Noninvasive Biomarkers to Advance Emerging DBS Electrode Technologies in Parkinson's Disease (SUNDIAL, SUbthalamic Nucleus DIrectionAL vs Circular Stimulation Study)

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Statistical Analyses. Each patient participates in all sub-Aims, therefore overall sample size is determined by the sub-Aim requiring the largest sample.

SA1. To test the hypothesis that specific contacts on a novel segmented DBS lead in the STN region activate functionally distinct populations of cortical axons within individual PD patients. SA1.1 will measure within-participant contrasts in therapeutic window and UPDRS part 3 change versus pre-op baseline across the different segments on the directional DBS lead with two-way repeated measures mixed models using Proc Mixed in SAS, with conventional versus current steering DBS contacts as factors and therapeutic window and change in UDPRS part 3 as data. The primary outcome measure for SA1.2 will compare whether intraoperative ERPs predict within-participant changes in the clinical outcomes from SA1.1. We will contrast the ERPs within and across stimulation sites with two-way repeated measures mixed models using Proc Mixed in SAS, with stimulus amplitude, location, and recording modality (EEG or ECOG) as factors and P1/N1 latency and HFO integrated area as data. Using linear contrasts from the regressions, we will directly compare whether EEG and ECOG measures of DBS amplitude thresholds (1) that change P1/N1 latency and (2) elicit the large amplitude HFOs better predict the size of the therapeutic window for a given DBS electrode contact. Secondary outcomes will correlate these amplitude thresholds with changes in the UPDRS part 3 score, UPDRS subscores, and other elements of the Motor battery measured in SA1.1. To control for potential subclinical corticospinal tract activation, we will report the latency and magnitude of EMG response(s) in the contralateral arm and leg muscles using residual analyses, when and if these responses are present. Sample size for SA1. Our preliminary findings show robust within- and between-subject changes in ERP latency that predict postoperative motor side effects. For the first primary outcome, a sample size of 18 will have 80% power to detect a difference between a null hypothesis regression slope of 0 and an alternative regression slope of 0.3 or higher standardized units, assuming that the standard deviation of the predictor variable, DBS amplitude threshold, is 2.370 mA (the standard deviation of the stimulus intensities) and the standard deviation of the normalized residuals (sd=1) of the therapeutic window using a t-test with a 0.05 two-sided significance level. Thus, we will be overpowered for SA1, because a large sample of 30 is dictated by SA2.3. As an additional secondary analysis, we will compare the predictive power of EEG versus ECOG, we will first regress the primary outcomes on EEG and then determine how much of the residual variance is explained by ECOG. If EEG explains 50% of the variance in the primary outcome, then we will have 80% power to detect an increase in the R-square of 8.6%. If the additive R-square of EEG is 25%, we will have 80% power to detect an increase of 12.9%. If we cannot demonstrate superiority of ECOG, we would default to the less invasive modality. We will look at the assumptions of the model by examining the residual plots in the regression models for both modalities.

SA2. To test the hypothesis that patient-specific combinations of active contacts on the segmented DBS lead, selected based upon behavioral versus ERP criteria, improve the efficacy and tolerability of DBS therapy. SAs 2.1 and 2.2 occur on the same day in an acute safety, feasibility, and dose-finding study to inform stimulation parameters for current steering in the double-blind, randomized crossover study in SA 2.3. For SAs 2.1 and 2.2, we will use two-way repeated measures linear mixed models using Proc Mixed in SAS to contrast (1) conventional DBS (as though the lead does not have current steering), (2) combinations of active contacts selected by behavior alone, and (3) combinations of active contacts

selected based cortical ERP physiology, using both therapeutic window and change in UPDRS part 3 as data nested within person. Secondary analyses will contrast the efficacy of these DBS adjustment strategies based upon changes in other elements of the Motor battery. In SA 2.3, we use the randomized, doubleblind crossover trial to compare changes in UPDRS and other measures of quality of life and motor, cognitive, behavioral, and speech function across the DBS programming strategies identified in SA 2.1. The primary statistical analysis will use Proc Mixed in SAS with active contact groupings including (1) conventional DBS, (2) multiple active contacts selected based on behavior, and (3) multiple active contacts based on ERPs as factor and patient preference and changes in PDQ-39 and UPDRS part 3 as data. Sample size for SA2. We will obtain multiple repeated measures within participants and can readily detect changes in patient preference, PDQ-39, UPDRS part 3, and other motor and non-motor variables of interest. Patient reported evidence for the hypothesis of superiority of current steering will be shown by determining that 20 or more of the 30 participants favor either current steering approach over conventional DBS using a binomial distribution based on patient preference (vote), PDQ-39, and UDPRS part 3. This would achieve a p value of < 0.049. We will declare current steering DBS to be clinically superior to conventional therapy based on patient preference if 20 or more patients meet this criterion. We will measure the frequency by which current steering provides better outcomes versus conventional DBS, which could still be highly relevant and significant clinically (even if preferred by <20 participants). Secondary measures will quantify within-participant changes in upper limb dexterity, gait speed test, posture and balance, cognitive/behavioral measures, speech, and motor diaries. Additionally, we will contrast the probability that active contacts are shared among the programming strategies (conventional DBS, current steering guided by behavior, and current steering guided by cortical physiology). The extent to which contacts and stimulation parameters are shared among these approaches could be informative and provide a useful internal validation of the current steering approach.