CLINICAL STUDY PROTOCOL

Title:	Tele-health outcomes as digital biomarkers of Parkinson's disease progression during extended follow-up of STEADY-PD III and SURE-PD3 trial participants.
Acronym:	AT-HOME PD [**A**ssessing **T**ele-**H**ealth **O**utcomes in **M**ultiyear **E**xtensions of **PD** trials]
Sub-Study Title:	AHPD – SUPER-PD Tele-visit Validation
Clinical Phase:	Observational
Sponsor:	National Institute of Neurological Disorders and Stroke (NINDS)
Principal Investigators:	E. Ray Dorsey, MD MBA Larsson Omberg, PhD Michael Schwarzschild, MD PhD Tanya Simuni, MD
Co-Principal Investigators:	Elise Kayson, MS, ANP Mike Kellen, PhD
Clinical Coordination Center:	University of Rochester Center for Health & Technology (CHeT) Clinical Trials Coordination Center (CTCC) 265 Crittenden Boulevard Rochester, New York 14620
Biostatistics Center:	Eric Macklin, PhD Massachusetts General Hospital MGH Biostatistics Center 50 Staniford St., Suite 560 Boston, MA 02114

DOCUMENT HISTORY

Version	Date of Issue	Summary of Changes
1.0	17 Sep 2018	Initial Version
2.0	21 Nov 2018	Investigator agreement page and throughout protocol: Replaced CTCC with CHeT when describing study site
2.0	21 Nov 2018	List of Abbreviations – added VC (video conference) and API (application program interface)
2.0	21 Nov 2018	Protocol Synopsis, Sections 4.2 and 5.1 – Added language to allow subjects from STEADY PDIII and SURE PD3 who declined consenting to future contact the ability to directly contact UR to request information about participating in AT-HOME PD
2.0	21 Nov 2018	Schedule of Activities and Section 5.5.2 – replaced tele-visit with video conference to describe the screening visit
2.0	21 Nov 2018	Schedule of Activities and Section 5.5.3 – Removed smartphone app registration from the list of activities performed at the baseline visit and added language to allow for registration in Synapse web portal to occur just prior to the visit date
2.0	21 Nov 2018	Section 1.1 – Updated the length of time DAT scan follow-up that will be conducted in SURE-PD3 to over a length of 1 to 2 years.
2.0	21 Nov 2018	Section 5.1 – Revised language regarding contacting SURE-PD3 subjects to allow contact after completion of SURE-PD3 study
2.0	21 Nov 2018	Sections 5.1 and 8 – Replaced subject payment method from debit card to check and added language offering additional standard internet and/or smartphone/data plan reimbursement for minorities.

Version	Date of Issue	Summary of Changes
2.0	21 Nov 2018	Sections 5.1, 5.5.1, 5.5.2, and 5.5.3 – Revised the window of timing for contacting SURE-PD3 participants and completing the prescreen call, screening video conference, and baseline tele-visit and replaced the description of the last in-person SURE-PD3 study visit from "on-drug" to "final visit (or equivalent) in the planned treatment period"
2.0	21 Nov 2018	Section 5.2 – Removed language stating CTCC team member will email reminders to participants to eConsent, revised language to specify screening visit will be scheduled during prescreen call, and added language to state AHPD staff may email participant the current UR IRB approved consent form, if requested during the prescreen call
2.0	21 Nov 2018	Section 5.4 – Revised to reflect REDCap entries will be created on all participants AHPD study team establishes direct contact with
2.0	21 Nov 2018	Section 5.5.1 – Clarified delivery method and timing of eConsent and technology survey
2.0	21 Nov 2018	Section 5.5.2 – Modified duration of screening visit to approximately 30 minutes
2.0	21 Nov 2018	Section 5.5.2 – Modified the list of information required for creating a participant's FI account and updated the description of events occurring if a participant is already enrolled in FI
2.0	21 Nov 2018	Section 5.5.4 – Removed SMS as the means of notification method for mPower reminders

Version	Date of Issue	Summary of Changes
2.0	21 Nov 2018	Section 6.1.3 – Removed sentences from MDS-UPDRS Part III stating that subjects on symptomatic dopaminergic therapy will be asked to (optionally) hold their morning dose during visit days
2.0	21 Nov 2018	Section 12 – Removed "enactment of Medical Safety Escalation Plan" from the list of reportable events and added a statement below that it should be reported to the CTCC PM
2.0	21 Nov 2018	Section 15.5 – Replaced "de-identified" with "transformed" to describe the transferred dataset
2.0	21 Nov 2018	Section 15.5 – Updated the description of tele-visit REDCap data access to state Sage Bionetwork access via API
2.0	21 Nov 2018	Section 17.2 – Added process of entering data during REDCap downtime via collection on paper CRFs
2.0	21 Nov 2018	Administrative changes throughout
3.0	06 Nov 2019	Replacement of Lara Mangravite with Larsson Omberg as a principal investigator
3.0	06 Nov 2019	Replacement of Lauren Bataille with Lindsey Riley as listed collaborator from MJFF
3.0	06 Nov 2019	Updated Steering Committee List
3.0	06 Nov 2019	Updated Acronyms List with addition of PD-PROP and SUPER-PD
3.0	06 Nov 2019	Protocol Synopsis and Section 13.4 – updated sample size determination and true concordance for SURE-PD3 and combined SURE-PD3 and SUPER-PD participants expected to complete at least one TV close in time to their in-person clinic visit.

Version	Date of Issue	Summary of Changes
3.0	06 Nov 2019	Updated Figures 1 and 2 with added data flow description from DMR to Qualified Researchers and added Figure 1a
3.0	06 Nov 2019	Addition of SUPER-PD sub-study throughout
3.0	06 Nov 2019	Administrative Changes Throughout

Table 1. List of abbreviations and definition of terms

Abbreviation or specialist term	Definition
ADAGIO	Attenuation of Disease Progression with Azilect Given Once-daily
AE	Adverse Event
AHPD	AT-HOME Parkinson's Disease
API	Application Program Interface
AUC	Area under the concentration-time curve
CAPA	Corrective and Preventive Action Plans
CDEs	Common Data Elements
CFR	Code of Federal Regulations
CGI-S	Clinician Global Impression – Severity
CHeT	University of Rochester Center for Health + Technology
CNS	Central Nervous System
Co-I	Co-Investigator
CRA	Clinical Research Associate
CRF	Case Report Form
CTCC	Clinical Trials Coordination Center
DAT	Dopamine transporter
DATATOP	Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism
DM	Data Management
DMR	Data Management Resource
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDL	Experiences of Daily Living
ET	Early Termination
FDA	Food and Drug Administration
FI	FoxInsight
GCP	Good Clinical Practice
GPS	Global Positioning System
GUID	Global Unique Identifier
HIPAA	Health Insurance Portability and Accountability Act
HSPP	Human Participant Protection Program

Abbreviation or specialist term	Definition
ICC	Intra-class correlation
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
ID	Identification Number
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-treat
IV/WRS	Interactive Voice/Web Response System
LONI	Laboratory of Neuro Imaging
MDS-UPDRS	Movement Disorders Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MJFF	Michael J Fox Foundation for Parkinson's Research
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
NINDS	National Institute of Neurological Disorders and Stroke
NW	Northwestern University
ORPA	Office of Research and Project Administration
PD	Parkinson's Disease
PD-PROP	Parkinson Disease Patient Reported Outcome of Problems
PDBP	Parkinson's Disease Biomarkers Program
PDF	Portable Document Format
PGI	Patient Global Impression
PI	Principal Investigator
PM	Project Management
PP	Per Protocol
PPMI	Parkinson's Progression Markers Initiative
PRO	Patient Reported Outcomes
PSC	Protocol Steering Committee
PSG	Parkinson Study Group

Abbreviation or specialist term	Definition
PT	Preferred Term
PW	Premature Withdrawal
QA	Quality Assurance
QC	Quality Control
RE	Reportable Events
REDCap	Research Electronic Data Capture
ROC	Receiver Operating Characteristic Curve
RSRB	Research Subjects Review Board
SA	Specific Aim
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Standard Deviation
SE	Standard Error
SEADL	Schwab & England Activities of Daily Living Scale
SMC	Safety Monitoring Committee
SOA	Schedule of Activity
SOC	System Order Class
SOP	Standard Operating Procedure
SP	Smartphone
ST	Symptomatic Dopaminergic Therapy
SUPER-PD	Sensor Use to Monitor Progression and Evaluate Symptoms Remotely in Parkinson's Disease
TBI	Traumatic Brain Injury
TV	Tele-visit
UPDRS	Unified Parkinson's Disease Rating Scale
UR	University of Rochester
URMC	University of Rochester Medical Center
USC	University of Southern California
VC	Video Conference

AT-HOME PD PROTOCOL SYNOPSIS

Protocol Title	Tele-health outcomes as digital biomarkers of Parkinson's disease progression during extended follow-up of STEADY-PD III and SURE-PD3 trial participants
Acronym	**AT-HOME PD** (**A**ssessing **T**ele-**H**ealth **O**utcomes in **M**ultiyear **E**xtensions of **PD** trials)
Protocol No.	**AHPD-U01NS107009**
Sponsor	NINDS
Investigators	Principal Investigators E. Ray Dorsey, MD MBA Larsson Omberg, PhD Michael Schwarzschild, MD PhD Tanya Simuni, MD
Institutions	Primary project performance Massachusetts General Hospital Northwestern University Sage Bionetworks University of Rochester Collaborating Michael J. Fox Foundation for Parkinson's Research Parkinson Study Group (PSG)
Steering Committee	Alberto Ascherio, MD DrPH James Beck, PhD Kevin Biglan, MD, MPH E. Ray Dorsey, MD MBA Alberto Espay, MD Robert Holloway, MD MPH Elise Kayson, MS ANP Caroline Tanner, MD PhD Eric Macklin, PhD Larsson Omberg, PhD David Oakes, PhD Michael Schwarzschild, MD PhD (SC Co-chair [initial]) Ira Shoulson, MD Tanya Simuni, MD (SC Chair [initial]) Dan Novak, PhD (Parkinson's Foundation PAIR program patient advocate) Codrin Lungu, MD (NINDS Scientific Program Director)

No. Study Centers	One: University of Rochester, Center for Health + Technology (CHeT)/Clinical Trials Coordination Center (CTCC)
Objectives	**1. To establish and implement an infrastructure for longitudinal remote follow-up of phase 3 trial cohorts:** a. Transition from site-based to a centralized site and coordination center to manage all participant activity in virtual extensions of SURE-PD3, with projected enrollment of ≥70% of final trial cohorts, and core data collection in accordance with Parkinson's Disease Biomarkers Program (PDBP) schedule of activities. b. Conduct an annual research visit (tele-visit) program and establish the feasibility and cross-sectional reliability of tele-visit versus in-person visit assessments in a subset of STEADY-PD III and SURE-PD3 participants. c. Deploy a smartphone application, based on the mPower study, for remote data collection in a clinical trial cohort as preliminarily characterized in the Smart*4*SURE sub-study of SURE-PD3. d. Establish a mechanism for linking STEADY-PD III and SURE-PD3 study data with data collected through smartphone-based assessments, tele-visits, and Fox Insight (FI), a separate longitudinal patient-reported outcomes (PROs) online research study. **2. To compare patient-driven (smartphone, web-based surveys) vs clinician-driven (tele-visit) outcomes by:** a. Correlating the smartphone and tele-visit platforms' component and composite features, and their changes over years. b. Comparing the smartphone and tele-visit platforms' abilities to: i) measure PD progression and predict clinical events and changes in PROs; ii) distinguish rapid vs slow progressors based on baseline Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, dopamine transporter (DAT) deficit (in SURE-PD3) or serum urate levels (in STEADY-PD III); iii) demonstrate persistence of any effects of isradipine or inosine in their respective trials. c. Comparing completion status and performance on FI and tele-visit PROs. **3. To explore novel smartphone-based real-life mobility biomarkers of PD disability and its progression** that are normally inaccessible with traditional office measures. We will investigate the ability of passively collected smartphone data on ambulation and location to enable assessments of physical activity and

	socialization that correlate with motor and non-motor functions.
Study/Observation Period	24 months (with rolling enrollment), after completion of the interventional phases of STEADY-PD III and SURE-PD3
Study Population	All individuals with early idiopathic PD enrolled in the STEADY-PD III (NCT02168842) and SURE-PD3 (NCT02642393) studies (N≈600) who have consented to be contacted for future research will be asked to participate or if a subject from these two studies directly contacts the University of Rochester (UR) to request information about study participation. We expect approximately 70% of STEADY-PD III and SURE-PD3 participants (N≈420) are expected to consent and participate in at least the tele-visit portion of the study. We expect approximately 80% of individuals who enroll in this study (N≈340) to participate in the smartphone portion (and thus the smartphone vs tele-visit comparison) of the study. We expect approximately 70% of individuals who participate in the smartphone portion of the study (N≈240) to consent to passive collection of motor and mobility data. We expect approximately 80% of individuals who enroll in this study (N≈340) to participate in the FI portion of the study.
Study Design	Observational study to characterize and compare long-term clinical outcomes data collected remotely through annual tele-visits, quarterly interactive smartphone app sessions, and web-based surveys in individuals with PD who have completed the interventional phases of STEADY-PD III and SURE-PD3 clinical trials.
Number of Participants	Approximately 420
Main Inclusion Criteria	1. Enrollment in STEADY-PD III or SURE-PD3 studies 2. Prior consent to be contacted by the University of Rochester (UR) or if a subject from STEADY-PD III or SURE-PD3 studies directly contacts UR to request information about study participation 3. Internet-enabled device that will support participation in tele-visits 4. Have created or willing to create a Global Unique Identifier (GUID) 5. Willing and able to provide informed consent 6. English fluency 7. For participants opting to participate in the smartphone component, possession of a suitable smartphone (iPhone

	or Android) with adequate data plan and cellular network access/signal or Wi-Fi access
Main Exclusionary Criteria	1. Inability to carry out study activities as determined by study staff
Study background and Rationale	At the launch of AT-HOME PD the STEADY-PD III and SURE-PD3 trials were active NINDS-funded phase 3 studies of potential disease-modifying interventions in PD. The long-term observation of participants from these trials, while challenging to implement, was deemed a valuable research opportunity. The reliance on in-person visits and snapshot assessments in a condition characterized by variable symptoms is an important limitation. Tele-visit, web-based surveys, and smartphone-based remote sensor assessments represent particularly promising methods for streamlining study conduct, reducing participant burden, and enabling the collection of data beyond the usual episodic, in-clinic assessments. The objective of this study is to leverage modern technology to develop, pilot and implement a 100% virtual model for long-term follow-up utilizing tele-visit and smartphone platforms for quantitative monitoring of clinician- and patient-reported outcomes (PROs).
Study Platforms and Outcome Measures	**Tele-visit platform** – Participants will complete a total of three tele-visits, which will occur at baseline, month 12, and month 24. Some activities will be completed either prior to or post tele-visit by the participant. Assessments will include: • Review of reportable events • Review of concomitant medications • MDS-UPDRS parts 1a, 3, and 4 (where applicable) • Montreal Cognitive Assessment (MoCA) • Schwab & England Activities of Daily Living Scale (SEADL) • Clinician Global Impression and Patient Global Impression – Severity and Change • Determination of Falls • Performance of one complete set of active motor and cognitive smartphone application tasks (when applicable) • Review of completion of MDS-UPDRS parts 1b and 2, self-reported falls, and patient global impression – severity and change (with direct link to survey sent ahead of visit) • Review of compliance with smartphone tasks and FI assessments where applicable • Preference and Burden Survey

