Trial No.:	001
Title:	Fox Investigation for New Discovery of Biomarkers (BioFIND)
Clinical Phase:	Observational Study
Sponsor:	Michael J. Fox Foundation For Parkinson's Research
Collaborator:	The National Institute of Neurological Disorders and Stroke (NINDS)
Principal Investigator:	Un Jung Kang, MD
Date of Protocol:	September 3, 2014
Final Version:	4.0

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PROTOCOL APPROVAL

Amendment 3
Fox **I**nvestigation for **N**ew **D**iscovery of **Bio**markers **(BioFIND)**

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Cynthia Casaceli, MBA Clinical Core	Date
Todd Sherer, PhD CEO, Michael J Fox Foundation (Sponsor)	Date

INVESTIGATOR AGREEMENT
Protocol Amendment 3

Fox Investigation for New Discovery of Biomarkers (BioFIND)

I have carefully read this protocol, including all appendices, and the investigator's drug brochure (if applicable), and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and guidelines [21 CFR (Code of Federal Regulations) Parts 11, 50, 54 and 56 and ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Topic E6 (R1)], and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to the pre-clinical and prior clinical experience, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study.

I will ensure that the drugs supplied to me for this study will be used only for administration to subjects enrolled in this study protocol and for no other purpose.

I agree to keep records on all subject information (case report forms, informed consent statements, drug shipment, drug return forms, and all other information collected during the study) in accordance with the current GCP, local and national regulations.

Site Number _____ Printed Site Name _____

Printed Site Investigator Name _____

Site Investigator Signature _____ Date _____

List of Abbreviations and Definitions

ADL	activities of daily living
AE	adverse event
BRC	Biospecimen Review Committee
CB	cerebellar
CBC	complete blood count
CFR	Code of Federal Regulations
CRF	Case Report Form
CSF	cerebral spinal fluid
CTCC	Clinical Trials Coordination Center
DBS	deep brain stimulation
DNA	Deoxyribonucleic acid
DTR	deep tendon reflex
eCRF	electronic Case Report Form
EDC	electronic data capture
GCP	Good Clinical Practice
HC	Healthy Control
HIPAA	Health Insurance Portability and Accountability Act
HSPP	Human Subject Protection Program
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
INR	International Normalized Ratio
LP	lumbar puncture
MDS-UPDRS	Movement Disorder Society Unified Parkinson Disease Rating Scale
miRNA	microRNA
MJFF	Michael J. Fox Foundation
MoCA	Montreal Cognitive Assessment
OTC	over-the-counter
PD	Parkinson disease
PPMI	Parkinson's Progression Markers Initiative
PT/PTT	Prothrombin Time/Partial Thromboplastin Time
PW	premature withdrawal
QA	quality assurance
QC	quality control
RBC	red blood cell
RBD	REM sleep behavior disorder
RNA	ribonucleic acid
REM	rapid eye movement
SAE	serious adverse event
SC	Steering Committee

BioFIND PROTOCOL SYNOPSIS

Protocol Number	001
Protocol Title	Fox Investigation for New Discovery of Biomarkers
Acronym/Title	BioFIND
Clinical Phase	Observational
Sponsor	Michael J. Fox Foundation For Parkinson's Research (MJFF)
Study Centers	8 U. S. Study Sites
Study Period	2.5 years (Q1 2015 estimated completion)
Study Objective and Specific Aims	The primary objective is to identify a cohort of clinically typical PD with controls to provide a valuable resource for discovery and validation of promising biomarkers based on biofluids. This will facilitate development of biomarkers of: 1) PD diagnosis 2) Progression, by serving as a bridge to the longitudinal cohort of PPMI studies 3) Clinical subtypes, by providing the most typical cohort which can serve as a standard for other PD cohorts, such as those with dementia or atypical features, and other Parkinson's Plus disorders. The specific aims to accomplish the primary objective are: a. Establish a bank of biofluids from a cross-sectional cohort of subject with "typical" PD b. Define control subjects for future biomarker studies
Study Design	Observational, multi-center study to identify biological markers in PD and healthy control subjects
Number of Subjects	Total number of subjects is 240 • 120 Parkinson's disease (PD) • 120 Healthy Controls (HC)
Main Eligibility Criteria	**Parkinson Disease (PD) Subjects** **Inclusion:** 1. Subjects must have bradykinesia and rigidity. 2. Current or history of well documented resting tremor. 3. Unilateral onset or persistent asymmetry, but not strictly unilateral at the time of enrollment.

