

## PostCEPT Protocol Synopsis With Amendment 2

<b>Study Title</b>	A Longitudinal Observational Follow-up of the PRECEPT Study Cohort (PostCEPT)
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<b>Steering Committee</b>	Fahn, Gauger, Goetz, Kieburtz, Kurlan, Lang, Marek, Oakes, Ravina, Schwid, Shoulson, Tanner, Gorbald (ex-officio), Shinaman (ex-officio)
<b>Study Period</b>	Planned enrollment period: 4 months Planned duration of subject participation: indefinite
<b>Study Centers</b>	55 PSG (former PRECEPT) sites in the United States and Canada
<b>Study Objectives</b>	<p>The overall objective of this project is to demonstrate the feasibility of enrolling a cohort of former clinical trial subjects into a follow-up observational study that will be used to develop biomarkers and assess the treated natural history of Parkinson's disease (PD). The required aspects of this study are the PD-DOC core data set items. Other activities such as FOUND and imaging are integrated studies that are encouraged. Specific objectives are to:</p> <ol style="list-style-type: none"> <li>1) Establish a mechanism for longitudinal follow-up of patients with PD who have participated in the Parkinson Study Group (PSG) PRECEPT study and determine rates of participation and retention for in-person and remote follow-up. Clear milestones will be used to assess the success of these efforts: <ol style="list-style-type: none"> <li>a) proportion of subjects initially enrolled into the follow-up project from the PRECEPT clinical trial cohort</li> <li>b) annual retention for in-person visits</li> <li>c) annual retention for SPECT imaging</li> <li>d) proportion of subjects providing DNA to NINDS Human Genetics Resource Center Repository at Coriell</li> <li>e) proportion of subjects participating in remote follow-up through the FOUND study</li> </ol> </li> <li>2) Demonstrate the feasibility of this mechanism to evaluate biomarkers and novel clinical signs in cross-sectional and longitudinal studies. This will be done through longitudinal use of <math>\beta</math>-CIT SPECT imaging in conjunction with olfactory (smell) testing using the University of Pennsylvania Smell Identification Test (UPSIT) to determine the sensitivity and specificity of smell testing for identifying subjects with and without dopaminergic deficiency on SPECT.</li> <li>3) Use this cohort to follow the natural history of PD (motor, cognitive and behavioral) in patients who are on treatment, to validate measures of cognition, and to develop models and prediction rules for motor and non-motor complications, including:</li> </ol>

	<p>a) administration of the Montreal Cognitive Assessment (MoCA) in conjunction with the NINDS Parkinson’s Disease Data and Organizing Center (PD-DOC) core clinical evaluation (R Kurlan, PI) to determine the MoCA’s sensitivity to change in PD.</p> <p>b) modeling of onset of motor complications, depression, and rate of cognitive decline in this treated natural history cohort in an attempt to identify specific risk factors.</p> <p>4) Make available, with appropriate consent and agreement, de-identified clinical and imaging data and biological specimens from this cohort to investigators with IRB-approved protocols for use in biomarker research and for developing hypotheses or historical controls for clinical trials.</p>
<b>Study Population</b>	PD patients who participated in the PRECEPT clinical study.
<b>Number of Participants</b>	Approximately 575 of the subjects who participated in the PRECEPT study.
<b>Study Design</b>	<p>This will be an observational study of PD patients who have participated in the PRECEPT study. Visits will occur at Baseline and then approximately once a year thereafter for an indefinite period. At each visit, subjects will be evaluated using the appropriate subset of the PD-DOC core dataset, the UPSIT and other measures (see Schedule of Activities &amp; Procedures). The PD-DOC cognitive and behavioral battery will be assessed every 3 years, beginning at the first follow-up visit after baseline. Blood will be collected for DNA extraction and storage in the NINDS Human Genetics Resource Center Repository at Coriell at the Baseline or Year 01 visit.</p> <p>Subjects may give permission at the Baseline visit or any time thereafter to be contacted for follow-up in the previously established PSG FOUND study (C Tanner, PI) using mail and telephone contact to assess clinical status between scheduled in-person visits. Subjects will also be given the opportunity to have ongoing <math>\beta</math>-CIT SPECT imaging scans, conducted in New Haven, CT (K Marek, PI).</p>
<b>Main Eligibility Criteria</b>	<p>1) participation in the PRECEPT study</p> <p>2) willing and able to provide informed consent</p>
<b>Study Intervention(s)</b>	Subjects will be cared for by their treating physician, and no experimental interventions will be administered as part of this observational study. Subjects may also enroll in interventional clinical trials during their ongoing participation in this observational study.
<b>Concomitant Medications</b>	There will be no restrictions on medications that patients are taking. All medications, prescribed and over-the-counter, including “nutritional supplements” that patients are taking at the time of their Baseline and annual visits will be entered into the study database.