	Investigators administering MDS-UPDRS part 3 (motor examination) will be neurologists or nurse practitioners who have obtained formal MDS-UPDRS certification and will have additionally undergone joint training to reconcile scoring differences and minimize inter-rater variability. Tele-visits will be scheduled in either the morning or afternoon according to participant preference and, for participants on symptomatic dopaminergic therapy, the MDS-UPDRS will be preferably performed in the usual ON state. **FI web-based survey platform** – Participants will be asked to complete a set of standard questionnaires every 3 months through an online observational companion study called FI. Study participants will be encouraged but not required to participate in FI. Standard assessments include: • The Parkinson's Disease Questionnaire, short-form 8 item version (PDQ-8) • MDS-UPDRS part 2 • Physical Activity Scale for the Elderly (PASE) • Your Cognition and Daily Activities (PDAQ-15) • Euroqol Five (EQ-5D) • Non-motor symptoms questionnaire (NMS-QUEST) • Geriatric Depression Scale, short form (GDS) • Parkinson's Disease-Patient Reported Outcomes of Problems (PD-PROP) Participants are invited to complete additional PRO surveys about, but not limited to, symptoms, disease progression, quality of life, patient preference or general health. **Smartphone session platform (mPower-based app)** – We will use mPower 2.0 developed by Sage Bionetworks on both iOS and Android. mPower will include active tasks to be completed (Scientific Aim (SA) 2) and allow passive collection of motor and mobility data with participant permission (for SA3). 14-day smartphone sessions will occur every 3 months. During these sessions, participants will complete smartphone-based motor tasks daily on at least 10 days and cognitive assessments on at least 3 days. Given diurnal variation in active task performance, participants will be asked to select morning or afternoon as their preferred window for completion and to consistently complete the active tasks according to their selected preference. Motor Tasks: • Gait task - a 30 second walk • Finger tapping task - 30 seconds of rapid finger tapping in each hand

	• Resting tremor task - 30 seconds of holding phone in each hand • Balance task - 30 seconds of standing still Cognitive Assessments: • Digit span • Digit symbol substitution • Spatial working memory Enrolled participants will also use the application to track their medication adherence relative to tasks and, optionally, self-reported symptoms and triggers. For those participants who optionally consent to passive data collection, the smartphone application will collect multiple streams of passive data including: movement patterns captured by location services on phone and walking patterns captured by accelerometer gyroscope, and pedometer.
Study Compliance	Compliance with all three study platforms will be monitored. CHeT/CTCC will monitor compliance through tele-visits and patient interview during the visit. Sage Bionetworks will utilize push notifications and Short Message Service (SMS) reminders to encourage compliance with smartphone-based assessments. MJFF will send automated e-mail reminders to complete the quarterly assessments after approximately 45 days and again after approximately 88 days. CHeT/CTCC will receive quarterly compliance reports from Sage Bionetworks and from MJFF (until a publicly-accessible research dashboard becomes available through University of Southern California's Laboratory of Neuro Imaging (LONI)).
Data Management	1) **Data collected during tele-visits** will be entered and maintained in REDCap (a secure web-based survey and data management system) and transferred to Synapse (an open source collaborative platform, for analysis). 2) **Survey data collected by FI** will be exported to LONI (a secure online neuroscience dataset sharing system of USC's) and then to Synapse. 3) **Data collected from smartphones** will be transferred to the Sage Bionetworks maintained Bridge server and then to Synapse. 4) **All platform data will be transferred from Synapse to PDBP-DMR** All data will be identified by the GUID, the date, time of the visit, and then transferred to the Sage Bionetworks managed Synapse. From Synapse the cleaned, processed, and event date and time transformed dataset will be transferred to the PDBP's Data Management Resource (DMR) for further distribution to PDBP investigators and will be made available to the wider research community through their qualified researchers program [See Resource Sharing Plan].

	All the data being shared will be detailed in the data user agreement (DUA).
Statistical Analysis (by Specific Aim)	**SA 1**: We will use results from the REACT-PD study to establish a calibration of tele-visit (TV) assessments to predict in-clinic MDS-UPDRS scores (Aim 1b). Lin's concordance correlation coefficient, r_c, will be used to summarize accuracy of the calibrated TV estimates vs. scores collected from in-person SURE-PD3 visits conducted close in time, accepting TV estimates as sufficiently accurate if $r_c > 0.8$. If we observe insufficient concordance, we will re-calibrate using all available data from both REACT-PD and the current study. **SA 2**: The study sample will be randomly split 2:1 into calibration and validation subsets. The calibration sample will be used to derive smartphone (SP) measures that best match the TV assessed composite scores of motor function (MDS-UPDRS part 3), non-motor function (MoCA total score), subjective function (including clinical global impression [CGI] scores, patient global impression scores, modified Schwab and England ADL scores, and MDS-UPDRS parts 1b and 2 scores), and estimates of MDS-UPDRS part 1-3 total scores (Aim 2a). The accuracy of calibrated SP measures will be tested in the reserved validation sample using Lin's concordance correlation coefficient, r_c. If we observe insufficient concordance, we will recalibrate using all available data from both the calibration and validation samples. TV assessments and calibrated SP measures of disease progression will be compared generally and between specific subsets of participants expected to progress at different rates (Aim 2b). Each measure will be standardized to 30% of the observed mean change over 2 years based on a random-slopes linear mixed model of the full sample such that a one-unit change of all standardized, calibrated measures would reflect an equivalent magnitude of change relative to natural rates of progression. Estimated measure-specific variance components will be used to estimate the standard error for a treatment group comparison from a two-arm trial assuming an assessment schedule appropriate for a given measure, e.g., annual for TV measures and quarterly for SP measures. The ratio of squared standard errors will be used to estimate the relative sample size required using one or another measure for designs with equivalent power. The same approach will be used to identify measures that are sensitive to biological subgroups (e.g., among participants stratified by their rate of MDS-UPDRS progression over the first 2 years of in-clinic follow-up in the parent trials) or treatment-based subgroups (e.g., participants randomized to isradipine or serum urate elevation). TV assessments and SP measures will also be compared with respect to their

	accuracy in predicting future clinical events and changes in PROs, e.g., dropping below 80% on the modified Schwab and England ADL, experiencing a fall and other PROs as captured by FI application including PD-PROP measures. **SA 3**: We will derive novel measures that best predict disease progression using passively collected SP data. We will split the sample 2:1 into discovery and validation subsets, like active tasks. A range of SP measures will be derived from passive data. For walking data (Aim 3a) these include but are not limited to time and frequency domain statistics, energy and entropy of frequency spectrum from the tri-axial accelerometer, along with absolute displacement measurements. For displacement information (Aim 3b) data will be summarized into variables such as furthest distance traveled, frequency of trips, average daily distance etc. Resulting summary metric will then be matched with the TV assessed composite scores of motor function (MDS-UPDRS part 3), Schwab and England ADL scores, MDS-UPDRS (parts 1b and 2 scores), and estimates of MDS-UPDRS part 1-3 total scores. The accuracy of the associations will then be tested in the validation data subset using Lin's concordance correlation coefficient, rc. Passive measures will be assessed for progression using the same methods as described in SA 2b.
Power Calculations	**SA 1b**. With a sample size of ~10 SURE-PD3 participants expected to complete at least one TV close in time to their in-person clinic visit, the study will have 80% power to conclude that the REACT-PD calibrated tele-visit estimates are sufficiently accurate (r_c > 0.8 at alpha = 0.05) if the true concordance is at least 0.89. **SA 2a**. With a 2:1 split of ~340 AT-HOME PD participants, yielding ~115 participants contributing to validation tests, the study will have 80% power to declare a given SP measure sufficiently accurate (r_c > 0.80 at alpha = 0.05) if the true concordance is at least 0. 87. **SA 2b**. With approximately 80% of participants participating in the SP portion of the study, yielding ~340 participants contributing to the smartphone vs tele-visit comparison, the study would have an 80% probability of selecting the true preferred measure from a pair of TV or SP if the preferred measure had lower standard error by an effect size of at least 0.065. **SA 3**. With a 2:1 split of ~240 participants, yielding ~80 in the validation sample and at least 25% experiencing at least an 8-point progression in MDS-UPDRS parts 1-3 total score, the study would have 80% power to declare a novel measure derived from passive SP monitoring to have a ROC AUC

	significantly greater than 0.80 if the true AUC were at least 0.95.

AHPD – SUPER-PD TELE-VISIT VALIDATION SUB-STUDY SYNOPSIS

Study Center	University of Rochester
Objectives	To establish the cross-sectional reliability of tele-visit versus in-person research visit assessments of participants with PD
Study Population	Individuals with PD enrolled in the University of Rochester's on-going **S**ensor **U**se to Monitor **P**rogression and **E**valuate Symptoms **R**emotely in **P**arkinson's **D**isease (SUPER-PD) study
Study Design	Individuals with PD from SUPER-PD will complete a single tele-visit within ±2 weeks of their SUPER-PD baseline or month 12 in-person study visit.
Number of Participants	Approximately 50
Main Inclusion Criteria	1. Enrollment in SUPER-PD 2. Diagnosis of idiopathic PD (as determined by UK Parkinson's Disease Brain Bank Criteria in SUPER-PD) 3. Have consented to future contact by the University of Rochester 4. Internet-enabled device that will support participation in tele-visits 5. Willing and able to provide informed consent
Main Exclusion Criteria	1. Inability to carry out study activities
Study Rationale	Tele-visits offer the promise of streamlining study conduct and reducing the burden on study participants. The objective of this sub-study is to establish the cross-sectional reliability of tele-visit assessments.
Study Outcome Measures	• MDS-UPDRS part 3 • Montreal Cognitive Assessment
Data Management	Data collected during tele-visits will be entered and maintained in REDCap (a secure web-based survey and data management system). Each participant's baseline demographic information, concomitant medications, and health history as well as clinical data including PD-PROP from the corresponding SUPER-PD visit, will be transferred from the SUPER-PD REDCap project to the AHPD sub-study REDCap project. All data will ultimately be transferred to Synapse (an open source collaborative platform) for analysis. For any sub-study participants who are participating in the mPower 2.0 component of SUPER-PD, their smartphone data from the corresponding SUPER-PD visit and associated remote 2-week burst will be linked with AT-HOME PD data within Synapse. From Synapse, the cleaned, processed, and event date- and time-transformed dataset will be transferred to the PDBP's Data Management Resource for further distribution to PDBP investigators and will be made available to the wider research community through their qualified researchers program.
Statistical Analysis	Paired MDS-UPDRS and MoCA scores from in-person and TV assessments of SUPER-PD participants will be pooled with data

	from SURE-PD3. The accuracy of predicted in-clinic scores based on TV assessments using calibrations from REACT-PD will be summarized by Lin's concordance correlation coefficient, r_c, equivalent to an intra-class correlation (ICC). The REACT-PD calibrations will be judged sufficiently accurate if $r_c > 0.8$. If we observe insufficient concordance, we will re-calibrate using all available data from REACT-PD, SURE-PD3, and SUPER-PD.
Sample Size	With a combined sample size of ~60 SURE-PD3 and SUPER-PD participants expected to complete at least one TV close in time to their in-person clinic visit, the study will have 80% power to conclude that the REACT-PD calibrated tele-visit estimates are sufficiently accurate ($r_c > 0.8$ at alpha = 0.05) if the true concordance is at least 0.89.

Table 1: AT-HOME PD Schedule of Activities (SOA)

	Pre-screen TC	Screen VC(within 30 days of eConsent)	Visit 1 BL Day 0*** TV	Month 3 SP	Month 6 SP	Month 9 SP	Visit 2 Month 12 (±28 days) TV	Month 15 SP	Month 18 SP	Month 21 SP	Visit 3 Month 24 (±28 days) TV	Unscheduled/PW TV
Study/Visit Setup												
Verify Consent		X										
Verify eligibility	X	X										
Pre-Screening Questionnaire	X											
eConsent	X											
Technology Survey	X											
Demographics		X										
Tele-visit Test connection		X										
Fox Insight Account Creation		X										
GUID Creation[1]		X										
SimplyBook.me Orientation		X										
Smartphone app orientation			X									
Tele-visits												
Reportable Events			X				X				X	
Concomitant Medications			X				X				X	X
MDS-UPDRS part 1a, 3, 4 (if applicable)			X				X				X	X
Self-Reported Falls[2]			X				X				X	X
MDS-UPDRS part 1b, 2[2]			X				X				X	X
MoCA			X				X				X	X
Schwab & England			X				X				X	X
CGI* and PGI**[2]– Severity			X				X				X	X
CGI* and PGI**[2]– Change							X				X	X
Determination of Falls			X				X				X	X
Performance of complete set of active smartphone tasks			X				X				X	X
Preference & Burden survey[3]			X				X				X	X
Review study compliance			X				X				X	
Early termination survey												X
Smartphone Sessions												
Motor tasks			X (x10)	X (x10)	X (x10)	X (x10)	X (x10)	X (x10)	X (x10)	X (x10)	X (x10)	
Cognitive tasks			X (x3)	X (x3)	X (x3)	X (x3)	X (x3)	X (x3)	X (x3)	X (x3)	X (x3)	
Fox Insight Surveys	**See Table 2**											

[1]If not already existing; [2] Completed pre-tele-visit; [3] Completed post tele-visit

*Completed by the investigator; ** Completed by the patients; *** Within 60 days of Screening/TV

Fox Insight Study 002.1

Table 2a: Schedule of Activities - Remote Cohort
Parkinson Disease (PD) Subjects

Visit Number	Hardcoded or QE?	Freq. (months)	Reg.	BL/ V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	V14	V15		V20	Rolling Until Completed (FROM BASELINE)
Visit Description Months (~30 days)			0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42		60	
FI Account (Registration)	HC	once	X																		
Informed Consent	HC	once	X																		
Privacy Agreement	HC	once	X																		
About You (Profile)	HC	12	X					X (SM)				X (SM)				X (SM)				X (SM)	X
Return Visit Questionnaire (PD)	HC	3			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Tell us how you are completing this study visit	QE	3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Side of Onset	QE	Once		X																	X
Your Medical History	QE	once		X																	X
Your Current Medical Conditions	QE	12		X				X (SM)				X (SM)				X (SM)					
Your Acute Medical Conditions	QE	12						X				X				X					
Your Medication History	QE	once		X																	X
Your Medications (PD)	QE	3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Your Family neurological history	QE	12		X				X (SM)				X (SM)				X (SM)				X (SM)	
Handedness Questionnaire (Edinburgh Handedness short form)	QE	Once		x																	X
PRO tools and surveys																					
Your Daily Living (PDQ-8)	QE	3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
What's Bothering You? (PD Patient Reported Outcome of Problem (PD-PROP; Shoulson))	QE	6		X		X		X		X		X		X		X		X		X	
Your Physical Experiences (EQ-5D)	QE	6		X		X		X		X		X		X		X		X		X	
Your Physical Activities (PASE)	QE	12		X				X				X				X				X	
Your Movement Experiences (MDS-UPDRS)	QE	6		X		X		X		X		X		X		X		X		X	
Impact of OFF Episodes (MJFF Off Survey)	QE	6				X		X		X		X		X		X		X		X	
Your Non-Movement Experiences (PD)	QE	3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Your Sleep Habits	QE	12		X	X (SM)				X (SM)				X (SM)				X (SM)				
Your Cognition and Daily Activities (PDAQ-15)	QE	6		X	X		X		X		X		X		X		X				
Your Mood (GDS)	QE	12		X				X				X				X					
Environmental exposure RFQ	QE	once																			

*Surveys will be presented in full versions unless noted that survey will be presented in summary mode (SM)

Updated 4/2018

Table 3: AHPD - SUPER-PD Cohort Schedule of Activities (SOA)

	Pre-Screen Contact (TC or in-person)*	Baseline Tele-Visit (±14 days of SUPER-PD baseline or month 12 visit)
Pre-Screening Questionnaire	X	
eConsent	X	
Verify Eligibility		X
Verify Consent		X
Reportable Events		X
MoCA		X
MDS-UPDRS part 3		X

*May occur either in-person (at time of their SUPER-PD visit) or by phone

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1. INTRODUCTION

1.1 Background

Disease modification is the primary unmet need in Parkinson's disease (PD) therapeutics. To aid in achievement of this goal, as recognized by NINDS, validated PD biomarkers that improve the efficiency of clinical trials are urgently needed. While discovery of biological signatures of the disease has been a central focus of PD biomarker research, a similarly important priority is the application of novel technologies to provide digital biomarkers of disease progression.