4. A well established response to one or more dopaminergic agents and/or amantadine (the presence of levodopa induced dyskinesia is acceptable but not required).
5. Subject has progressive PD of 5 to 18 years of duration from the onset of symptoms.
6. Male or female age of onset of PD 50 to 75 by history. Current ages would range from 55 to 93 based on #5 and #6 requirements.
7. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
8. Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

Exclusion:

1. Has other serious neurological disorders (clinically significant stroke, brain tumor, hydrocephalus, epilepsy, other neurodegenerative disorders, encephalitis, repeated head trauma).
2. Had early severe autonomic involvement. Symptomatic orthostatic, hypotension or urinary incontinence within one year of onset of disease symptom.
3. Has a history of cancer (other than basal and squamous cell skin cancers), autoimmune disorder, liver disease, or hematologic disorders within the past 5 years.
4. Current treatment with anticoagulants (e.g., Coumadin, heparin) that might preclude safe completion of the lumbar puncture.
5. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
6. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
7. Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
8. Has lower body predominant symptoms.
9. Has supra-nuclear gaze palsy, cerebellar abnormalities, corticospinal track signs.
10. Has had brain surgery including pallidotomy, thalamotomy, subthalamotomy or deep brain stimulator (DBS) implantation.

Healthy Control (HC) Subjects

Inclusion:

1. Male or female age 55 to 93 years or older at visit 1.
2. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.

	3. Willing and able to comply with scheduled visits, required study procedures and laboratory tests. **Exclusion:** 1. Family history of PD in first degree relatives. 2. Has other serious neurological disorders (clinically significant stroke, brain tumor, hydrocephalus, epilepsy, other neurodegenerative disorders, encephalitis, repeated head trauma). 3. Has a history of cancer (other than basal and squamous cell skin cancers), autoimmune disorder, liver disease, or hematologic disorders within the past 5 years. 4. Current treatment with anticoagulants (e.g., Coumadin, heparin) that might preclude safe completion of the lumbar puncture. 5. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia. 6. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation. 7. Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10). 8. MoCA score <26.
Sample Size Considerations	*This study is a prospective study without a predefined assay, and therefore there is no power analysis. However, we considered sample size based on three examples:* 1. The sample size was initially calculated using Khoo's miRNA data using 50% quartile of variance to detect 2.5 fold changes with 80% power at alpha=0.0025. 2. Based on Kang lab's preliminary data on the ratio of oxidized DJ-1 to total DJ-1 in RBC in 12 subjects, 120 PD subjects will provide 85% power to detect 33% difference at alpha=0.05. 3. We also surveyed other biomarker studies involving PD diagnosis. The studies with the largest number of subjects included about 120 PD subjects of various stages of PD [1, 2] and were able to detect differences between PD and controls for various markers.

BioFIND Schedule of Activities						
PARKINSON DISEASE (PD) SUBJECTS						
Visit Description	**Level #**	**Baseline/V01 Day 0**	**V02 Day 14**	**Telephone Call T01[6]**	**FNL**	**Unscheduled Visit[5]**
Confidential Subject Identification Log		X				
Written Informed Consent		X				
Screening/Demographics	02	X				
Socio-Economics	04	X				
CTCC Unique ID	06	X				
Inclusion/Exclusion - PD	08	X				
PD Features	10	X				
Primary Diagnosis	12	X				
Medical History (General)	14	X				
Smoking and Alcohol Questionnaire	15	X				
Family History (PD)	16	X				
General Neurological Exam	18	X				
Vital Signs	20	X	X			X
Fasting Status	21	X	X			
Use of PD Medication	22	X	X			
MDS-UPDRS 1	24	X				
MDS-UPDRS 2	24	X				
MDS-UPDRS 3/Hoehn & Yahr	24	X	X[1]			
MDS-UPDRS 4	24	X				
Modified Schwab & England ADL	26	X				
Montreal Cognitive Assessment (MoCA)	30	X				
REM Sleep Disorder Questionnaire	32	X				
DNA Sample	34	X				
Laboratory Procedures	36	X[2]	X[4]			
Saliva and Urine Samples	37		X			
Clinical Labs	38	X[3]				
Lumbar Puncture	40		X			
Investigator Signature	42	X	X	X		X
Visit Status	44	X	X	X		X
Adverse Event Log	46		X	X		
Concomitant Medication Log	50	X	X	X		X
Adverse Event Follow-up Log[7]	54			X		
Conclusion of Study Participation	52				X	

1 MDS-UPDRS part 3 motor only
2 10ml plasma between 1-3 hours after meds
3 CBC, platelet count, PT/PTT
4 Laboratory procedures include PAXgene™ and plasma EDTA purple top
5 Assessments at the discretion of the Investigator and to be recorded in source document
6 Adverse events assessed by phone 7 - 10 days following LP
7Any AE ongoing at the 7 to 10 day reporting telephone visit should be followed until resolution or stabilization, but not more than 30 days from lumbar puncture.

