PhD, MD, Wendy Galpern, MD, PhD, John Marler, MD, Joanne Odenkirchen, National Institute of Neurological Disorders and Stroke, Bethesda, MD.

Appendix

The NINDS NET-PD Investigators are: Jordan J. Elm, PhD, Medical University of South Carolina, Charleston, SC; Robert Hauser, MD, University of South Florida, Tampa, FL; Barbara C. Tilley, PhD (principal investigator [PI], statistical center), University of Texas Health Science Center at Houston, Houston, TX; Karl Kieburtz, MD, MPH (PI, coordination center), University of Rochester, Rochester, NY; Michael J. Aminoff, MD, FRCP, University of California San Francisco, San Francisco; Erika Augustine, MD, Susan Bennett, AAS, University of Rochester, Rochester, NY; Ivan G. Bodis-Wollner, MD, State University of New York Downstate Medical Center, Brooklyn, NY; Franca Cambi, MD, University of Kentucky, Lexington, KY; Julie H. Carter, RN, MS, ANP, Oregon Health & Science University, Portland, OR; Kelvin Chou, MD, University of Michigan, Ann Arbor, MI; Chadwick W. Christine, MD, University of California San Francisco, San Francisco, CA; Rohit Dhall, MD, MSPH, Barrow Neurological Institute, Phoenix, AZ; Richard B. Dewey, Jr., MD, University of Texas Southwestern Medical Center, Dallas, TX; Rodger J. Elble, MD, PhD, Southern Illinois University, Springfield, IL; John Fang, MD, Vanderbilt University Medical Center, Nashville, TN; Andrew Feigin, MD, North Shore-LIJ Health System, Manhasset, NY; Wendy Galpern, MD, PhD, National Institutes of Health, Bethesda, MD; Irenita Gardiner, RN, CCRC, Jennifer Harman, PhD, CCRP, University of Rochester, Rochester, NY; John Goudreau, DO, PhD, Michigan State University, East Lansing, MI; Jorge L. Juncos, MD, Emory University School of Medicine, Atlanta, GA; Maureen Leehey, MD, University of Colorado Denver, Aurora, CO; Cornelia Kamp, MBA, CCRC, University of Rochester, Rochester, NY; Mark F. Lew, MD, University of Southern California, Los Angeles, CA; Grace S. Lin Liang, MD, The Parkinson's Institute and Clinical Center, Sunnyvale, CA; Zoltan Mari, MD, Johns Hopkins University, Baltimore, MD; Wayne Martin, MD, University of Alberta, Edmonton, Alberta, Canada; Martha Nance, MD, Sotirios Parashos, MD, Struthers Parkinson's Center, Golden Valley, MN; Rajesh Pahwa, MD, Kelly E. Lyons, PhD, University of Kansas Medical Center, Kansas City, KS; Helen Petrovitch, MD, Pacific Health Research and Education Institute, Honolulu, HI; Brad A. Racette, MD, Washington University School of Medicine, St. Louis, MO; Bernard Ravina, MD, MSCE, Biogen Idec, Cambridge, MA; G. Webster Ross, MD, Pacific Health Research and Education Institute, Honolulu, HI; Jacob I. Sage, MD, UMDNJ Robert Wood Johnson Medical School, New Brunswick, NJ; Lisa Shulman, MD, University of Maryland School of Medicine, Baltimore, MD; David K. Simon, MD, PhD, Beth Israel Deaconess Medical Center, Boston, MA; Tanya Simuni, MD, Northwestern University, Chicago, IL; Carlos Singer, MD, University of Miami, Miami, FL; John T. Slevin, MD, University of Kentucky, Lexington, KY; Oksana Suchowersky, MD, University of Calgary, Alberta, Canada; Caroline M. Tanner MD, PhD, The Parkinson's Institute, Sunnyvale, CA; Aleksandar Videnovic, MD, Northwestern University, Chicago, IL; Tiffini S. Voss, MD, University of Virginia, Charlottesville, VA; Harrison Walker, MD, University of Alabama, Birmingham, AL; Anne-Marie Wills, MD, Brigham & Women's Hospital, Boston, MA; Richard Zweig, MD, LSU Health Science Center Shreveport, Shreveport, LA.

References

1. Ravina BM, Fagan SC, Hart RG, et al. Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment. Neurology 2003;60:1234–1240.
2. NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006;66:664–671.
3. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology 2007;68:20–28.
4. NINDS NET-PD Investigators. A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. Clin Neuropharmacol 2008;31:141–150.
5. Jenner P, Schapira AH, Marsden CD. New insights into the cause of Parkinson's disease. Neurology 1992;42:2241–2250.