Clinical trials of therapies aiming to slow PD progression have been hindered by the need for study participants to repeatedly visit a research clinic for in-person testing. Tele-visits, web-based surveys and smartphone-based remote sensor assessments represent particularly promising opportunities to streamline study conduct, reduce participant burden, and allow for the collection of data beyond the usual episodic, in-clinic assessments. Demonstrating the accuracy of these relatively inexpensive and accessible platforms for the measurement of PD progression would facilitate long-term follow-up of participants after completion of interventional studies. New infrastructure will be required to implement tele-visit and smartphone-based remote sensor assessments.

This project will investigate novel strategies for measuring the progressive disability of PD using tele-visits from participants' homes and smartphone technology in order to overcome limitations of traditional clinical trials and thereby accelerate development of improved treatments for people with PD.

1. Tele-health alternatives to traditional in-clinic outcomes data collection

a. Advantage of telemedicine (tele-visit) versus in-office research visits and current state of the field

Telemedicine, the use of real-time synchronous videoconferencing with patients, could revolutionize clinical trial design. Telemedicine-based virtual research encounters between participants and clinical investigators (tele-visits) can be conducted on readily available internet-enabled devices and in any location where privacy can be established. Numerous studies have shown that telemedicine is feasible for patients with PD (1,2). In the largest randomized controlled trial of telemedicine in PD to date, 91% of 388 scheduled telemedicine visits were completed (3). With some modifications, the Unified Parkinson's Disease Rating Scale (UPDRS) motor component can be administered remotely and demonstrates good test-retest reliability and good overall agreement with in-person UPDRS motor assessment (1,4). A modified version of the UPDRS, with rigidity and postural instability items removed, has been shown to be reliable and valid (5). There have not been any published studies examining the remote administration of the MDS-UPDRS and

evaluation is needed to determine if this is a valid and reliable tool when administered remotely. Non-motor assessments, including the Montreal Cognitive Assessment (MoCA), can also be feasibly administered remotely (6). The majority of patients are satisfied or more than satisfied with telemedicine visits (1, 3). Individuals are interested in participating in studies of telemedicine (3) and may be more interested in participating in trials that incorporate tele-visits delivered outside of the home (7). Telemedicine visits result in a reduction in distance travelled, time associated with the visit, and cost (8). The incorporation of tele-visits into clinical trials could reduce the burden on participants, enable individuals with greater disability or other (e.g., geographic or economic) travel barriers to participate, allow for long-term clinical trial follow up, enable a shift towards centralized raters (9), and allow for remote obtainment of informed consent (10,11).

b. Value of smartphone-based data acquisition – PD is readily monitored using remote sensors embedded in smartphones or wearables (12-14) due to the outward manifestations of the disease. While wearables have gained popularity for measuring gait within the context of clinical trials, smartphones provide a more flexible, less invasive approach for long-term at-home evaluation. Motor symptoms can be captured using smartphones using built-in accelerometers, pressure sensor in screens and microphones for assessment of phonation, and non-motor symptoms can be tracked by electronic patient-reported outcomes (PROs) or other activities. Smartphones have the potential to provide objective, frequent, and sensitive assessments of PD.

In the mPower study (NCT02696603), participants have been tracked longitudinally as they perform daily active tasks and PROs. The smartphone application associated with the mPower study was adopted by over 12,000 individuals in the first 6 months who together performed over 200,000 active tasks. Modifications of the application have been deployed in several sub studies, including in Smart*4*SURE in a collaboration between PIs Mangravite, Dorsey and Schwarzschild, and in the PDBP-sponsored Harvard Biomarker Study. Preliminary evaluation of mPower features relative to in-clinic disease assessments – initiated through collaboration between Co-I Omberg and Dorsey – demonstrated that motor metrics captured by mPower corresponded well with in-clinic assessment of MDS-UPDRS motor exam ($R=0.89$, $p<10^{-5}$ for tapping) and were able to identify daily fluctuations in disease burden associated with L-dopa administration or natural diurnal variations (15). In addition to the ability for remote, self-administered monitoring of proxy for standard disease measures, smartphone assessments also provide multiple opportunities to extend understanding of disease beyond in-clinic measures including 1) the ability to evaluate the impact of disease on quality of life (see Aim 3), and 2) the ability to observe natural fluctuations in disease symptoms over time and in relation to environmental or lifestyle choices (16).

In addition to their utility for remote administration of active disease evaluations, smartphones possess the capacity for passively monitoring the impact of PD on daily life over time. Novel measures of ambulatory and social behaviors may be extracted from smartphone (e.g., GPS map) systems to shed light on PD disability inaccessible with traditional in-office measures. Smartphones are generally carried around throughout the day and can provide a low burden approach to collect a continuous stream of passive data including movement patterns (travel distances and location displacements throughout the day), daily activity and exercise patterns, and communication patterns. In contrast to the episodic nature of standard disease assessments, these patterns provide a continuous measure that has been successfully used to monitor disease in neuropsychiatric and cognitive disorders, where changes in daily activity patterns are markers for changes in disease status. In conjunction with collection of active measures as described in **SA 1** and **SA 2**, **SA 3** will evaluate the ability to collect passive data over long periods of time and use these data to identify markers of relative and absolute changes in disease severity.

2. Importance of long-term follow up of participants completing interventional studies

Even if an intervention appears effective early in the course of the disease, it remains to be proven that the benefit will persist. This has proven problematic in studies of other potentially neuroprotective drugs. For example, the initial data from the DATATOP trial (17-19) conducted by the Parkinson Study Group (PSG) pointed to a disease-modifying effect of selegiline that was not supported by the long-term data at least in regard to the primary outcome (20). A more recent example is the inconclusive result of the ADAGIO study of rasagiline (21). Promptly initiated long-term follow up of the cohort would have been highly valuable for further data interpretation. Such an effort was undertaken but unfortunately with a gap of two years post completion of ADAGIO, accounting for a 42% dropout rate from the original cohort, which made data interpretation much less meaningful (22). Nevertheless, a number of important observations on major milestones of PD progression were made by extending the follow up of the DATATOP and ADAGIO cohorts (20-24). Similarly, follow-up studies evaluating the impact of initiating therapy with dopamine agonists versus levodopa have found that early differences do not necessarily result in longer duration benefits (25,26). Thus, the interpretation of multiple studies of several different potentially disease-modifying therapies has been obscured by the lack of long-term follow up. Unplanned longer-term follow up of participants in these studies has generated valuable observations though conclusions have been limited by delays in extension phase initiation with substantial participant dropout and by post-hoc analysis.

AT-HOME PD is a 24-month observational study that will seamlessly transition from two parent trials to enroll the majority of their participants. This additional observation may not be sufficiently long to see emergence of long-term disability like postural instability and cognitive impairment, but most of the participants will be approaching

the 6-7 year-mark from PD onset when the dopaminergic therapy (DT) 'honeymoon' has ended (27) and such events begin to manifest in earnest. Thus, the follow up of these merged phase 3 trial cohorts, comprising one of the longest observational studies of a baseline de novo PD population, is likely long and large enough to provide insight into: 1) any persistent or delayed effect of isradipine or inosine on relevant motor and non-motor outcomes, and 2) milestones of disease progression in the current era of PD therapeutics. The cohort will be especially valuable as it is enriched by DNA and other biologics data (with sequentially collected plasma samples +/- DAT imaging), which will be fully integrated into the PDBP database, and the dataset will be open to the public. The only other baseline de novo cohort of similar size is the Parkinson's Progression Markers Initiative (PPMI; clintrials.gov NCT01141023). While PPMI has a tremendously rich biologics dataset, it is an observational study that never had an interventional arm and currently does not incorporate telemedicine or smartphone assessments. **The novelty** of AT-HOME PD stems not only from long-term follow up of combined PD trial cohorts but also from accomplishing it by virtual assessment tools.

The AHPD – SUPER-PD Tele-visit Validation sub-study is a single tele-visit occurring in close proximity to in-clinic assessments that will help evaluate the accuracy of tele-visit assessments.

a. Overview of STEADY-PD III (clintrial.gov NCT02168842), Phase 3 Double-blind Placebo-controlled Parallel Group Study of Isradipine as a Disease Modifying Agent in Participants with Early Parkinson Disease. The study is based on preclinical studies that demonstrated a neuroprotective effect of isradipine via antagonism of calcium channels (28), as well as a number of epidemiological studies suggesting reduced incidence of PD in users of calcium channel antagonist antihypertensive agents (29-33). The Phase 3 study was also supported by our open-label and Phase 2 multicenter safety, tolerability and dose selection studies (34,35). The primary hypothesis of the study is that patients with early PD treated with isradipine IR will have slower progression of PD disability as determined by the change in the total UPDRS (36) score between baseline and 36 months in 336 participants with early PD not yet requiring dopaminergic therapy (DT). The STEADY-PD III study design and methodology have been published (37).

b. Overview of SURE-PD3 (**clintrial.gov NCT02642393**), A Randomized, Double-blind, Placebo-controlled Trial of Urate-elevating Inosine Treatment to Slow Clinical Decline in Early PD.

The primary objective of SURE-PD3 is to determine whether the urate precursor inosine dosed to moderately elevate serum urate over 2 years slows clinical decline in early PD. Urate elevation is targeted based on preclinical evidence of its neuroprotective antioxidant properties, together with epidemiological and clinical biomarker studies showing that higher levels of urate predict a reduced risk of PD and a slower rate

of progression. Our phase 2 trial demonstrated our ability to produce long-term CSF and serum urate elevation with adequate safety and tolerability (38). SURE-PD3 has been conducted at ~60 US PSG clinical sites.

Unique features of SURE-PD3 include its enrichment for participants with lower serum urate (predictive of faster clinical decline) and its exclusion of subjects without a striatal dopamine transporter (DAT) deficit demonstrated on a screening DAT scan, which can increase the likelihood of an accurate diagnosis of PD, in early, untreated disease. SURE-PD3, like STEADY-PD III, includes a biomarker sub-study with blood collected for DNA (e.g., for whole genome sequencing) and serial plasma sample storage. In addition, a follow-up DAT scan will be conducted in SURE-PD3 to estimate rates of striatal DAT binding site loss over one to two years as a neuroimaging biomarker of PD progression.

c. Overview of SUPER-PD

SUPER-PD is a 24-month single-center observational study to develop and validate novel PD measures using sensor-based technologies. The study is enrolling individuals with PD and controls in order to evaluate ability of various technologies to differentiate those with PD from those without, to detect disease progression, to assess response to current medications, and to produce novel insights into PD that cannot currently be ascertained from in-clinic measurements.

1.2 Tele-visit and Smartphone Experience

Preliminary data

1. **REACT-PD,** a recent observational study of 40 individuals concurrently enrolled in STEADY-PD III, aimed to establish the feasibility, reliability, and value of web-based tele-visits in the conduct of a clinical trial in PD. Participants were scheduled for a tele-visit within 2-4 weeks of a corresponding in-person STEADY-PD III visit over 12 months, with visit frequency dependent on the participant's STEADY-PD III visit schedule. All clinical trial assessments performed at the preceding in-person visit were performed remotely during the tele-visit, including motor assessments, non-motor assessments, and orthostatic vital signs. Visits were performed on smartphones that were provided to participants.

Study results:

1) **Feasibility**:

Preliminary data suggests that tele-visits are feasible. The study started recruitment in April 2016 and successfully completed recruitment of 40 participants within ~4 months. 38/40 participants

completed all three tele-visits and 84% of tele-visits were completed within window.

2) **Reliability**:

There was excellent correlation between in-person visits and tele-visits for non-motor outcome measures. Intra-class correlation (ICC) coefficients for the Montreal Cognitive Assessment (MoCA), MDS-UPDRS 1A, MDS-UPDRS 1B, and MDS-UPDRS II were 0.78, 0.83, 0.88, and 0.90 respectively. There was good correlation for the MDS-UPDRS Part III (ICC 0.53).

3) **Value:**

Participant satisfaction has been positive with >90% of participants being satisfied or very satisfied with the convenience, connection, and comfort of the tele-visit. More than 75% of participants agreed or strongly agreed that they would be more interested in participating in future clinical trials if some visits could be conducted virtually.

Final longitudinal analysis will be completed once STEADY-PD III database is locked

2. Smart*4*SURE is an ongoing remote observational study embedding technology from mPower into the SURE-PD3 trial. Designed as a feasibility study, the primary aim is to determine the ability to track disease progression using remote assessment via a smartphone. Smart*4*SURE longitudinally collects measures of parkinsonian motor (speeded tapping, phonation, gait, balance, and resting/postural/action tremor) and non-motor (short-term memory) deficits via scheduled activity tasks and of PROs via periodic surveys. The sub-study and planned analyses are described in the SURE-PD3 protocol.

3. Readiness of both cohorts to transition to a virtual extension study and centralized coordination

Both cohorts are prepared to efficiently transition to long term remote participant's ascertainment and have necessary ethical and logistical provisions in place: 1) both studies have a consent clause asking for permission to be contacted for future research, which may be obtained by a centralized coordination center; 2) both studies have agreed with the NINDS to use DMR to upload clinical datasets: 3) both studies are currently putting provisions in place to generate global unique identifiers (GUID) to link participants in study datasets; 4) both studies have met with all involved stakeholders to create a flow diagram and timeline for data and sample transfers; 5) both studies are conducted under the auspices of the Parkinson Study Group (PSG) and as such function under common PSG by-laws ensuring uniform governance and publication policy; and 6) both studies use the CTCC data coordination center, streamlining the current database development and transition plan. CTCC will be responsible for the project and data management of AT-HOME PD.

a. Readiness to recruit a new sub-study cohort

The study team is well-positioned to efficiently recruit participants from SUPER-PD, which has the following necessary ethical and logistical provisions in place: 1) the study has a consent clause asking for permission to be contacted for future research; 2) the study currently generates global unique identifiers (GUID) to link participants in study datasets; 3) the study team is currently working on creating a flow diagram and timeline for data and sample transfers; and 4) the study uses the same data management system as AHPD (REDCap), streamlining new database development and transition planning. CTCC will be responsible for the project and data management of the AHPD – SUPER-PD Tele-visit Validation sub-study.

2. STUDY OBJECTIVE

2.1 Specific Aims:

1. To establish and implement an infrastructure for longitudinal remote follow-up of phase 3 trial cohorts:

a. Transition from site-based to a centralized site and coordination center to manage all participant activity in virtual extensions of STEADY-PD III and SURE-PD3, with projected enrollment of ≥70% of final trial cohorts, and core data collection in accordance with Parkinson's Disease Biomarkers Program (PDBP) schedule of activities.
b. Conduct an annual research visit (tele-visit) program and establish the feasibility and cross-sectional reliability of tele-visit versus in-person visit assessments in a subset of SURE-PD3 and SUPER-PD participants.
c. Deploy a smartphone application, based on the mPower study, for remote data collection in a clinical trial cohort as preliminarily characterized in the Smart*4*SURE sub-study of SURE-PD3.
d. Establish a mechanism for linking STEADY-PD III and SURE-PD3 study data with study data collected through smartphone-based assessments, tele-visits, and Fox Insight (FI), a separate longitudinal patient-reported outcomes (PROs) online research study.

2. To compare patient-driven (smartphone, web-based surveys) vs clinician-driven (tele-visit) outcomes by:

a. Correlating the smartphone and tele-visit platforms' component and composite features, and their changes over years.
b. Comparing the smartphone and tele-visit platforms' abilities to: i) measure PD progression and predict clinical events and changes in PROs; ii) distinguish rapid vs slow progressors based on baseline Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, dopamine transporter (DAT) deficit (in SURE PD-3) or serum urate levels (in STEADY-PD III); iii) demonstrate persistence of any effects of isradipine or inosine in their respective trials.
c. Comparing completion status and performance on FI and tele-visit participant-reported outcome measures.