BioFIND Schedule of Activities						
HEALTHY CONTROL (HC) SUBJECTS						
Visit Description	**Level #**	**Baseline/V01 Day 0**	**V02 Day 14**	**Telephone Call T01[6]**	**FNL**	**Unscheduled Visit[5]**
Confidential Subject Identification Log		X				
Written Informed Consent		X				
Screening/Demographics	02	X				
Socio-Economics	04	X				
CTCC Unique ID	06	X				
Inclusion/Exclusion - HC	09	X				
Primary Diagnosis	12	X				
Medical History (General)	14	X				
Smoking and Alcohol Questionnaire	15	X				
Family History (PD)	16	X				
General Neurological Exam	18	X				
Vital Signs	20	X	X			X
Fasting Status	21	X	X			
MDS-UPDRS 3/Hoehn & Yahr	24	X[1]				
Montreal Cognitive Assessment (MoCA)	30	X				
REM Sleep Disorder Questionnaire	32	X				
DNA Sample	34	X				
Laboratory Procedures	36	X[2]	X[4]			
Saliva and Urine Samples	37		X			
Clinical Labs	38	X[3]				
Lumbar Puncture	40		X			
Investigator Signature	42	X	X	X		X
Visit Status	44	X	X	X		X
Adverse Event Log	46		X	X		
Concomitant Medication Log	50	X	X	X		X
Adverse Event Follow-up Log[7]	54			X		
Conclusion of Study Participation	52				X	

1 MDS-UPDRS part 3 motor only
2 10ml plasma between 1-3 hours after meds
3 CBC, platelet count, PT/PTT
4 Laboratory procedures include PAXgene™ and plasma EDTA purple top
5 Assessments at the discretion of the Investigator and to be recorded in source document
6 Adverse events assessed by phone 7 - 10 days following LP
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1. INTRODUCTION

1.1. Background

Diagnosis and monitoring therapeutic response of Parkinson's disease (PD) would be greatly aided by simple objective laboratory tests, as are available in many other disorders such as diabetes mellitus or thyroid disorders. Although some biomarkers have been shown to have predictability for PD diagnosis, most show suboptimal sensitivity and specificity. In addition, most studies have not been validated in an independent population and not well controlled for various factors such as medication use. They have employed a wide spectrum of PD patients and clinical heterogeneity of PD population may be a major obstacle for understanding their pathogenesis and progression. There are currently no progression markers, indicators of therapeutic target engagement, or markers for subtypes of PD. The implementation of the Parkinson's Progressive Marker Initiative (PPMI) study is a major and ambitious undertaking, following early de novo patients for five years for biomarker collection in order to discover progression markers of PD. However, few candidate markers have sufficiently solid evidence and are ready to take the next step of testing their change with progression of the disease. The present proposal complements PPMI by providing the platform for a new discovery and a solid confirmation of biomarkers in a well-defined typical moderately advanced PD population compared to appropriately matched controls. This will facilitate the selection of candidate markers of disease progression.

1.2. Rationale for BioFIND

We have chosen to focus on a cohort with the most "typical" PD in moderate stages, that is, in people who would be seen in a typical medical practice, as a first step to test potential biomarkers. This will provide a benchmark population of individuals who are less subject to misdiagnosis, that often plagues studies involving early untreated cohort of PD, and our approach will therefore reduce heterogeneity. A robust finding in this study will serve as a firm foundation for future studies involving a wider spectrum of PD and other related disorders. In addition, we hope to capture an active process of neurodegeneration present in this population in mid-stages as opposed to advanced PD, with the possibility to identify potentially important molecular markers that contribute to PD pathogenesis.

2. STUDY OBJECTIVE

2.1. Primary Objective and Specific Aims

The primary objective of the study is to collect biospecimens from 120 PD and 120 healthy controls with well defined clinical characteristics for future biomarker assays.

3. STUDY DESIGN

3.1. Overview

BioFIND is an observational, multi-center study to provide a valuable resource for discovery and validation of PD biomarkers. BioFIND is a two and a half-year study (2-week involvement for each subject) of PD patients and healthy controls. Two visits of about a 2-week interval will take place. First visit is to rigorously screen patients based on the clinical information and draw blood samples for clinical labs and post-dose blood specimen and the second visit is to collect pre-dose specimen of blood, saliva, urine, and cerebral spinal fluid (CSF) in subjects who meet the criteria for the enrollment.