6. Zhang Y, Dawson V, Dawson T. Oxidative stress and genetics in the pathogenesis of Parkinson's disease. Neurobiol Dis 2000;7:240–250.
7. Marsden C, Olanow C. The causes of Parkinson's disease are being unraveled and rational neuroprotective therapy is close to reality. Ann Neurol 1998;44:S189–S196.
8. Tarnopolsky MA, Beal MF. Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. Ann.Neurol 2001;49:561–574.
9. Matthews RT, Ferrante RJ, Klivenyi P, et al. Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol 1999;157: 142–149.
10. McCall W, Persky AM. Pharmacokinetics of creatine. Subcell Biochem 2007;46:261–273.
11. Williams M, Branch J. Creatine supplementation and exercise performance: an update [see comments]. J Am Coll Nutr 1998;17: 216–234.
12. Gordon A, Hultman E, Kaijser L, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. Cardiovasc Res 1995;30:413–438.
13. Clark J. Creatine: a review of its nutritional applications in sport. Nutrition 1998;14:322–324.
14. Hauser RA, Auinger P, Oakes D; Parkinson Study Group. Levodopa response in early Parkinson's disease. Mov Disord 2009;24: 2328–2336.
15. Guimaraes P, Kieburtz K, Goetz CG, et al. Non-linearity of Parkinson's disease progression: implications for sample size calculations in clinical trials. Clin Trials 2005;2:509–518.
16. Fahn S, Elton RL; the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden C, Calne D, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan Healthcare Information; 1987:153–163.
17. Huang P, Goetz CG, Woolson RF, et al. Using global statistical tests in long-term Parkinson's disease clinical trials. Mov Disord 2009;24:1732–1739.
18. Huang P, Woolson RF, Granholm A. The use of a global statistical approach for the design and data analysis of clinical trials with multiple primary outcomes. Exp Stroke 2009;1:100–109.
19. Schwab R, England A, Jr. Projection technique for evaluating surgery in Parkinson's disease. In Gillingham F, Donaldson I, eds. Third Symposium on Parkinson's Disease. Edinburgh: E. & S. Livingstone; 1969:152–157.
20. Smith A. Symbol Digit Modalities Test Manual. Los Angeles, CA: Western Psychological Services; 2002.
21. Jenkinson C, Fitzpatrick R, Norquist J, Findley L, Hughes K. Cross-cultural evaluation of the Parkinson's Disease Questionnaire: tests of data quality, score reliability, response rate, and scaling assumptions in the United States, Canada, Japan, Italy, and Spain. J Clin Epidemiol 2003;56:843–847.
22. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
23. Beck A, Steer R, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–597.
24. Shoulson I, Kurlan R, Rubin A, et al. Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype. In Munsat T, ed. Quantification of Neurologic Deficit.. Boston, MA: Butterworths; 1989:271–283.
25. Marinus J, Visser M, Verwey NA, et al. Assessment of cognition in Parkinson's disease. Neurology 2003;61:1222–1228.
26. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
27. O'Brien P. Procedures for comparing samples with multiple endpoints. Biometrics 1984;40:1079–1087.
28. Huang P, Tilley BC, Woolson RF, Lipsitz S. Adjusting O'Brien's test to control type I error for the generalized nonparametric Behrens-Fisher problem. Biometrics 2005;61:532–539.
29. Luo S, He B, Lawson AB, Elm JJ, Tilley BC. Multivariate longitudinal Bayesian imputation for Global Statistical Test, with applications to Parkinson's disease. Presentation at the Joint Statistical Meetings (JSM), July 31–August 5, 2010, Vancouver, British Columbia, Canada.
30. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 2004;61:1044–1053.
31. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Ann Neurol 1996;39:37–45.
32. Shannon KM, Elm JJ, Goetz CG, Tilley BC. The Modified Rankin Scale as an outcome measure in Parkinson's disease patients on dopaminergic therapy. American Academy of Neurology 58th Annual Meeting, April 1–April 7, 2006, San Diego, CA, 2006 Scientific Program. 2006;S43.002.
33. Kieburtz K, McDermott M, Como P, et al. The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease. Neurology 1994;44:1756–1759.
34. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative Symbol Digit Modalities Test performance in a community-based sample. Arch Clin Neuropsychol 2006;21:23–28.
35. Olanow CW, Kieburtz K, Stern M, et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. Arch Neurol 2004;61:1563–1568.
36. Huang P, Woolson RF, O'Brien PC. A rank-based sample size method for multiple outcomes in clinical trials. Stat Med 2008;27:3084–3104.
37. Friedman L, Furberg C, DeMets D. Fundamentals of Clinical Trials. Littleton, MA: PSG; 1985.
38. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988–1993. Am J Epidemiol 1995;142:820–827.
39. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 2003;157:1015–1022.
40. Morens D, Davis J, Grandinetti A, Ross G, Popper J, White L. Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. Neurology 1996;46:1044–1050.
41. Schneider M, Swearingen C, Ye J, Baumgerten M, Tilley BC. Minority enrollment in Parkinson's disease clinical trials. Parkinsonism Relat Disord 2009;15:258–262.
42. Hauser RA, Holford NH. Quantitative description of loss of clinical benefit following withdrawal of levodopa-carbidopa and bromocriptine in early Parkinson's disease. Mov Disord 2002;17:961–968.
43. Hauser R, Panisset M, Abbruzzese G, Mancione L, Dronamraju N, Kakarieka A. Double-blind trial of levodopa/carbidopa/entacapone versus levodopa/carbidopa in early Parkinson's disease. Mov Disord 2009;24:541–550.
44. Parkinson Study Group.A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 2002;59:1937–1943.
45. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498–2508.
46. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009; 361:1268–1278.
47. Tilley BC, Mainous A, Elm JJ, et al. A randomized recruitment intervention trial in Parkinson's disease to increase participant diversity: early stopping for lack of efficacy. Clin Trials 2012;9:188–197.
48. Koller WC, Hutton JT, Tolosa E, Capilldeo R. Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology 1999;53:1012–1019.
49. Lees AJ, Katzenschlager R, Head J, Ben Shlomo Y. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. Neurology 2001;57:1687–1694.
50. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000;342:1484–1491.
51. Capildeo R. Implications of the 5-year CR FIRST trial. Sinemet CR Five-Year International Response Fluctuation Study. Neurology 1998;50:S15–S17.
52. Tomlinson C, Stowe R, Patel S, Rick C, Gray R, Clarke C. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649–2653.