3. **To explore novel smartphone-based real-life mobility biomarkers of PD disability and its progression** that are normally inaccessible with traditional office measures. We will investigate the ability of passively collected smartphone data on ambulation and location to enable assessments of physical activity and socialization that correlate with motor and non-motor functions.

3. STUDY DESIGN

3.1 Overview

In this 24-month observational study, we will enroll STEADY-PD III and SURE-PD3 participants in order to prospectively and remotely characterize long-term clinical outcomes through the use of tele-visits, smartphone assessments, and web-based surveys. The overall study design is conceptualized below in Figure1.

As schematized in Figure 1, our objectives will be pursued by first developing a study infrastructure, which will establish tele-visit and smartphone assessment platforms while sequentially transitioning the parent study cohorts from site-based to centralized coordination. The data collected over 2 years of serial (annual) tele-visits and (quarterly clusters of) smartphone assessments of the combined cohort will be characterized and compared to gauge their clinicometric properties and relative potential for monitoring clinical progression in future PD studies. Lastly, data collected passively (with participant permission) from the smartphone sensors will be explored as a novel strategy for mobility and socialization correlates of PD progression.

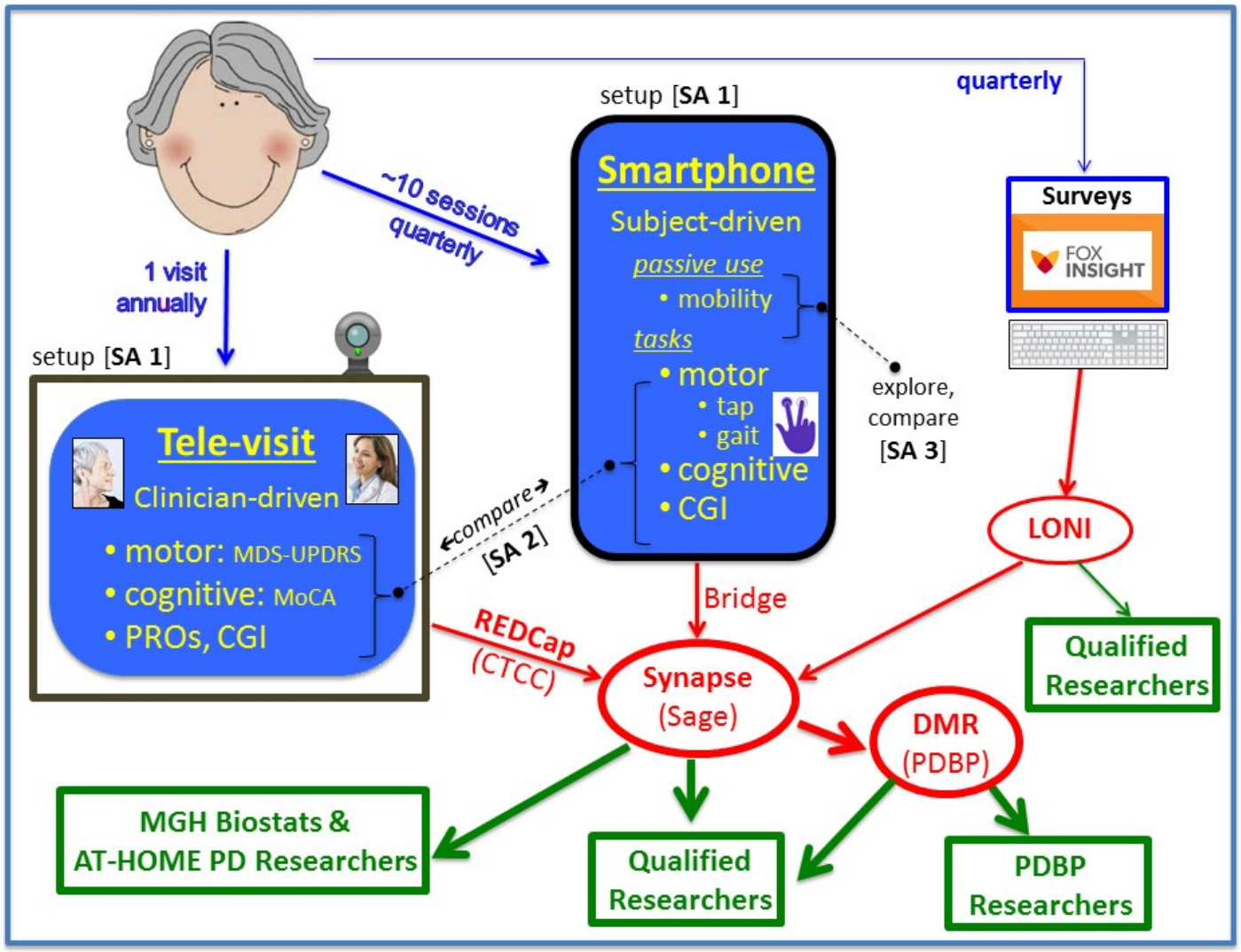


Figure 1. Aims of the AT-HOME PD study in context of data flow.
Each participant (depicted upper left) will contribute data (blue arrow) in annual tele-visits and may contribute data in more frequent smartphone sessions and FI sessions. Cleaned data are transferred (red arrow) and aggregated in Synapse and then the DMR for distribution (green arrow) to the Biostats Core and the broader research community.

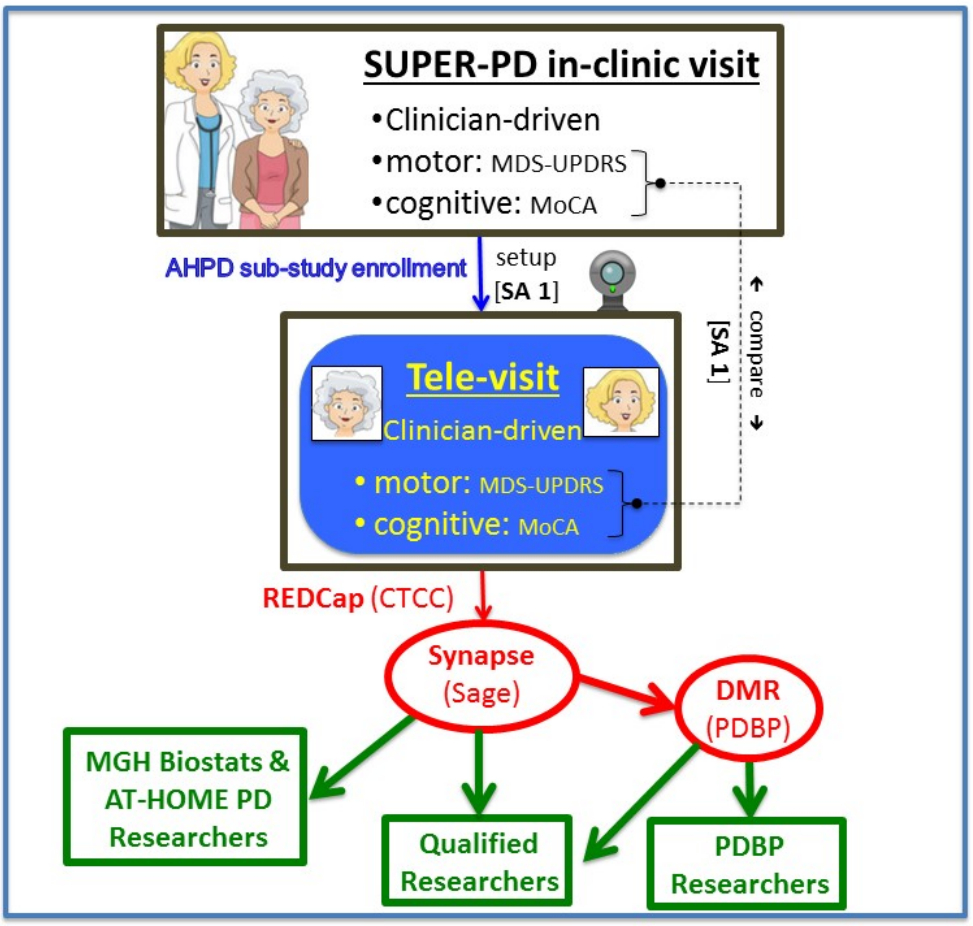


Figure 1a. Aims of the AHPD – SUPER-PD Tele-visit Validation sub-study in context of data flow.
Each SUPER-PD participant (depicted top), once enrolled in AHPD sub-study, will contribute data (blue arrow) in one tele-visit. Cleaned data are transferred (red arrow) and aggregated in Synapse and then the DMR for distribution (green arrow) to the Biostats Core and the broader research community.

Study Platforms

• **Tele-visit platform** – Participants will participate (from home or other preferred private environment) in three approximately one hour-long tele-visits using a web-based video platform with accessibility on any internet-enabled device. The first tele-visit will occur shortly after screening and then annually for two subsequent visits. Each visit will include a series of PROs, which will be completed by the participant in REDCap, a cognitive test (MoCA), and clinician-conducted assessments including a modified MDS-UPDRS part 3, SEADL and CGI; see SOA.

• **FI web-based survey platform** – AT-HOME PD participants will be asked to complete a set of standard questionnaires every 3 months through a companion study called Fox Insight (FI). This online observational study, sponsored by The Michael J. Fox Foundation (MJFF), seeks to better understand experiences of daily living (EDL) in PD and how they change with disease progression. Over 22,000 FI participants have enrolled to complete web-based surveys (on a quarterly basis for up to 5 years) (https://foxinsight.michaeljfox.org). The PRO data collected via FI are largely complementary and more extensive than those collected through the smartphone and tele-visit components, allowing for a comparison of motor and cognitive tasks. The modest overlap between a few surveys (e.g., MDS-UPDRS part 2 on EDL) is by design as comparison of these results will allow assessment of whether state-of-art web-based PRO data collection by FI can still be enhanced (with respect to completion rates, variability and predictive power) by investigator oversight, even if provided remotely via tele-visits. FI data, linked to a participant's GUID, will be made available to the research team as well as PDBP and the broader research community through FI's data repository (LONI).

• **Smartphone platform (mPower-based app)** – The mPower application captures sensor data within the context of self-administered activity tasks (motor and cognitive). Processed sensor data is converted into multiple features that are evaluated individually and in aggregate as digital biomarkers for disease severity. Building on experience gained in the mPower and Smart*4*SURE studies, a new application will be deployed to assess motor and cognitive functions sensitive to PD progression (see SOA; Table 2). The mPower 2.0 app is compatible with Android as well as iPhone devices, and has been modified to allow passive collection of gait and mobility data with participant permission (for SA3). The application will include a defined set of tasks; described below under Study Procedures. As per the SOA, participants will be asked to complete a four to six-minute battery of motor tasks daily for at least 10 days and an eight-minute battery of cognitive tasks daily for at least 3 days within a two-week period every quarter. The two-week burst will be considered successful if we are able to collect at least 10 daily activities and can be extended by 5 days if this minimum is not met.

3.1.1 Sub-Study Overview

Individuals with PD from SUPER-PD will complete a single tele-visit within ±14 days of their SUPER-PD baseline or month 12 in-person study visit.

3.2 Discussion of Study Design

a. Rationale for Study

Disease modification is the primary unmet need in PD therapeutics. To aid in achievement of this goal, validated PD biomarkers that improve the efficiency and thereby the results of clinical trials are urgently needed. While discovery of biological signatures of the disease has been a central focus of PD biomarker research, a similarly important priority is the application of novel technologies to provide digital biomarkers of disease progression. Telemedicine and smartphone-based remote sensor assessments represent particularly promising opportunities to streamline study conduct, reduce participant burden, and allow for the collection of data beyond the usual episodic, in-clinic assessments. Demonstrating the utility of these relatively inexpensive accessible platforms for the measurement of PD progression would also establish the infrastructure for long-term follow up of participants after completion of interventional studies.

Long-term observation of participants from STEADY-PD III and SURE-PD3, together comprising ~600 early PD participants, would be invaluable not only in characterizing any persistent or delayed benefits of either treatment but also in the development of tele-health outcomes to facilitate future interventional trials in PD and of neurotherapeutics more broadly.

The objective of this study is to leverage modern technology to develop, pilot and implement a 100% virtual model for long-term follow up utilizing telemedicine and smartphone platforms for quantitative monitoring of clinician- and patient-reported outcomes (PROs).

The objective of the sub-study is to improve our estimates of the accuracy of tele-visit assessments relative to in-clinic assessments.

4. STUDY POPULATION

4.1 Participant Numbers

4.1.1 AT-HOME PD Participants

Approximately 420

All individuals with early idiopathic PD enrolled in the STEADY-PD III (NCT02168842) and SURE-PD3 (NCT02642393) studies (N≈600) who have consented to be contacted for future research will be asked to participate. We expect approximately 70% of them (N≈420) to consent and participate in at least the tele-visit portion of the study. We expect approximately 80% of enrolled individuals (N≈340) to participate in the smartphone portion (and thus the smartphone vs tele-visit comparison) of the study. We expect approximately 70% of participants in the smartphone portion (N≈240) to consent to passive data collection (and thus contribute to Aim 3). We

expect approximately 80% of enrolled individuals (N≈340) to participate in the FI portion of the study.

4.1.2 AHPD – SUPER-PD Tele-visit Validation Sub-study Participants

Approximately 50 individuals with PD enrolled in the University of Rochester's on-going Sensor Use to Monitor Progression and Evaluate Symptoms Remotely in Parkinson's Disease (SUPER-PD) study (N≈160) who have consented to be contacted for future research will be asked to participate. Participants will complete a single tele-visit and will not be asked to participate in the smartphone or Fox Insight portions of the AT-HOME PD study.

4.2 Inclusion Criteria

1. Enrollment in STEADY-PD III or SURE-PD3 studies
2. Prior consent to be contacted by the UR unless a subject from STEADY-PD III or SURE-PD3 studies directly contacts UR to request information about study participation
3. Internet-enabled device that will support participation in tele-visits
4. Have created or willing to create a Global Unique Identifier (GUID)
5. Willing and able to provide informed consent
6. English fluency
7. [For participants opting to participate in the smartphone component] possession of a suitable smartphone (iPhone or Android) with adequate data plan and cellular network access/signal or Wi-Fi access.

Sub-Study Inclusion Criteria

1. Enrollment in SUPER-PD
2. Diagnosis of idiopathic PD (as determined by UK Parkinson's Disease Brain Bank Criteria in SUPER-PD)
3. Have consented to future contact by the University of Rochester
4. Internet-enabled device that will support participation in tele-visits
5. Willing and able to provide informed consent

4.3 Exclusion Criteria

1. Inability to carry out study activities as determined by study staff.

4.4 Discussion of Participant Characteristics

Only individuals who are currently enrolled or completed participation in STEADY-PD III or SURE-PD3 will be eligible for participation in this study. Only individuals currently enrolled in the SUPER-PD study will be eligible for participation in the sub-study. Because of the nature of the study, an internet-enabled device with web-camera capacity or compatibility is necessary to participate. Participants without a camera will be provided with a suitable external camera.

5. STUDY PROCEDURES

5.1 Recruitment

Cohort Recruitment and Retention (SA1)

The study will recruit solely from STEADY-PD III and SURE-PD3. The sub-study will recruit solely from SUPER-PD. All STEADY-PD III and SURE-PD3 participants who have consented to be contacted by the University of Rochester (UR) for future research or independently contacts the UR will have their personal contact information, study-specific unique identifier, CTCC unique identifier, and GUID (where available) entered into a secure HIPAA-compliant database at the UR. These individuals will be contacted by an AT-HOME PD study team member during or following their completion of the parent study. The AT-HOME PD study team member will provide an overview of the study, assess interest, and pre-screen for eligibility. Participants who have not already created a GUID will be required to create a GUID for this study. Recruitment for the sub-study will occur either via telephone or during a SUPER-PD study visit by an AT-HOME PD study team member.