3.2. Discussion of Study Design

3.2.1 Rationale for Study

To minimize the influence of drug therapy and understand its potential effect on biomarkers, we will collect biospecimen in practically defined "off" state for all PD subjects, complemented by a smaller collection during broadly defined "on" state. This will provide a critically needed, well-defined cohort for the PD biomarker research community, and will complement the early stage longitudinal cohort of PPMI study.

4. SELECTION OF STUDY POPULATION

4.1. Subject Numbers

Approximately 120 PD patients and 120 healthy controls will be recruited from about 8 clinical sites.

4.2. Inclusion Criteria (Parkinson Disease Subjects)

1. Subjects must have bradykinesia and rigidity.
2. Current or history of well documented resting tremor.
3. Unilateral onset or persistent asymmetry, but not strictly unilateral at the time of enrollment.
4. A well established response to one or more dopaminergic agents and/or amantadine (the presence of levodopa induced dyskinesia is acceptable but not required).
5. Subject has progressive PD of 5 to 18 years of duration from the onset of symptoms.
6. Male or female age of onset of PD 50 to 75 by history. Current ages would range from 55 to 93 based on #5 and #6 requirements.
7. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
8. Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

4.3. Exclusion Criteria (Parkinson Disease Subjects)

1. Has other serious neurological disorders (clinically significant stroke, brain tumor, hydrocephalus, epilepsy, other neurodegenerative disorders, encephalitis, repeated head trauma).
2. Had early severe autonomic involvement. Symptomatic orthostatic, hypotension or urinary incontinence within one year of onset of disease symptom.
3. Has a history of cancer (other than basal and squamous cell skin cancers), autoimmune disorder, liver disease, or hematological disorders within the past 5 years.
4. Current treatment with anticoagulants (e.g., Coumadin, heparin) that might preclude safe completion of the lumbar puncture.
5. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
6. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
7. Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
8. Has lower body predominant symptoms.
9. Has supra-nuclear gaze palsy, cerebellar abnormalities, corticospinal track signs.
10. Has had brain surgery including pallidotomy, thalamotomy, subthalamotomy or deep brain stimulator (DBS) implantation.

4.4. Inclusion Criteria (Healthy Control Subjects)

1. Male or female age 55 to 93 years or older at visit 1.
2. Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
3. Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

4.5. Exclusion Criteria (Healthy Control Subjects)

1. Family history of PD in first degree relatives.
2. Has other serious neurological disorders (clinically significant stroke, brain tumor, hydrocephalus, epilepsy, other neurodegenerative disorders, encephalitis, repeated head trauma).
3. Has a history of cancer (other than basal and squamous cell skin cancers), autoimmune disorder, liver disease, or hematological disorders within the past 5 years.
4. Current treatment with anticoagulants (e.g., Coumadin, heparin) that might preclude safe completion of the lumbar puncture.
5. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.

6. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
7. Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
8. MoCA score <26.

4.6. Age and Gender Matching

Enrollments will be monitored centrally by the Clinical Trials Coordination Center (CTCC) through statistical personnel and enforced by the BioFIND Steering Committee (SC) with the goal of achieving age and gender balance across the study overall. Individual sites should generally attempt to match healthy control subjects as closely as possible in age (target within 5 years) and gender to the PD subjects enrolled at the site. Sites will be instructed if recruitment restrictions need to be implemented as the study progresses in order to maintain a balanced population.

5. INVESTIGATIONAL PLAN

5.2. Subject Identification Numbers

5.2.1 Subject Identification (ID) Number

A Subject ID Number will be assigned in sequential order by the site from a list provided to the site by the CTCC. This 4-digit number will be used to identify the subject on all study forms and on safety and research lab specimens. When the research lab distributes samples to other researchers this 4-digit number will be replaced by a different, linked number to protect confidentiality.

5.2.2 C**TCC Unique Identification (ID) Number**

Subjects will be instructed how to obtain a 9-digit Unique Identification Number at the Baseline Visit. This ID system has the ability to track individual subjects across multiple CTCC studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC Unique ID Number that is associated with their electronic "fingerprint."

Once a subject signs the informed consent he/she will be directed to a secure website where he/she or the site study coordinator (if the subject requests/prefers) will enter the subject's nine data elements. The CTCC Unique ID Number will be printed and provided to the subject. The study coordinator will record this number on the CTCC Unique ID CRF and Confidential Subject ID Log.

It will not be considered a protocol deviation if the subject refuses the creation of the CTCC Unique ID. In this case, the corresponding field on the CRF will be left blank. Documentation of the refusal should be included in the subject's source documentation along with documentation of the informed consent process and a comment made to the signature page in the EDC System.

If a subject has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, this number will be used for this study. A subject can regenerate his/her CTCC Unique ID Number. He/She can return to the secure website, enter the same nine data elements in the exact same way they were entered the first time and will receive their same CTCC Unique ID Number.