<p><b>Longitudinal Assessments</b></p>	<ol style="list-style-type: none"> <li>1. Subjects will be evaluated at Baseline only with the following: <ul style="list-style-type: none"> <li>• Demographics</li> <li>• PD Features</li> <li>• Mini-Environmental Risks Questionnaire for PD Baseline</li> </ul> </li>   <li>2. Subjects will be evaluated at Baseline and Year 4 (then repeated every 3 years thereafter) with the following: <ul style="list-style-type: none"> <li>• Primary Diagnosis</li> <li>• Atypical Symptoms</li> <li>• Family History</li> </ul> </li>   <li>3. Subjects will be evaluated at Baseline and annually thereafter with the following: <ul style="list-style-type: none"> <li>• MMSE</li> <li>• MoCA</li> <li>• UPDRS Parts I-IV</li> <li>• New UPDRS Parts I and II</li> <li>• Modified Hoehn and Yahr Scale</li> <li>• Modified Schwab and England ADL Scale</li> <li>• UPSIT</li> <li>• PDQ-39</li> <li>• Geriatric Depression Scale (GDS-15)</li> </ul> </li>   <li>4. PD-DOC cognitive and behavioral function assessments will be conducted every 3 years, starting at the first annual visit, and will include: <ul style="list-style-type: none"> <li>• Cognition/Behavior Questionnaire</li> <li>• Hopkins Verbal Learning Test</li> <li>• Verbal Fluency Test</li> <li>• Letter Number Sequencing Test</li> <li>• Neuropsychiatric Inventory Questionnaire (NPI-Q)</li> </ul> </li> </ol>
<p><b>Novel Clinical Signs and Biomarkers</b></p>	<ol style="list-style-type: none"> <li>1) Olfaction (all subjects). At each visit, subjects will be evaluated using the UPSIT.</li> <li>2) DNA for future analyses (all consenting subjects). Blood will be collected for DNA extraction and storage in the NINDS Human Genetics Resource Center Repository at Coriell at the Baseline or Year 01 visit.</li> <li>3) Future studies of potential biomarkers may be planned to include some or all subjects, as well as healthy controls and patients with other forms of parkinsonism.</li> </ol>
<p><b>Sample Size and Statistical Considerations</b></p>	<p>In performing an observational cohort study, the larger the sample size used for data analysis, the more applicable the results are to the population as a whole. Although PostCEPT will initially be limited to the living patients (N=802) previously enrolled in PRECEPT, demonstrating feasibility of this mechanism will pave the way for enrollment of other clinical trial cohorts</p>

where the interventional phase has been concluded. It is estimated that about 500-600 PRECEPT subjects will consent to participate in PostCEPT. Sample size and power will increase as additional clinical trial cohorts are enrolled with standardized collection of clinical and imaging data.

The Table below gives detectable effect sizes for three types of statistical analysis that may be performed on the PostCEPT data. For each analysis the two-sided alpha level is set to 0.05 and the beta level to 0.80. The first column gives the total sample size assumed to be available for the analysis, ranging from 200 (25% of the PRECEPT cohort) to 600 (75% of the cohort). The second column gives the detectable correlation coefficient between two continuous measures (e.g., change in striatal beta-CIT uptake vs. change in total UPDRS). The third column gives the detectable difference in prevalence rates of some characteristic (e.g. presence of dopaminergic side effects) between two “halves” of the sample (e.g. the younger patients vs. the older patients, with age dichotomized at the median for the entire group). The fourth column gives the detectable “effect size”, expressed as ratio of difference in means to standard deviation, for comparing two “halves” of the sample (e.g. younger vs. older patients as above) in relation to a continuous measure (e.g. change in total UPDRS).

Total sample size	Detectable Correlation	Detectable Difference in Prevalence	Detectable Difference in Means (Standardized)
200	0.20	21%	0.40
300	0.16	17%	0.33
400	0.14	14%	0.28
500	0.13	13%	0.25
600	0.11	12%	0.23

Biochemical and genetic studies will be proposed to delineate the genetic and environmental effects on relevant phenotypic characteristics. The antecedent clinical information in the PRECEPT database and sensitivity analyses will help define characteristics such as rapid or slow progressors. A sufficiently large sample size of a relevant clinical characteristic (e.g., rapid or slow progressors, or those with or without dopamine deficiency by SPECT imaging) will provide adequate statistical power to detect a relevant risk factor (e.g., genotype, medication use) that influences the clinical characteristic and might meaningfully serve as a covariate for planned clinical trials.