AT-HOME PD study participants from STEADY-PD III cohort:
A majority of STEADY-PD III participants (who consent to being contacted for future research by the UR) will have already completed their STEADY-PD III participation when this study commences and will be approached post-study completion. The remainder will be contacted either while still actively participating or shortly after completion of the study.

AT-HOME PD study participants from SURE-PD3 cohort:
All SURE-PD3 participants will be contacted following completion of their last SURE-PD3 visit in the planned treatment period.

AHPD – SUPER-PD Tele-visit Validation sub-study participants from SUPER-PD:
SUPER-PD participants with PD (who consented to being contacted for future research by the UR) will be contacted during their participation in the SUPER-PD study.

We have developed a proactive plan for recruitment and retention, relying on our experience with the parent studies. The STEADY-PD III and SURE-PD3 parent studies have had excellent retention, with both having enrolled ahead of schedule. We expect recruitment will be facilitated by the PD

research community that has been cultivated in both parent cohorts and by conveying the value of the AT-HOME PD study to which these parent study participants are uniquely able to contribute. We project that approximately 420 participants, or 70% of the original parent cohorts, will enroll in AT-HOME PD. We expect that essentially everyone will have access to an internet-enabled device that will support participation in tele-visits. According to the Pew Research Center, 88% of adults use the internet, including 87% of those aged 50-64 (http://www.pewinternet.org/fact-sheet/internet-broadband/) and 77% of adults own a smartphone, including 74% of those aged 50-64 (http://www.pewinternet.org/fact-sheet/mobile/). Moreover, the study procedures were reviewed by patient advocates and considered feasible.

In addition, although the pre-specified recruitment pool provides minimal opportunity to enhance racial and ethnic diversity of the study, we intend to maximize the proportion of minority participants who enroll by earmarking resources to assist any minority participant currently enrolled in STEADY-PD III or SURE-PD3 who is interested and otherwise eligible to enroll but does not have the requisite technical resources. For these participants the costs of standard internet access and/or a smartphone/data plan (above the reimbursement payment) would be reimbursed. We anticipate enrolling a relatively high proportion of women given their enrichment in SURE-PD3 (due to a screening process that targets people with lower serum urate, and given women, on average, have a substantially lower serum urate than men).

If AT-HOME PD study participants will be considered for any future follow up research their contact information will be obtained from the University of Rochester (UR) secure HIPAA compliant database based on original consent. If the subject declined contact in the original study, the subject will be allowed to contact the UR AHPD study team directly with an interest in study participation.

Considering the low participant burden of remote data collection, an inherent advantage of the outcome measures under investigation, we anticipate a modest dropout rate of ~15% from the tele-visit component over the two-year extension study. In addition, recruitment and retention will be motivated by multiple tested strategies ranging from reasonable reimbursement payments (to be paid in three installments following each tele-visit via check) to regular communication with participants.

Formative research through patient interviews indicates that long-term data collection in a remote setting will only be sustainable with a smartphone application that is specifically designed to meet the needs and interests of the participant population. Based on initial interviews, engagement strategies will focus on altruism, self-exploration, education, and community. These are implemented through the application using news feeds, infographics, participation dashboards, and notifications. Importantly, participants will be provided with the option to view the outcomes of their assessments in a manner that was highly effective at

promoting engagement within mPower but was not feasible during the smartphone sub-study (Smart*4*SURE) of SURE-PD3.

5.2 Process of Consent

Interested and eligible potential participants who possess the necessary technology, as determined by phone pre-screening, will be emailed a direct link to an IRB-approved eConsent document in REDCap. Potential participants will be asked to review this document and indicate their consent electronically if they are willing to participate. As this is a minimal risk study and electronic signature is not recognized by the Research Subjects Review Board (RSRB) and the Office of Research and Project Administration (ORPA), a waiver of documentation of informed consent will be requested. As part of the eConsent document, potential participants will be provided with the contact information for a study team member in the event that they have study-related questions. If there is no response to the emailed eConsent link, the participant will be sent follow-up reminder(s).

In order to ensure that passive data collection does not have a major negative impact on overall enrollment, participants will be asked to opt into passive data collection as an optional sub-study in the mPower application.

The participant's screening visit will be scheduled during their prescreen phone call with an AT-HOME PD team member. If requested during the initial contact, an AHPD study team member will email the current UR IRB approved informed consent form to the participant and schedule a follow-up phone call to complete the prescreening visit and/or schedule the participant's screening visit. At the screening visit, via video conference (VC), which is described in detail below, a study team member trained in human participant's protection in accordance with UR IRB procedures will verify that the participant understands why the study is being done, what will happen during the study, possible risks and benefits, how personal information will be protected, and what to do if there is a problem or question. The study team will ensure that prospective participants have sufficient knowledge and understanding of the details of the study to allow them to make an informed decision whether or not to participate. Prospective participants will be provided with an opportunity to ask questions. The study team member will verify the identity of the participant (via photo ID or by asking verification questions) and electronically record in REDCap that informed consent has been confirmed.

5.3 Schedule of Activities

See Schedule of Activities (SOA) for AT-HOME PD study and sub-study activities.

5.4 Participant Identification Numbers (ID) Number

For all prospective participants with whom the study team has been able to establish contact, the study team will create a new record in REDCap assigning the potential participant a prescreening unique participant identifier. This record will be used to complete the pre-screening process and eConsent process. If the participant appears eligible on the basis of pre-screening questions and provides eConsent, the study team will create a new record in REDCap assigning the potential participant their Global Unique Identifier (GUID) as their unique ID.

Within REDCap, the participant's contact information will be stored for UR staff to email the assessments and surveys to be completed by the participants before and after their tele-visits. This contact information will remain within REDCap database and will NOT be transferred. Once the GUID is assigned, the GUID will be the only identifier used.

a. Global Unique Identifier (GUID)

Participants may have already been assigned a Global Unique Identifier (GUID) as part of their participation in STEADY-PD III or SURE-PD3. For those participants who have not already created a GUID, a study team member will create a GUID for them. Sub-study participants will have already been assigned a GUID as part of their participation in SUPER-PD.

The GUID is a universal participant ID that enables researchers to share and track participant data across multiple studies without exposing any personally identifiable information. The GUID Tool uses multiple pieces of personal information (first name at birth, presence of middle name, middle name, last name at birth, data of birth, city of birth, country of birth, and sex at birth) to generate a unique 10 (14 if created manually)-character ID.

5.5 Study Visits

a. Pre-Screening Call

The Pre-Screening Call will be conducted via telephone by an AT-HOME PD team member. For SURE-PD3 participants it should generally occur within approximately 90 days after the participant's last SURE-PD3 visit in the planned treatment period. It is expected to take approximately 10-15 minutes to complete.

The following activities will be completed:

- Overview of the study and assessment of interest

If the individual is interested in participating:

- Pre-screen questionnaire for eligibility
- eConsent (link to REDCap emailed)
- Technology survey (automatically follows eConsent in REDCap)

b. Screening Visit (within 30 days following eConsent)

The Screening Visit will be conducted remotely using a web-based video platform (VC). For SURE-PD3 participants it should occur after the final SURE-PD3 visit in the planned treatment period. It is expected to take approximately 30 minutes to complete.

The following activities will be completed:

- Verify consent (see 5.2 Process of Consent)
- Verify participant's identity (photo ID or answering verification questions)
- Verify eligibility (see below)
- Demographics
- Test connection
- Creation of FI Account (see below)
- Creation of GUID (if not already created)
- Simplybook.me orientation

Eligibility Verification:
The study team member will verify eligibility. All of the inclusion criteria and none of the exclusion criteria must be met unless a study PI or designee provides a waiver for certain criteria. More detail regarding this process and instructions for the requirements for waivers can be found in the Operations Manual.

Eligibility Identification:
The study team member will verify the participant's identity at the time of eConsenting. The study participant will be asked to verify their identity by showing the study team member their photo ID. The identity verification will be done by only viewing the ID during the tele-visit and this information will not be collected. If a photo ID is not available, every effort will be made to verify the participant's identify by asking the questions below:

i. ask the participant to repeat their name
ii. ask the participant to state their year of birth
iii. ask the participant to provide their address of record

If for any unforeseen reason the study team member is unable to verify the identity of the participant by photo ID or verification questions, the study team member will document the reason and continue with completing the eConsenting process and enrolling the eligible participant in to the study. This will ensure that the study is able to meet the recruitment numbers (from a limited patient population), as well as ensure that the study is able to enroll all - otherwise eligible - participants.

FI Account Creation:
A study team member will create a FI account for the participant using email address and GUID. If the participant is already enrolled in FI, the participant will receive an email notifying them that their FI profile has

been linked to the AT-HOME PD study. If the participant is not already enrolled in FI, he/she will receive an email from FI with instructions regarding how to verify their new account. Once this has been done, the participant will be prompted to complete the registration and consent process for FI.

SimplyBook.me Orientation:
A study team member will introduce the participant to the SimplyBook.me HIPAA-compliant scheduling software, which will be used to schedule tele-visits and send tele-visit reminders. The participant will be asked to choose whether they would like to schedule tele-visits in the morning or afternoon and all tele-visits will be scheduled according to their preference. Follow-up tele-visits will preferentially be scheduled with the same provider, unless that is logistically impossible (due to staffing schedules or the like). In order to reduce variability related to diurnal fluctuation, participants should select the same time window (morning or afternoon) for performance of smartphone tasks.

c. Tele-Visits (Baseline (Day 0; within 60 days of Screening/VC), Month 12 (+/- 28 days), Month 24 (+/- 28 days)

STEADY-PD III
STEADY-PD III participants will undergo visits per the SOA. The baseline tele-visit will occur within 0-60 days of the screening visit.

SURE-PD3
All SURE-PD3 participants who have not yet (or have recently) completed their participation in SURE-PD3 should have their baseline tele-visit after their final in-person study visit (or equivalent) in the planned treatment period. Ideally, this baseline tele-visit will occur within 28 days of the final in-person study visit (or equivalent) in the planned wash-out period to allow validation of tele-visit data acquisition versus that of the standard in-office visits. The baseline visit will occur within 0-60 days of the screening visit.

- All of the tele-visits will be conducted remotely using a web-based video platform and are expected to take approximately 60-90 minutes to complete.
- All of the tele-visits will consistently be attempted to be conducted in either the morning or the afternoon, according to participant preference, to reduce the effect of diurnal symptom variation. For participants on symptomatic dopaminergic therapy, the Movement Disorder Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS) part 3 will be obtained in the usual ON state. The timing of last dopaminergic medication intake will be recorded.
- A +/- 28-day window (from baseline TV) will be used for the Month 12 and Month 24 visits, however, visits should ideally be scheduled such that they are conducted during the corresponding 14-day smartphone session.

Pre-tele-visit – Up to one week prior to each visit, participants will be emailed the direct links to the following REDCap surveys, which will need to be completed before the tele-visit.

- MDS-UPDRS parts 1b and 2.
- Self-Reported Fall Questionnaire
- Patient Global Impression (PGI)-Severity. PGI-Change will be completed during month 12 and month 24 visits only.

The following assessments will be completed during the tele-visit:

- Review Reportable Events
- Review Concomitant Medications
- MDS-UPDRS parts 1a, 3 and 4 (where applicable). Part 4 will only be completed for individuals who are receiving dopaminergic therapy.
- Montreal Cognitive Assessment (MoCA)
- Modified Schwab & England Activities of Daily Living Scale (SEADL)
- Clinical Global Impression (CGI)-Severity. CGI-Change will be completed during month 12 and month 24 visits only.
- Determination of Falls
- Confirmation of participant completion of MDS-UPDRS parts 1b and 2, self-reported falls assessment, and PGI-severity and change
- Review of participant compliance with smartphone tasks and FI patient-reported outcome measures where applicable
- Where applicable, smartphone application registration will occur shortly prior to the baseline visit and orientation will occur during the baseline tele-visit (see below).
- Completion of a complete set of smartphone active motor and cognitive tasks (where applicable)

Post-tele-visit

- Participant Preference and Burden Survey. Following completion of the visit, participants will be emailed a direct link to REDCap to complete this survey.

Smartphone Application Registration:
The study team member will initiate the registration process by inputting the participant's GUID, smartphone number and visit date into Sage Bionetworks Synapse web portal a couple of days before the participants orientation visit. This will create a mPower account for the participants in the Sage Bionetworks Bridge service. During the baseline tele-visit the study team member will help the participants to download and install the application. After installation, the study team member will review proper performance of each task and direct the participant towards helpful resources in the event that they have any further questions about the

tasks. A study team member will remotely supervise the participant while he/she completes a complete set of smartphone tasks.

d. Smartphone Sessions (Baseline, Month 3, 6, 9, 12, 15, 18, 21, 24)

- 14-day smartphone sessions will occur on a quarterly basis.
- Given diurnal variation in active task performance, participants will be asked to select morning or afternoon as their preferred window for completion and to consistently attempt to complete the active tasks according to their selected preference.
- Participants will be notified one day before the start of each 14-day session

During these 14-day sessions, participants will be asked to complete daily 4 to 6-minute smartphone-based motor tasks. If they fall behind and are not able to complete at least 10 daily activity sets they can optionally continue for up to 5 additional days.

The following motor activities will be completed by the participant:

- Gait Task
- Finger Tapping Task
- Resting Tremor Task
- Balance task

During these 14-day sessions, participants will be asked to complete an approximately 8-minute set of smartphone-based cognitive assessments on at least 3 of the days.

The following activities will be completed by the participant:

- Digit Span
- Digit Symbol Substitution Tests
- Spatial Working Memory

Participants will be asked to provide basic demographic information through the application once. Participants will also use the application to track their medication adherence relative to tasks and, optionally, self-reported symptoms and triggers. Additionally, participants may perform the active tasks at any time outside of the 14-day smartphone sessions if desired.

Compliance will be actively monitored.

- Participants will receive reminders if they do not perform the activities for two consecutive days and/or after not performing the activities for four days of the 14-day session.
- Participants who enable notifications will receive daily notifications during each 14-day session
- Sage Bionetworks will make quarterly reports available to CHeT/CTCC that will include each participant's compliance status.

e. FI Sessions (Baseline, Month 3, 6, 9, 12, 15, 21, 24)

- AT-HOME PD participants will be asked to complete a set of standard questionnaires through a companion study called FI, (https://foxinsight.michaeljfox.org).
- Participants will be asked to complete the questionnaires in the SOA every 90 days. [Refer to SOA] The baseline visit takes approximately one hour to complete; subsequent visits take only 10-15 minutes to complete.

- Participants will have a 90-day window in which to complete the questionnaires. However, they will be encouraged to complete the Baseline, Month 12, and Month 24 FI questionnaires within 28 days of the corresponding tele-visit.

Compliance will be actively monitored.

- Those participants that fail to complete all of the assessments will be sent an email reminder by FI after approximately 45 days.
- FI will send another email reminder after approximately 88 days if all of the assessments still have not been completed.
- FI will send quarterly reports to CHeT/CTCC that will include each participant's compliance status. This will continue until a publicly-accessible FI research database is available through LONI.

f. Premature Withdrawal Visit

Premature withdrawal will be defined as withdrawal from the tele-visit component (or the full study) prior to completion of the month 24 tele-visit. Participants have the right to withdraw from the study, or any individual component of the study, at any time without prejudice. Although not anticipated, an investigator may withdraw a participant from the study if participation places the participant at undue risk or if the participant dies or experiences another reportable event that precludes further study participation. In all other circumstances, all participants should be retained in the study regardless of compliance to limit bias from informative drop-out.

In the event of premature withdrawal from the study, the Premature Withdrawal (PW) Visit procedures and evaluations should be completed whenever possible whether or not the withdrawal is determined at a regularly scheduled study visit or at an unscheduled visit.

Reasons for withdrawal of the participant prior to completion of the study must be stated in the eCRF for all study participants who were enrolled in the study.