6.0 STUDY PROCEDURES

6.1. Study Procedures at Each Visit

Subjects will undergo all procedures as outlined in the sections below for each cohort as identified in the table. Assessments that require completion by the site investigator (unless otherwise approved and delegated) include: Neurological Exam, MDS-UPDRS Part Ia (coordinator may conduct if requested in advance, as long as the assessment is completed consistently for all subjects/all visits), Part III, Part IV, Hoehn & Yahr Stage, Modified Schwab & England ADL, and Primary Diagnosis.

Specific procedures for the clinical labs, biomic labs and lumbar puncture are indicated in the corresponding Operations Manual.

6.2. Baseline Visit/Visit 01 (BL/V01)

All subjects will undergo a baseline visit. This visit will include the activities in the table below.

Blood draw and MDS-UPDRS part 3 motor examine should occur between 1 – 3 hours of the last PD medications. If there are multiple PD meds, the timing will be counted from the last levodopa or dopamine agonist if not on levodopa. If subjects are on neither medication, the timing will be counted from their amantadine or MAO-B inhibitors if not on amantadine. Because a high fat diet can potentially interfere with some biological assays in the blood, it is desirable, but not required, that subjects consume a low fat diet before coming in for V01.

Activity and Assessments	PD	Control
Written Consent: An explanation of the purpose, procedures, potential risks and benefits of this study and informed consent will be obtained	+	+
Inclusion/Exclusion Criteria: The investigator will determine that all eligibility criteria have been met and the subject may be enrolled into the study	+	+
Demographics: Demographics and socio-economic data will be collected	+	+
Family History of PD: Review of subject's family history	+	+
Medical History: Review of subject's medical history	+	+
Smoking and Alcohol Questionnaire: Review of subject's use of cigarettes and alcohol	+	+
Vital Signs: Measure height, weight, temperature, sitting heart rate, and sitting blood pressure	+	+

Concomitant Medication: Review and record concomitant medications	+	+
Montreal Cognitive Assessment (MoCA)	+	+
Modified Schwab & England (ADL)	+	N/A
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)	+ all parts including part 3 motor	+ part 3 motor only
Hoehn and Yahr Stage	+	+
Sleep (RBD) Questionnaire	+	+
Neurological Exam; Check for CB signs, ocular movements, and DTR and spasticity	+	+
PD Features	+	N/A
Primary Diagnosis	+	+
CBC, platelets, PT/PTT: Clinical labs to determine eligibility for LP	+	+
DNA: **Collect blood sample in yellow top ACD for DNA**	+	+
10 ml plasma between 1-3 hours after meds	+	+

6.3. Final Visit/Visit 02(FNL/V02)

This visit should occur within 2 weeks of Baseline/Visit 01 if possible or soon thereafter if necessary. The results of CBC, platelets, and PT/PTT are checked to make sure that normal values are documented before LP. If abnormal, Visit 02 can occur for other activities without LP.

Blood draw, saliva and urine collections, LP, and MDS-UPDRS part 3 motor examine should occur early in the morning before any PD medication dose. Preferably subjects

should be fasting. If fasting is not feasible, a low fat diet is recommended. Subjects are to refrain from eating, drinking or using oral hygiene products for at least one hour prior to saliva collection.

With subject permission, samples determined to be unusable may be recollected at a later date.

Activity and Assessments	PD	Control
Vital Signs: Measure temperature, sitting heart rate, and sitting blood pressure	+	+
Concomitant Medication: Review and record concomitant medications	+	+
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)	+ part 3 motor portion only	N/A
Hoehn and Yahr Stage	+	N/A
Blood draw: **3 × 2.5 ml PAXgene™** **3 × 10 ml plasma EDTA purple top**	+	+
Saliva collection: **About 5 ml**	+	+
Urine collection: **About 15 ml**	+	+
Lumbar Puncture: Collection of cerebral spinal fluid	+	+
Adverse Event: Review and record adverse events from LP through 7-10 day follow-up call	+	+

6.4. Unscheduled Visits or Telephone Contacts (Visit U01 or T01, etc)

An unscheduled visit or telephone contact may be performed at any time during the study at the subject's request or as deemed necessary by the site investigator. The date and reason for the unscheduled visit or telephone contact will be recorded in the source documentation. In addition, unscheduled visits will be documented in the database.

7. STUDY ASSESSMENTS

7.1. Clinical Assessments

7.1.1 MDS-UPDRS

The MDS-UPDRS is a multimodal scale assessing both impairment and disability and is separated into 4 subscales (Parts I-IV). The MDS-UPDRS includes components assessed by the study investigator as well as sections completed by the subject. Every effort should be made to have the same investigator (or coordinator if delegated) perform the ratings for an individual subject throughout the course of the study.

- Part I: This assesses non-motor experiences of daily living and is comprised of two components:
  - ❖ Part IA contains 6 questions that are assessed by the investigator and focuses on complex behaviors.
  - ❖ Part IB contains 7 questions that are part of the Patient Questionnaire completed by the subject.
- Part II: This assesses motor experiences of daily living. There are an additional 13 questions that are also part of the Patient Questionnaire completed by the subject.
- Part III: This assesses the motor signs of PD and is administered by the investigator.
- Part IV: This assesses motor complications, dyskinesias and motor fluctuations using historical and objective information for subjects taking PD medications. The investigator will complete this assessment.

7.1.2 Hoehn and Yahr Stage

The Hoehn and Yahr is a commonly used system for describing how the symptoms of Parkinson's disease progress. The scale allocates stages from 0 to 5 to indicate the relative level of disability. This scale is included within the MDS-UPDRS and will be completed for all subjects.

- Stage 0: No symptoms.
- Stage 1: Symptoms on one side of the body only.
- Stage 2: Symptoms on both sides of the body. No impairment of balance.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Wheelchair-bound or bedridden unless assisted.

7.1.3 Modified Schwab & England Activities of Daily Living

The Modified Schwab & England Activities of Daily Living (ADL) scale reflects the speed, ease, and independence with which an individual performs daily activities, or personal chores, such as eating, toileting, and dressing. This scale uses a rating scale from 0% to 100%, with 100% representing complete independence in performing daily activities and 0% representing a vegetative, bedridden state.

7.1.4 Neuropsychological and Cognitive Assessments

The Montreal Cognitive Assessment (MoCA): In early Parkinson's disease, when cognitive deficits occur, they are subtle and mild and the patients usually perform in the normal range on the widely used Mini Mental State Examination (MMSE). The Montreal Cognitive Assessment (MoCA) is a rapid screening instrument like the MMSE but was developed to be more sensitive to patients presenting with mild cognitive complaints. It assesses short term and working memory, visuospatial abilities, executive function, attention, concentration, language and orientation. The total score ranges from 0 to 30.

7.2. Safety Assessments

7.2.1 Medical History and Neurological Examination

Medical, smoking, alcohol, and family history, as well as a neurological exam will be captured on all subjects at Baseline.

7.2.2 Vital Signs/Weight/Height/Temperature

Height, weight, sitting pulse rate, sitting blood pressure, and oral temperature will be determined at the Baseline Visit. At Visit 02 pulse rate, blood pressure, and temperature will again be determined. The blood pressure and pulse rate will be determined after 1-3 minutes of quiet sitting.

7.2.3 Clinical Laboratory Tests

Routine clinical laboratory tests will be performed according to the visit schedule. All samples for laboratory analysis must be collected, prepared, labelled, and sent according to the local laboratory's requirement as detailed in the Operations Manual. The total amount of blood needed for the clinical lab tests will be no more than 13 ml.

The coagulation panel (PT/PTT) and platelet counts will be collected and processed at each local lab for analysis at the Baseline Visit. Sites will be provided with supplies from the central lab; however, the sample should be sent to a local lab facility for analysis. Results will be evaluated to determine, in the opinion of the investigator, whether there are any issues that may preclude conduct of the follow-up lumbar puncture. Results should be maintained as part of the subject's study documents; however, they will not be included in the study database.

No more than 40 ml will be drawn at any visit, including both clinical and research blood samples.

7.3. Other Assessments

7.3.1 Biologic Sampling (Blood, Saliva and Urine)

Blood, saliva, and urine samples will be collected. Blood (about 10-30 ml) will be collected to conduct proteomic, metabolomic and other analyses at each visit. Blood will be obtained (about 8 ml) for the extraction of DNA to conduct sequencing and genomic analyses. Blood will also be obtained (about 7.5 ml) for the extraction of RNA to conduct biochemical analyses. Saliva (about 5 ml) will be collected to conduct biochemical analyses. Additionally, urine (about 15 ml) will be collected to conduct analyte analyses. It is strongly advised that the research blood samples are collected in a fasted state (i.e., minimum of 8 hours since last meal/food intake) to ensure the quality of samples for future analyses**.** If fasting is not possible, then subjects should be strongly advised to eat a low lipid diet as provided. Subjects are to refrain from eating, drinking or using oral hygiene products for at least one hour prior to saliva collection. A part of the research samples will be sent to a central repository and the rest will be stored locally indefinitely for research purposes. Samples will be made available to researchers to conduct analyses related to PD and other disorders. Subjects will not receive any individual results of analysis or testing conducted on the biologic samples.