The premature withdrawal tele-visit is expected to take approximately 60 minutes to complete.

Pre-tele-visit – up to one week prior to each visit, participants will be emailed the direct links to the following REDCap surveys, which will need to be completed before the tele-visit.

- MDS-UPDRS parts 1b and 2.
- Self-Reported Fall Questionnaire
- Patient Global Impression (PGI)-Severity. PGI-Change will be completed during month 12 and month 24 visits only.

The following assessments will be completed during the tele-visit:

- Review Reportable Events
- Review Concomitant Medications
- MDS-UPDRS parts 1a, 3 and 4 (where applicable). Part 4 will only be completed for individuals who are receiving dopaminergic therapy.
- Montreal Cognitive Assessment (MoCA)
- Modified Schwab & England Activities of Daily Living Scale (SEADL)
- Clinical Global Impression (CGI)-Severity. CGI-Change will be completed during month 12 and month 24 visits only.
- Determination of Falls
- Confirmation of participant completion of MDS-UPDRS parts 1b and 2, self-reported falls assessment, and PGI-severity and change
- Review of participant compliance with smartphone tasks and FI patient-reported outcome measures where applicable
- Smartphone application registration and orientation, where applicable, will occur during the baseline tele-visit (see below).
- Completion of a complete set of smartphone active motor and cognitive tasks (where applicable)
- Early termination survey

Post tele-visit

- Participant Preference and Burden Survey. Following completion of the visit, participants will be emailed a direct link to REDCap to complete this survey.

g. Passive Data Collection

For participants that optionally consent to passive data collection, the smartphone application will collect multiple streams of passive data: movement patterns captured by location services (including GPS) and motor activity patterns captured by accelerometers and gyroscopes. To reduce issues relating to patient privacy concerns, movement patterns will be collected using displacement vectors without storing actual GPS coordinates. To reduce burden relating to use of data plans for data transfer, the application will transfer data on a daily basis and preferably using a Wi-Fi connection. In order to ensure that monitoring is naturalistic, participants will not be given any instructions regarding how or when to carry their smartphone.

5.5.1 Sub-study Study Visits

a. Pre-Screen

The Pre-Screen will be conducted via telephone or during a potential participant's SUPER-PD study visit by an AT-HOME PD team member. It is expected to take approximately 10-15 minutes to complete.

The following activities will be completed:

- Overview of the study and assessment of interest

If the individual is interested in participating:

- Pre-screen questionnaire for eligibility
- eConsent (link to REDCap emailed)

b. Tele-Visit (within 14 days of SUPER-PD baseline or month 12 study visit)

- The tele-visit will be conducted remotely using a web-based video platform and is expected to take approximately 30 minutes to complete.
- For participants on symptomatic dopaminergic therapy, the Movement Disorder Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS) part 3 will be obtained in the usual ON state. The timing of last dopaminergic medication intake will be recorded.

The following assessments will be completed during the tele-visit:

- Verify eligibility and eConsent
- MDS-UPDRS part 3
- Montreal Cognitive Assessment (MoCA)
- Reportable Events

6. ASSESSMENTS

6.1 Primary Assessments

a. Pre-Screening Questionnaire

The pre-screening questionnaire includes questions regarding access to an internet-enabled device that will support participation in tele-visits, possession of a web-camera, and possession of a suitable smartphone.

b. Technology Survey

Survey questions were originally adapted from the Pew Internet & American Life Project Question database. The survey includes questions regarding access and use of specific technology and prior experience with tele-visits.

c. Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS)

The MDS-UPDRS will be conducted per the Schedule of Activities. The MDS-UPDRS was designed by movement disorders experts to address weaknesses of the original UPDRS (e.g., by adding questions on constipation and sialorrhea) while preserving its overall format. The MDS-UPDRS has four parts:

- **Part I (non-motor experiences of daily living)**, comprising
  - Part Ia concerning behaviors that are assessed by the CHeT Site Investigator with all pertinent information from patients and caregivers
  - Part Ib that is completed by the patient with or without the aid of the caregiver, but independently of the Investigator.
- **Part II (motor experiences of daily living)**, designed to be a self-administered questionnaire like Part Ib, but similarly can be reviewed by the study team to ensure completeness and clarity.
- **Part III (motor examination)** has instructions for the rater to give or demonstrate to the patient; it is completed by the clinician rater. Given the remote nature of our evaluations, we will administer a modified version of part III that does not include assessment of rigidity or postural instability.
- **Part IV (motor complications)** with instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater. **Complete Part IV only if ST has been initiated.**

Participants will self-administer Parts Ib and II, through completion of REDCap surveys, but the study team member will review responses for completion and ask the participant to complete it during the tele-visit if incomplete. Use of MDS-UPDRS is responsive to core instrument recommendations for the Quality of Life subdomain of the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) for PD, and to the Food and Drug Administration (FDA) guidance encouraging use of PROs as a substantial portion of the responses are patient-reported. The investigators are neurologists or board-certified nurse practitioners who have received formal MDS-UPDRS certification (by the MDS) and will have additionally undergone joint training to reconcile scoring differences and minimize inter-rater variability.

Ideally, the same Site Investigator should assess all participants on parts Ia, III, and IV (when applicable) of the MDS-UPDRS at all study visits.

D. Montreal Cognitive Assessment (MoCA)

In early PD, when cognitive deficits occur, they are subtle and mild, and the participants usually perform in the normal range of the widely used Mini-Mental State Exam (MMSE). The MoCA is a rapid screening instrument like the MMSE but was developed to be more sensitive to patients presenting mild cognitive complaints. It is designated an NINDS CDE for PD. The MoCA assesses short-term and working memory, visual-spatial abilities, executive function, attention, concentration, language and orientation. As completion of the MoCA requires performance of some tasks on paper, the participant will be sent a copy of the relevant portions of the MoCA (trail-making, cube copying) prior to the tele-visit. Ideally, this will be sent in a sealed envelope and the participant will be asked to open the envelope only during their tele-visit. However, it may alternatively be sent via email with instructions to print immediately prior to the tele-visit. During the tele-visit, the participant will be instructed on how to complete these tasks and will be asked to display their responses such that they can be visualized and evaluated by the study team member. The total score ranges from 0 to 30 (highest function).

E. Modified Schwab and England Activities of Daily Living Scale (SEADL)

The SEADL is an Investigator and participant assessment of the participant's level of independence. The participant will be scored on a percentage scale reflective of his/her ability to perform acts of daily living. Printed scores with associated descriptors range from 100% to 0% in increments of 10%, where 100% is "participant has full ability and is completely independent; essentially normal" and 0% is "vegetative functions such as swallowing, bladder and bowel functions are not functioning; bedridden". Scores should be coded in increments of 10, (i.e. 090, 080, 070). This assessment will be completed jointly by the participant and Investigator.

F. Clinical Global Impression and Patient Global Impression Scales (CGI)

The CGI is an observer-rated scale that measures illness severity (CGIS) and global improvement of change (CGIC). Each component of the CGI is rated separately; the instrument does not yield a global score.

The CGIS is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the

most severely ill patients). CGIC scores range from 1 (very much improved) to 7 (very much worse).

Similarly, the PGI is a patient-rated scale that measures illness severity (PGIS) and global improvement of change (PGIC).

g. Falls Assessment

Falls will be assessed using two questionnaires, which have been incorporated into an on-going large prospective study (PPMI). The self-reported falls assessment is a 1-item questionnaire that will be completed by the participant. The determination of falls assessment, which will be completed by the investigator, includes questions about freezing of gait and falls over two time periods (the past week and the past 12 months).

6.2 Smartphone Assessments

The following motor activities will be completed by the participant:

- Gait Task - A 30 second walking task where the participant will walk with their phone in their pocket to measure gait using the phone accelerometer and gyroscope.
- Finger Tapping Task - A 30 second speeded tapping task in each hand where screen presses are captured.
- Resting Tremor Task - A 30 second task in each hand where the participants hold the phone with their hand in their lap while the phone records accelerometer and gyroscope readings.
- Balance task - A standing task where the participant tries to stand still while the phone measures accelerometer and gyroscope readings.

The participant will be asked to complete cognitive tasks, which may include the following:

- Digit Span - A short term memory test in which the participant reports back a series of numbers that were displayed rapidly to them.
- Digit Symbol Substitution Tests - A neuropsychological test sensitive to brain damage, dementia, age and depression. It consists of (e.g. nine) digit-symbol pairs followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible.
- Spatial Working Memory - A neuropsychological test that tests memory and manipulation visuospatial information.

6.3 Fox Insight (FI) Assessments

FI is a separate online research study with a separate consent process. As such, the assessments will not be described in detail. The following validated assessments are included in FI:

- The Parkinson's Disease Questionnaire, short-form 8 item version (PDQ-8)
- MDS-UPDRS part 2
- Physical Activity Scale for the Elderly (PASE)
- Your Cognition and Daily Activities (PDAQ-15)
- Euroqol Five (EQ-5D)
- Non-motor symptoms questionnaire (NMS-QUEST)
- Geriatric Depression Scale, short form (GDS)
- Parkinson's disease-Patient Reported Outcomes of Problems (PD-PROP)

The complete list of assessments can be found in the SOA. Participants are also invited to complete additional PRO surveys about, but not limited to, symptoms, disease progression, quality of life, patient preference and general health.

6.4 Safety Assessments (see Section 9 Reportable Events)

As this is a minimal risk observational study that does not involve a drug or device intervention, adverse events are not anticipated and will not be assessed. Safety assessments will be limited to the collection of reportable events either spontaneously offered by the participant or observed by a study team member during a tele-visit.

6.5 Assessment of Participant Compliance

At each tele-visit, the Investigator and/or study team member will assess the participant's compliance with the study requirements. This will include checks of protocol compliance, including completion of surveys for tele-visits, smartphone tasks (where applicable), and FI survey completion (where applicable). More detail regarding the monitoring of compliance can be found in Section 5.5.

While we will strive to retain all participants, we will consider successful participants to be those who complete at least six of nine smartphone-based test batteries over 24 months- including two of the three sets that coincide with the tele-visits.

7. COSTS TO THE SUBJECT

There is no direct cost to the participants to participate in this study. If they participate in the smartphone component of this study, data collected through the app may count against their existing mobile data plan. The internet connection can be configured within the app to only use Wi-Fi connections to limit the impact running this app has on the data costs. Subjects will not have to pay for research procedures.

8. PAYMENT FOR PARTICIPATION

Participants will be compensated $50 for each tele-visit completed, as applicable (baseline, month 12 and month 24) for a total of up to $150 for expenses incurred to participate in the AHPD study via a check. They will not be paid for tele-visits that they do not complete. If a web camera is provided to the participants, they will be allowed to keep it after completion of the study for their own use.

The costs of standard internet access and/or a smartphone/data plan (above the compensation amount) will be reimbursed for minority participants currently enrolled in STEADY-PD III or SURE-PD3 who are interested and otherwise eligible to enroll but do not have the requisite technical resources.

9. RISK/BENEFIT ASSESSMENT

9.1 Potential Risks

The risks of participating in this study are very low.

- The most common risk is discomfort with some of the questions or assessments.
- Some of the questions in the questionnaires may be upsetting or make the participant feel uncomfortable. They may feel frustrated while taking a test used to evaluate the memory or thinking: it is meant to be challenging.
- During the tele-visits the study team will watch the participant walk, and there is a possibility that they could fall.
- Another risk is breach of confidentiality if someone were to access the study information without authorization. Because this study involves collecting personal, identifiable information, there is a potential for invasion of privacy or breach in confidentiality. Accidental release of information to the public may occur due to unintended data breaches. In such an event, that the data may be misused or used for unauthorized purposes.

Smartphone Application

There are a few additional risks to participating in the smartphone assessments:

- Other people may glimpse the study notifications and/or reminders on the smartphone and may become privy to the information that the participant is enrolled in this study. This can make some people feel self-conscious.
- There is a potential for invasion of privacy or breach of confidentiality. The data collected through the mPower app will be encrypted on the smartphone, transferred electronically and stored securely in Synapse. Sage team will separate the participant account information (name, email, contact information, etc.) from the study.
- Sage will not access the personal contacts, other apps, text or email message content, or websites visited.

9.2 Protection Against Risks

- Participants are free to stop a test at any time. Participants can take breaks as needed.
- If they typically walk with an assistive device (such as a cane or walker) or with the help of a caregiver, they will only be asked to walk under their usual conditions. Participants will not be asked to try to walk if they typically use a wheelchair or if they or the investigator has concerns about the risk of falling. If a participant does fall during the visit, or have another medical event during the tele-visit that requires emergent evaluation, the study investigator or a team member will assist in contacting emergency services if needed.
- Every effort will be made to maintain confidentiality and protect personal information obtained as a result of this study.
- Study team will assign a GUID number instead of labeling the information collected from the participant with their name (or medical record number). Study team will use GUID instead of the name on all the study data. Information about the GUID number will be kept in a secure system. Only the study investigators and some technical staff for AHPD, STEADY-PD III or SURE-PD3 studies and some FI clinical operations staff will have the key to link the coded study data to the participant name and account information.
- Study will use a HIPAA compliant, secure video-conferencing system for the tele-visits. Note: real time video conferencing will be used to complete the assessments which will not be recorded.
- The software that will be used for the surveys and to store the information from the tele-visits has been specifically designed to protect the privacy of research subjects and access to the database is restricted.
- Data obtained through Fox Insight questionnaires are stored in a secure databank. Only the Fox Insight study team will have access to this information before any parts that could identify the participants will be removed.
- The study combined data will be stored securely in Sage Bionetworks' databank Synapse (synapse.org), using Amazon-Web Cloud Services.

9.3 Potential Benefits to Subjects

Participants will not benefit directly from being in this research study. Benefits may include contributing to the future research advances and experiencing new ways of tracking and measuring the disease.

9.4 Alternatives to Participation

If the participant elects not to participate in the study, there are no alternatives available.

10. CONCOMITANT MEDICATIONS

10.1 Required Therapy

There is no restriction on medications in this study. All concomitant medications will be recorded.

11. PARTICIPANT WITHDRAWALS/DROPOUTS

Participants will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or sponsor's discretion at any time.

Premature withdrawal will be defined as withdrawal from the tele-visit component (or the full study) prior to completion of the month 24 tele-visit. If a participant who has started the study terminates the study prematurely, every effort should be made to complete the premature withdrawal visit. Reasonable effort should be made to contact any participant lost to follow-up during the course of the study in order to complete study related assessments and retrieve any outstanding data. Participants may be deemed lost to follow-up after 15 months without contact. Contact attempts may include phone calls, emails, and physical mail. Such efforts should be documented in the source documents.

A participant may withdraw or be withdrawn from the study for the following reasons:

- Administrative

    1. Withdrawal of consent
    2. Participant deemed lost to follow-up
    3. Premature withdrawal of study

- Medical Events

    1. Death
    2. Other reportable event that precludes further study participation

Participant premature withdrawal should be reported to the CTCC Project Manager within 5 business days of site's knowledge of the event.
The Demographic form must be completed for all study participants who provide informed consent. This includes participants who completed the study or withdrew/were withdrawn from the study or were screened and provided consent but did not start the study.

The Conclusion of Study Participation form should be completed for all participants who have been enrolled. If a participant withdraws due to a reportable event, the site must ensure that the event is captured on the reportable event form.

12. REPORTABLE EVENTS

Based on the nature of the study, routine adverse events will not be collected. In this study, the following pre-specified events that are thought to be relevant to the safety and feasibility of the study population will be considered Reportable Events (RE). REs will be assessed at the tele-visits and reported on the RE log within 72 hours of the event, or the CHeT Site Investigator's knowledge of the event.