7.3.2 Lumbar Puncture

The lumbar puncture (LP) is performed by the site investigator or another qualified clinician appointed by the investigator. A lumbar puncture for the collection of 15-20 ml of CSF will be conducted for all subjects per the visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. With subject permission, a problematic lumbar puncture may be repeated on the same day or another day and guided by ultrasound or fluoroscopy. Two (2) ml of CSF will be processed at the site's local lab facility (unless the lab is not able to process the CSF within 4 hours) to conduct standard analyses on cell count, protein and glucose levels. Subjects will be closely monitored during the procedure and following the procedure. Subjects will be contacted by phone 7 to 10 days following an LP to assess for any adverse events. A portion of CSF samples will be sent to a central repository and the rest will be stored indefinitely for research purposes. The CSF samples will be made available to researchers to conduct analyses related to PD and other disorders.

8. CONCOMITANT MEDICATIONS

8.1. Concomitant Medications

The medication used is at the discretion of the treating physician. The investigator will document any new medications or changes in medication at each study visit on the Concomitant Medication Log.

8.1.1 Use of Concomitant Medications

Concomitant medications, including over-the-counter (OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted during the study period. All concomitant medications reported at the time of the Baseline Visit and for the duration of the subject's participation should be recorded on the Concomitant Medication Log.

9. INTERCURRENT ILLNESS

In the event of an intercurrent illness and at the discretion of the investigator, the subject may be continued in the study. All intercurrent illnesses must be recorded in the eCRF as adverse events if they occur during the period from the LP to the 7-10 day follow-up reporting call.

10. SUBJECT WITHDRAWALS

Subjects 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. A subject should be withdrawn from the study if the investigator considers it to be medically necessary, or if the subject withdraws consent. All reasons for subject withdrawals from the study will be recorded in the source documentation and appropriate eCRF.

11. SAFETY/ADVERSE EXPERIENCES

Site investigators and coordinators will be instructed to assess for adverse events from the time the LP is conducted through the telephone follow-up 7 to 10 days following the LP.

Each subject must be carefully monitored for adverse events (AEs). An assessment must be made of the seriousness, intensity, and relationship to the study procedure.

See table below for adverse event monitoring timelines:

Procedure	Assessed from time of procedure		7 to 10 day telephone contact
Lumbar Puncture	X		X

11.1. Adverse Event Definitions

Adverse Events (AE)

An AE is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to an investigational product or trial procedures.

Pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Baseline Visit) will be recorded on the medical history CRF page. These conditions will

not be reported as an AE unless they worsen in intensity or frequency during the reporting period defined above.

Serious Adverse Event (SAE)

An SAE is an AE that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening AE is an AE that, in the view of the investigator, places the subject at immediate risk of death from the reaction, as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Inpatient admission in the absence of a precipitating, study related, clinical adverse event is not subject to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE
- Social admission (e.g., subject has no place to sleep)
- Protocol-specific admission during a clinical study (e.g., for a procedure required by another study protocol)
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)

Inpatient admission does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits
- Outpatient/same-day/ambulatory procedures
- Observation/short-stay units
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Custodial care facilities

11.2. Recording of Adverse Experiences

Adverse experiences, whether observed by the investigator, elicited from or volunteered by the subject, should be recorded on the Adverse Event Log. This will include a brief description of the experience, the date of onset, the date of resolution, the severity, and seriousness and whether the event was related to participation in the research study.

Any AE ongoing at the final 7 to 10 day reporting telephone visit should be followed until resolution or stabilization, but not more than 30 days from LP.

11.3. Responsibilities for Reporting Serious Adverse Experiences

- The investigator should notify the CTCC Project Manager by telephone within 24 hours of his/her becoming aware of the occurrence of a serious adverse experience.

- Upon completion of the telephone report, the CTCC Project Manager will enter the appropriate subject information into the Incident Module.

- The following information should be supplied if available at the time of the telephone call: study number, site number, subject number, subject age and gender, date of onset of event, event description, whether event required treatment, death and autopsy report, an identification of which criteria for a serious experience have been met, the investigator's current opinion of the relationship between the event and study participation.

- The investigator will comply with his/her local Institutional Review Board (IRB) regarding the reporting of adverse experiences.

12. REPORTABLE EVENTS

The following incidents will be considered reportable events and will be reported to the CTCC within 24 hours of the event, or the site investigator's knowledge of the event.

- Change of clinical diagnosis
- Participation in any other clinical trial or study
- Premature withdrawal (e.g. withdrawal of consent)
- SAE
- Death

13. REFERRALS

If a research assessment or lab result reveals a clinically significant abnormality the subject should be informed of this result and instructed to follow up with his or her primary care physician. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the investigator should provide the subject with the appropriate referral as necessary.