- Compromise of confidentiality
- Loss of competence to consent
- Withdrawal from the study
- Severe depression and suicidal ideation
- Suicide attempt
- Hospitalization for serious (non-elective) medical issues (including childbirth)
- Any psychiatric hospitalization
- Participant intends to or has participated in another research study involving experimental interventions
- Any neurologic event (e.g., TBI, Seizure, etc.)
- Identification of a safety concern warranting referral for medical evaluation
- Identification of a safety concern warranting referral for psychiatric evaluation
- Death

Although not a reportable event the enactment of the Medical Safety Escalation Plan should be reported to the CTCC PM

Enactment of the Medical Safety Escalation Plan (see section 9.2)

12.1 Recording of Reportable Events

At each tele-visit the study team member will assess REs by recording all voluntary complaints of the participant and by assessment of clinical features.

All REs, whether observed by the Investigator or volunteered by the participant, should be recorded on the eCRF RE Log. This will include the type and description of the event, the date of onset, investigator opinion of relatedness to study participation, and any action taken.
This recording will commence with the institution of protocol-specific procedures and continue until either withdrawal or study completion.

The CHeT Site Investigator will comply with the UR Institutional Review Board (IRB) regulations regarding the reporting of reportable events.

12.2 Emergency Actions

A Medical Safety Escalation Plan has been created for urgent and non-urgent medical situations (see Operations Manual). The purpose of the Medical Safety Escalation Plan is to responsibly manage complex or acutely escalating medical issues that may arise during a tele-visit to ensure participant safety.

13. STATISTICAL ANALYSIS

Planned analyses are summarized here. Additional details will be included in a separate Statistical Analysis Plan (SAP). In the event of a conflict between the protocol and the SAP, the SAP will take precedence.

13.1 Data Processing and Quality Control (QC) for Smartphone (SP) Based Measures:

Data QC and cleaning: As data from the SP are deposited on a daily basis into Synapse, we will have a clear measure of compliance and engagement. Additionally, data streams can be monitored for quality. Data scientists and statisticians at Sage Bionetworks have developed an extensive pipeline to monitor and QC active task measurements from smartphone applications (e.g., https://github.com/Sage-Bionetworks/mpowertools). These tools will be adopted and expanded to monitor and QC passive data streams. During the development stage of the application we will run small scale internal experiments where user use Android and iOS devices concurrently to establish bounds on differences between devices.

Data processing/feature extraction: Quality processed data will be summarized into features using extensions of our feature extraction pipelines for active tasks. These include but are not limited to time and frequency domain statistics, energy and entropy of frequency spectrum from the tri-axial accelerometer, along with absolute displacement measurements. For displacement information (Aim 3b) data will be summarized into variables such as furthest distance traveled, frequency of trips, average daily distance etc. Also, additional specific features will be selected based on previously published studies using passive data and expert knowledge of behavioral patterns of PD patients. These measures will be summarized to a single measure by training a n-fold cross-validated machine learning model using the discovery data subset. Additionally, features will be evaluated by test-retest reliability across time. Data analysis will be performed as described in SA 3.B and 3.C below.

13.2 Statistical Analysis Plan

Aim 1: To evaluate concordance between in-clinic and tele-visit MDS-UPDRS assessments (Aim 1b), we will use results from the REACT-PD study to calibrate tele-visit assessments to in-clinic MDS-UPDRS scores, matching means and standard deviations cross-sectionally. We will use Lin's concordance correlation coefficient, r_c, to summarize accuracy of the

calibrated tele-visit estimates vs. scores collected from in-person SURE-PD3 and SUPER-PD visits conducted close in time, accepting tele-visit estimates as sufficiently accurate if $r_c > 0.8$. If we observe insufficient concordance, we will investigate contributions of bias, scale difference, and imprecision and re-calibrate using all available data from both REACT-PD and the current study.

Aim 2: We will assess the calibration and correlation between tele-visit (TV) and SP metrics both cross-sectionally and longitudinally (Aim 2a). We will generate SP-derived metrics that best match composite scores of motor function (MDS-UPDRS part 3), non-motor function (MoCA total score), subjective function (including global impression (CGI) scores, Schwab and England ADL scores, MDS-UPDRS parts 1b and 2 scores, and estimates of MDS-UPDRS part 1-3 total scores. We will randomly split our sample 2:1 into calibration and validation subsets. For each measure, we will use the calibration sample to develop a transformation of SP data that best matches the TV measurement machine learning models using a variety of machine learning techniques with a final selection based on overall accuracy by 10-fold cross-validation. We will test the accuracy of calibrated SP measures in the reserved validation sample using Lin's concordance correlation coefficient, r_c. If we observe insufficient concordance, we will investigate contributions of bias, scale difference, and imprecision and re-calibrate using all available data from both the calibration and validation samples.

We will compare TV vs. calibrated SP measures of disease progression generally, as predictors of future clinical events and changes in patient reported outcomes, and between specific subsets of participants expected to progress at different rates (Aim 2b) due to biology or treatment. After calibration, we will estimate the standard error for a treatment-group comparison from a two-arm trial using measure-specific variance components from a bivariate random-slopes linear mixed model for each pair of TV and SP measures and assuming an assessment schedule appropriate for each measure, e.g., annual for TV measures and quarterly for SP measures. Preferred measures would have smaller standard errors, and specifically, the ratio of squared standard errors provides an estimate of the relative sample size required. We will use the same approach to identify measures that are significantly more sensitive to biological subgroups (e.g., among participants stratified by their rate of MDS-UPDRS progression over the first 2 years of in-clinic follow-up in the parent trials) or treatment-based subgroups (e.g., participants randomized to Isradipine or serum urate elevation). To compare TV assessments and SP measures with respect to their accuracy in predicting future clinical events and changes in patient reported outcomes, we will use the same 2:1 training: validation split and train separate models using TV and SP metrics collected over the first year of follow-up to predict clinical events and changes in PROs over the second year of follow-up. Clinical events will include dropping below 80% on the modified Schwab and England ADL and experiencing a fall. PROs of interest will include summary scores from the PDQ-8, EQ-5D, and PDAQ-15 and measures

derived from the PD-PROP. Selection of the best training models will be based on 10-fold cross-validated accuracy for binary outcomes and residual sum of squares for continuous measures. Positive and negative predictive values of TV and SP-derived predictions will be estimated from the validation sample for binary outcomes and compared by logistic regression. For continuous outcomes, RSS estimates will be compared between TV and SP-derived predictions. As an exploratory analysis, additional models that combine TV and SP measures will be constructed and tested for accuracy relative to models derived from TV or SP measures alone.

Completion rates of PROs collected during TVs vs. those collected online via FI will be compared by mixed effect logistic regression with participant-specific and participant x form random effects (Aim 2c). Concordance between PROs assessed during TVs vs. those obtained online via FI will be estimated using Lin's concordance correlation coefficient (Aim 2c).

Aim 3:
We will evaluate the feasibility to collect and use passive data to track disease progression. Passive data collection will come in two flavors - displacement tracking that captures a participant's life space, i.e. their mobility patterns and collection of accelerometer and gyroscope readings when the participants are walking throughout the day. The walking data will be analyzed exactly the same as the actively collected data as described in Aim 2. The displacement tracking requires more care and will require us to first determine feasibility of data collection (Aim 3a) and extensive norming before assessing ability to track progression (Aim 3b).

Evaluation of Data Collection:
The first component of this Aim will focus on evaluating the feasibility of collecting passive data from individuals over a 2- year time period. This includes addressing two potential barriers to data collection: (1) Participant willingness to provide permission for passive monitoring and (2) the ability to collect passive data continuously over a 2-year period despite infrastructure changes caused by smartphone hardware and software upgrades.

Hypothesis: 70% of AT-HOME PD participants who participate in the smartphone component will consent to collection of passive data.

This will be evaluated by observing the number of active participants willing to enroll in this sub-study.

Hypothesis: Passive data will be collected in a persistent manner for the full 2-year study in at least 75% of consented individuals. Data collection will be monitored on a continuous basis.

We will evaluate the ability to use passive motor measures to predict relative changes in disease severity within a participant. Due to the highly individualized nature of activity patterns, it is unknown whether passive

data can be used to derive absolute measures of disease severity. However, we expect that relative changes in activity patterns over time will provide a mechanism to track disease progression on an individualized basis. Features from displacement data such as total daily movement, number of daily trips, etc. will be generated and normed per individual before evaluation of disease progression using the same methods as described in SA 2b.

We will evaluate the use of passive measures to directly assess disease severity. The longitudinal nature of the displacement data provides the ability to identify personalized changes in disease burden over time and to evaluate whether changes in activity patterns over time are comparable to changes in disease severity as evaluated within the other components of this study. By focusing on changes in app active task performance and changes in tele-visit evaluations we can test the ability to track disease severity. Daily displacement will be evaluated per individual relative to: finger tapping, gait assessment, and overall composite score for smartphone-based motor evaluation using passive data collected during the burst periods using Lin's concordance correlation coefficient, r_c Likewise we will perform the same analysis on the tele-visit assessments.

Anticipated outcomes and alternatives:
The overarching goal of Aim 3 is to evaluate whether and how passive data collection can be used for long-term monitoring of PD symptoms in clinical research cohorts. If we can observe relative changes in disease state, it could be used to trigger standard assessments – providing a way to reduce clinic burden and cost by deploying expensive clinic visits only when necessary rather than at regular time intervals. The use of these data also provides a mechanism to augment existing severity measures by directly evaluating the impact of disease on daily life. While not explicitly described in this proposal, the data collected within the program can be used to evaluate additional approaches to passive monitoring. For example, collection of accelerometer data provides the opportunity to develop an algorithm to monitor gait and balance from daily activities rather than formal assessments. Such assessments are exploratory for PD assessment but have demonstrated utility in the context of other neurological disorders.

13.3 Go/No-go Milestones, Challenges and Opportunities

Our systematic approach to building the study's main tele-health assessment platforms and then sequentially recruiting its sub-cohorts suggests realistic prospects of meeting our project timeline and of reaching pivotal Go/No-go milestones set at 75% of recruitment and retention goals to ensure a reasonable likelihood of accomplishing our SAs. However, in the event that a milestone was not achieved then NINDS program staff would determine in discussion with the SC whether the study should be continued and/or adapted.

Just as our infrastructure plans (under SA1) rely on logistical capabilities, our experimental hypotheses (under SAs 2 and 3) depend on scientific assumptions, which if challenged would lead us to consider contingencies accordingly. For example, the ability to compare disability progression measured by tele-health platforms relies on true disease progression during two years of cohort follow up. However, this period coincides with the so-called 'honeymoon' phase of treatment after DT initiation when observable motor progression may be modest due to early, uncomplicated medication titration (40). Anticipating this possible pitfall, we will incorporate an adjustment for levodopa dose equivalents in our motor score-based progression analysis. We will also explore dopa-resistant cognitive outcomes and would proactively consider options to further extend the cohort into subsequent phases of non-motor and dopa-resistant disability accumulation. In addition, we will remain open to new opportunities to leverage the project's resources; for example, adopting potentially more sensitive wearable technologies in this rapidly evolving mobile health field, or assessing events to which the study cohort may be uniquely suited such as the impact of parent trial results, which should be announced during the follow-up period.

13.4 Sample Size Determination

SA 1b. With a sample size of ~10 SURE-PD3 and ~50 SUPER-PD participants expected to complete at least one TV close in time to their in-person clinic visit, the study will have 80% power to conclude that the REACT-PD calibrated tele-visit estimates are sufficiently accurate ($r_c > 0.8$ at alpha = 0.05) if the true concordance is at least 0.89.

SA 2a. With a 2:1 split of ~340 AT-HOME PD participants, yielding ~115 participants contributing to validation tests, the study will have 80% power to declare a given SP measure sufficiently accurate ($r_c > 0.80$ at alpha = 0.05) if the true concordance is at least 0. 87.

SA 2b. With approximately 80% of participants participating in the SP portion of the study, yielding ~340 participants contributing to the smartphone vs tele-visit comparison, the study would have an 80% probability of selecting the true preferred measure from a pair of TV or SP if the preferred measure had lower standard error by an effect size of at least 0.065.

SA 3. With a 2:1 split of ~240 participants, yielding ~80 in the validation sample and at least 25% experiencing at least an 8-point progression in MDS-UPDS parts 1-3 total score, the study would have 80% power to declare a novel measure derived from passive SP monitoring to have a ROC AUC significantly greater than 0.80 if the true AUC were at least 0.95.

13.5 Non-Compliance, and Withdrawals

All available data will be included in the primary analyses regardless of protocol compliance. Secondary analyses may restrict the sample to participants meeting pre-specified compliance criteria.

We will summarize the proportion of eligible participants in the parent trials who enroll in AT-HOME PD and the proportion of those enrolled who (1) complete each tele-visit, (2) complete each FI quarterly assessment, (3) download and install the AT-HOME PD app, (4) complete periodic AT-HOME PD tasks, and (5) consent to passive data collection.

13.6 Safety Analysis

RE information collected at study tele-visits will be summarized. All participants will be included in the safety analysis. At a minimum, individual report information will be displayed, and RE rates tabulated.

PART B - GOOD CLINICAL PRACTICE/ADMINISTRATION

14. REGULATORY/ETHICS

14.1 Compliance Statement

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the FDA, and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 54, 56, 312 and 314.

All procedures not described in this protocol will be performed according to the study Operations Guide/Manual unless otherwise stated.

14.2 Informed Consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. NINDS and the CHeT/CTCC must be given an opportunity to review the consent form prior to site IRB submission and before it is used in the study.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be provided to each participant. Each participant will electronically sign such an informed consent form.

The proposed research poses minimal risk to participants. Waiver of documentation of consent will be sought as eConsenting is not recognized by the Office of Research and Project Administration.

The participant must be assured of the freedom to withdraw from participation in the study at any time.

It is the study team's responsibility to make sure that the participant understands what she/he is agreeing to and that informed consent is obtained before the participant is involved in any protocol-defined with the exception of those pre-screening questions. It is also the study team's responsibility to verify participant identity, verify completion of the eConsent form and participant understanding of the study.

The consent process for each participant who provides consent will be documented in the participant's electronic source record and should include the date eConsent was provided, the date participant understanding was verified by the study team, and the date of the screening visit.

14.3 Institutional Review Board/Independent Ethics Committee

The study team will supply the CHeT/CTCC with all necessary information for submission of the protocol and consent form to the IRB for review and approval. The CHeT Site Investigator agrees to provide the IRB with all appropriate material. The study will not begin until the Investigator has obtained appropriate IRB approval. A copy of the approval letter listing all documents and versions that were approved and the approved electronic consent form must be placed on file at the CHeT/CTCC.

The CHeT Site Investigator will request from the IRB a composition of the IRB members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB and NINDS in accordance with institutional and government regulations. It is the CHeT Site Investigator's responsibility to notify the IRB when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site IRB's acknowledgement of study completion must be filed at the CHeT/CTCC.

The CHeT Site Investigator will discuss any proposed protocol changes with the CTCC Project Manager and no modifications will be made without prior written approval by NINDS, except where clinical judgment requires an immediate change for reasons of participant welfare. The IRB will be informed of any amendments to the protocol or electronic consent form, and approval, where and when appropriate, will be obtained before implementation.

14.4 Protocol Amendments

Changes to the protocol should only be made via an approved protocol amendment. Protocol amendments must be approved by the Sponsor, the study's Steering Committee and the respective site's IRB prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of participants. (See Investigator's Agreement.)

14.5 Participant Confidentiality

The CHeT Site Investigator must assure that the privacy of participants, including their personal identity and personal medical information, will be maintained at all times. In the U.S. there are additional privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). Participants will be identified by code numbers on case report forms and other documents.

After a participant agrees to study participation via an eConsent form, it is required that the CHeT Site Investigator permit the study monitor, independent auditor or regulatory agency personnel to review the completed informed consent(s) and that portion of the participant's medical record that is directly related to the study.

The participant's authorization allows the Sponsor and CHeT/CTCC to receive and review the participants' protected health information that may be re-disclosed to any authorized representative of the Sponsor, CHeT/CTCC for review of participant medical records in the context of the study.

15. DOCUMENTATION

15.1 Investigator Site File

As part of the Trial Master File, the CHeT Site Investigator should have the following study documents accessible for review during the study.

i. *Curriculum vitae* for investigator and staff signed and dated within 2 years of initiation of involvement in study

ii. The signed IRB/IEC form/letter stating IRB/IEC approval of protocol, eConsent forms, and advertisement notices, documentation of the IRB/IEC composition, and all IRB/IEC correspondence including notification/approval of protocol amendments, notification of reportable events to the IRB/IEC per local reporting requirements, and IRB/IEC notification of study termination

iii. IRB/IEC approved electronic consent form (sample) and advertisement materials

iv. Signed protocol (and amendments, where applicable)

v. Electronically consented and dated participant electronic consent forms will reside in the REDCap database.

vi. Access to eCRF source records

vii. Delegation Log with names, signatures, initials, and functional role of all persons completing protocol assessments, providing back-up to the CHeT Site

Investigator and Coordinator, if applicable, as well as staff entering data to the REDCap system.

viii. Any source data not kept within the participant's REDCap database.

ix. Signed and dated receipt of equipment if required for the study.

x. Record of all monitoring visits made by NINDS personnel

xi. Copies of correspondence to and from NINDS, including all other platforms and CHeT/CTCC.

xii. Record of any Corrective and Preventive Action Plans (CAPA) as required by the NINDS

xiii. Certificate for Human Participant Protection Program (HSPP) training for each individual named on the Delegation Log who have direct participant contact

xiv. Copy of professional licensure/registration, as applicable, for each individual named on the Delegation Log, who has direct participant contact ensuring licensure is in the state in which the study will be conducted

xv. A Note to File indicating the assessments that will be considered source documents, if applicable

xvi. Any other documentation as required by the CHeT/CTCC (e.g., Conflict-of-Interest/Financial Disclosure)

The CHeT Site Investigator must also retain all printouts/reports, which are not recorded in REDCap.

15.2 Maintenance and Retention of Records

It is the responsibility of the CHeT Site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by NINDS and the federal regulations in a secure and safe facility with limited access for one of the following time periods based on notification from NINDS and/or CHeT/CTCC.

The CHeT Site Investigator will be instructed to consult with NINDS and/or CHeT/CTCC before disposal of any study records and to notify NINDS and/or CHeT/CTCC of any change in the location, disposition, or custody of the study files.

Electronic Records:
An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study (see Sections 15.5 and 17.3).

At the conclusion of the study a PDF (portable document format) file depicting the eCRFs for each site will be prepared by CTCC Data Management. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

15.3 QA Review

During the course of the study and after it has been completed, QA review may be undertaken by authorized representatives of the Sponsor or CHeT/CTCC.

The purpose of the review is to determine whether or not the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. This review will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

If such reviews are to occur, they will be arranged for a reasonable and agreed time.

15.4 Regulatory Inspections

The study may be inspected by regulatory agencies. These inspections may take place at any time during or after the study and are based on the local regulations as well as ICH guidelines.

15.5 Data Management

All outcomes, demographics and other data originating from participants will flow through the 3 study platforms for data collection before converging for analysis in the Sage Bionetworks-managed Synapse platform for project analysis. From Synapse the fully transformed dataset will be transferred to the PDBP's Data Management Resource (DMR) and further distributed to the wider research community. See Resource Sharing Plan for more detail.

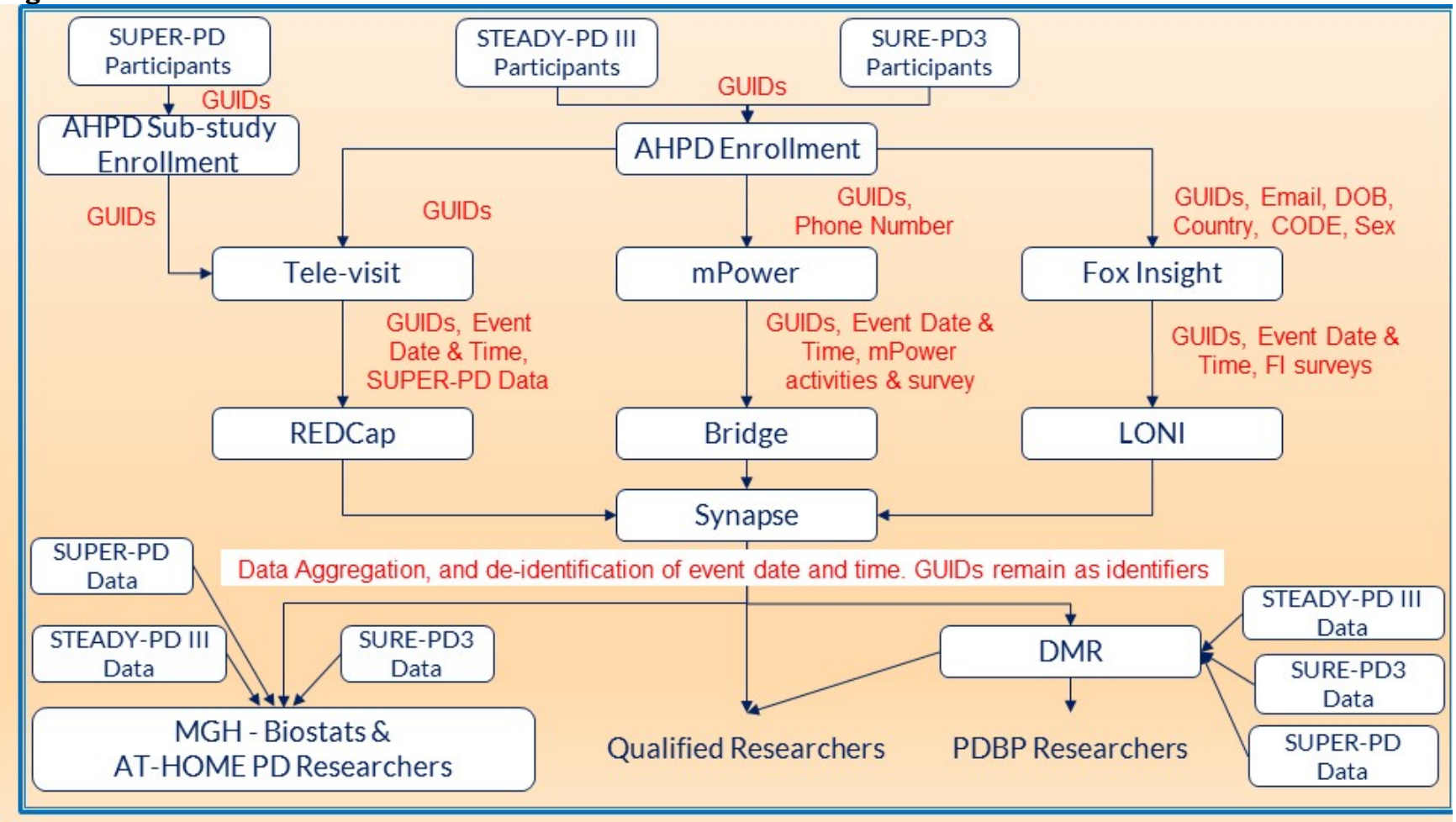
Specifically, **1) data collected during tele-visits** will be entered and maintained in REDCap (a secure web-based survey and data management system routinely employed by CHeT/CTCC) with GUIDs, date and time of visit as identifiers, where it will be accesses via an application program interface (API) by Sage Bionetworks. **2) Survey data collected by FI** will be, stored, and accessed from a FI researcher portal developed by LONI (USC's Laboratory of Neuro Imaging which specializes in secure archival and sharing of neuroscience data) with GUIDs, date and time of visit as identifiers from which automated data transfer to Synapse will be configured **3) Data collected from participant smartphones** will be transferred from users' phones in real time on completion to the Sage Bionetworks-maintained Bridge server, where

data will be aggregated, coded, and transferred to Synapse with GUIDs, date and time of visit as identifiers on a daily basis where it will be in real time accessible to all research partners involved in this study. For any sub-study participants who are participating in the mPower 2.0 component of SUPER-PD, their smartphone data from the corresponding SUPER-PD visit and associated remote 2-week burst will be linked with AT-HOME PD data within Synapse.

The Bridge server is actively maintained by a team of engineers at Sage Bionetworks and has been effectively used to manage smartphone-based research studies including Smart*4*SURE and mPower. Synapse is a scientific data management and research collaboration platform designed and actively maintained by Sage Bionetworks (http://synapse.org).

All the SP and FI data will be aggregated and cleaned within Synapse prior to combination with the tele-visit data using GUIDs, date and time of visit as key identifiers. Data combined from all three platforms is further transformed in Synapse using a random number of days that will be added to all dates for that subject, to obscure actual dates but maintain durations and relative dates. Standard pipelines developed at Sage Bionetworks provide tools for data cleaning and feature extraction that will automatically be run on the raw data streams. Accelerometer readings, click streams etc. are converted into hundreds of distinct measures of disease severity capturing different aspects of the PD that correspond to multiple phenotypic subtypes of behavior. Sage Bionetworks will continue to monitor and update both quality control methodology and features being extracted as new devices and technology are used by study cohort. Once cleaned and processed compatible data will be deposited in the PDBP's DMR (see Data Sharing Plan).

Figure 2. Data Flow Details



Utilizing Electronic Data Capture (EDC). Research Electronic Data Capture (REDCap), an Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. The REDCap system is designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study on an ongoing basis to the study principal and co-investigators. REDCap is a free, secure, HIPAA-compliant, web-based application used for electronic capture and management of research and clinical study data. The REDCap system, developed by Vanderbilt University, provides an intuitive user interface to enter, audit, monitor, and export data. It also helps users create web-based surveys.

Data review and query processing will be done through interaction with the CHeT/CTCC and site personnel. Once the data are entered into REDCap, it is immediately stored in the central study database located at the URMC Data Center and is accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail.

The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all participants have completed the study.

Aggregated data, where event dates and times are transformed, will be made available through Synapse using version data snapshots to the Biostatistics Center. Once the Biostatistics Center and the CHeT/CTCC, in conjunction with the Sponsor and the principal investigator, agree that all queries have been adequately resolved and the database has been deemed “clean”, the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) to the database are removed at this time.

The Massachusetts General Hospital (MGH) Biostatistics Center will be responsible for creation of analytical databases and the statistical analysis plan. Data management staff at the CHeT/CTCC will facilitate creating the data management plan, however, each collaborator will be individually responsible for data collection specific to their platform as well as providing documentation to be added to the overall data management plan.

There will be a data user agreement put in place for the use and transfer of data between CTCC and Sage Bionetworks. The University of Rochester Information Security Office has reviewed and approved methods of data transfer and storage with entities outside the University [including Sage Bionetworks].

16. INVESTIGATOR/SITE

The protocol, informed consent form, and advertisement notices will be approved by the UR IRB (RSRB).

The CHeT Site Investigator is responsible for providing copies of the protocol and all other information relating to the prior clinical experience, which were furnished to him/her, to all physicians and other study personnel responsible to them who participate in this study. The CHeT Site Investigator will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study. The CHeT Site Investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.

17. SAFETY MONITORING

All aspects of the study will be monitored by the CHeT Site Investigator and designees in compliance with Good Clinical Practice (GCP) and applicable regulations. There is no clinical monitor or safety monitoring committee for this study. The Steering Committee will review collected reportable events on a quarterly basis.

17.1 Study Committees

a. Steering Committee

The Steering Committee (SC) is composed of the 4 project Principal Investigators (PIs), study biostatistician, and independent investigator members of the Parkinson Study Group with expertise in PD and allied fields of study, a patient advocate, and scientific or programmatic officers of partner institutions. The roles of SC Chair and Co-chair are filled by rotating pairs of its PI members according to the project's Multiple PI Leadership Plan as approved by NINDS. The SC is responsible, along with the Sponsor, for the design of the study protocol and analysis plan and oversees the clinical trial from conception to analysis and publication.

17.2 Case Report Forms

Utilizing Electronic Data Capture (EDC). Site will enter participant information and data into an electronic case report form (eCRF) in the Electronic Data Capture (EDC) application - REDCap. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Authorized study personnel will each be granted access to the EDC tool via provision of a unique password-protected user-ID that will limit access to enter and view data. ***Data should be directly entered into the EDC system at the time of the participant's tele-visit.***

Data will be directly entered into eCRFs via computer stations connected remotely to the central server through an Internet browser. In the event of REDCap unavailability paper CRFs will be used and the data will be entered when REDCap is available.

CHeT Site Investigator approval of eCRFs:
An approval from the CTCC Site Investigator is required on the following eCRFs:

- Signature Form

A form with the Investigator signature, either wet or electronic signature, will be uploaded into the database.

It is the CHeT Site Investigator's responsibility to ensure that entries are proper and complete. Error checks will be implemented in the EDC based upon specifications defined in the data management plan.

At the conclusion of the study, the CTCC Data Management Team will create a PDF file depicting eCRFs for each participant. The PDF file should be printed for each participant in the study and filed in the participant's binder.

17.3 Primary Source Documents

The Investigator will maintain primary source documents supporting significant data for each participant in REDCap. Any relevant telephone conversations with the participant regarding the study or possible adverse events and attempts to reach participants by telephone or mail regarding medical events and/or compliance will also reside in REDCap.

17.4 Closeout Visit

Following the completion of the study, the study team will ensure all the data is entered and queries are resolved, any protocol deviations are documented appropriately, all relevant study data has been retrieved, and that the Investigator has copies of all study-related data/information on file.

17.5 Closeout Plan

A study closeout plan will be developed that provides information about study close-out procedures and timelines internally as well as externally. Full details will be documented in the operations manual.

18. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Parkinson Study Group, Steering Committee and in accordance with the International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals

(http://www.icmje.org/urm_main.html). Any presentation, abstract, or manuscript will be made available for review by the Sponsor NINDS prior to submission.

19. RESOURCE SHARING PLAN

Data will be collected across individual sites (U. Rochester for tele-visit data; Sage Bionetworks for smartphone data; MJFF-sponsored portal in LONI for FI data). Data from all three sites will be aggregated in a centralized location using Synapse. Synapse is a cloud based scientific data management and research collaboration platform designed and actively maintained by Sage Bionetworks (https://www.synapse.org/) that is used to coordinate data across dozens of consortia and collaborations. All data will be aggregated within Synapse using GUIDs, event dates and times as unique identifiers. Following aggregation, event dates and times are transformed by transferring them to duration since a random first visit for analysis and for distribution to the PDBP Data Management Resource (DMR) on a recurring, regular basis that complies with NINDS program requirements. Data is cleaned on an on-going basis, however, until the database is locked changes in data may occur. Deposition will use standard DMR protocols for clinical and PRO data. Because the DMR is not yet set up to receive sensor data, the appropriate deposition protocols will be developed in collaboration with the DMR. As these are developed, we have the alternative of working with NINDS to develop a system that provides PDBP and DMR-approved investigators with access to sensor data directly through the Synapse platform.

Data sharing will be performed in two additional ways. The smartphone data, tele-visit data, and FI data will be distributed for secondary use through the mobile health data repository that Sage Bionetworks has developed and that is also housed in Synapse. The shared study dataset will be made available to qualified researchers who are registered users of Synapse and who have agreed to use the data in an ethical manner, to do no harm and not attempt to re-identify or re-contact participants. No name or contact information will be included in this shared study dataset. Researchers will have access to the shared study data but will be unable to map any particular data to the identities of the participants. The qualified researcher program is operated through an IRB-approved Synapse data governance plan. For more information about the data practices in the context of the Synapse research platform, see the Synapse Governance Overview (http://docs.synapse.org/articles/governance.html). In addition, data will be collected as part of FI, an IRB-approved web-based study. All data collected through FI will be automatically deposited into a research portal hosted at LONI (http://www.loni.usc.edu/) for use by the research community.

The code used to run the smartphone application developed for this study will be made public through github (https://github.com/) and

made available to the research community for reuse under an open license. The study will be registered at clinicaltrials.gov.

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