14. POTENTIAL RISKS

14.1. Blood Sampling

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn.

14.2. Lumbar Puncture

The most common risks of a lumbar puncture are pain at the site and a temporary headache usually due to a small amount of CSF leakage around the needle insertion site. Lying down for a few hours after the test can make a headache less likely to occur. There is a slight risk

of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria. A temporary numbness to the legs or lower back pain may be experienced. There is a small risk of bleeding in the spinal canal. Subjects will have blood drawn at Baseline to test for coagulopathies.

15. STATISTICAL ANALYSIS

15.1. Sample Size Determination

This study is a prospective study without a predefined assay, and therefore does not have power calculation. However, we considered sample size based on three examples:

1. The sample size was initially calculated using Khoo's miRNA data using 50% quartile of variance to detect 2.5 fold changes with 80% power at alpha=0.0025.

2. Based on Kang lab's preliminary data on the ratio of oxidized DJ-1 to total DJ-1 in RBC in 12 subjects, 120 PD subjects will provide 85% power to detect 33% difference at alpha=0.05.

3. We also surveyed other biomarker studies involving PD diagnosis. The studies with the largest number of subjects included about 120 PD subjects of various stages of PD[1, 2] and were able to detect differences between PD and controls for various markers.

15.2. Treatment Failures, Non-Compliance, and Withdrawals

Those who have abnormal platelet counts (<50,000/ul or by local lab standard), PT (below or above 11.8 – 14.5 or local lab normal values), PTT (below or above 24.0 – 34.0 or local lab normal values), or INR values (below or above 0.9 – 1.1 or local lab normal values) will be excluded from LP, but undergo blood draw and other activities in the second visit. Those whose spinal tap is unsuccessful in producing CSF will be included in the study with only clinical data and blood samples.

16. REGULATORY/ETHICS; GOOD CLINICAL PRACTICE/ADMINISTRATION

16.1. 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 Food and Drug Administration (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 Manual unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the central laboratory manual unless otherwise stated.

16.2. Informed Consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. The 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 read and/or explained to each subject. Each subject (or subject's legally authorized representative, if applicable) will sign such an informed consent form or give verbal consent.

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

It is the investigator's responsibility to make sure that the subject or legal guardian understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is also the investigator's responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form.

The consent process for each subject who signs informed consent will be documented in the subject's source (e.g., research file, research progress note) and should include the title of the study, that the consent was discussed with an opportunity for questions and answers, how the subject demonstrated comprehension, that the consent was signed prior to the first study procedure, and that the subject received a signed copy of the consent.

16.3. Institutional Review Board/Independent Ethics Committee

The CTCC will supply all necessary information to the investigator for submission of the protocol and consent form to the IRB/IEC for review and approval. The investigator agrees to provide the IRB/IEC all appropriate material. The trial will not begin until the investigator has obtained appropriate IRB/IEC approval. A copy of the approval letter listing all documents and versions that were approved and approved consent form must be submitted to the CTCC.

The investigator will request from the IRB/IEC 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/IEC and the CTCC in accordance with institutional and government regulations. The CTCC will notify the site when the IRB/IEC may be notified of study completion. It is the 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/IEC's acknowledgement of study completion must be submitted to the CTCC.

The investigator will discuss any proposed protocol changes with the CTCC Project Manager and no modifications will be made without prior written approval by CTCC, except where clinical judgment requires an immediate change for reasons of subject welfare.

The IRB will be informed of any amendments to the protocol or consent form, and approval, where and when appropriate, will be obtained before implementation.

16.4. 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 SC and each respective site's IRB/IEC prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of subjects. (See Investigator's Agreement.)

16.5. Subject Confidentiality

The site investigator must assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional privacy obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA). Subjects will be identified by initials and code numbers on case report forms and other documents submitted to the Sponsor and the CTCC.

After a subject signs an informed consent, it is required that the site investigator permit the study monitor, independent auditor or regulatory agency personnel to review the signed informed consent(s) and that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (when available).

The subject's Authorization allows the Sponsor and CTCC to receive and review the subject's protected health information that may be re-disclosed to any authorized representative of the Sponsor, CTCC, central laboratory/repository facility, or data repository for review of subject medical records in the context of the study.

17. DOCUMENTATION

17.1. Study File and Site Documents

The investigator should have the following study documents accessible to the Monitor during the study.

i. *Curriculum vitae* for investigator and staff listed on the Delegation Log
ii. The signed IRB/IEC form/letter stating IRB/IEC approval of protocol, consent forms, and advertisement notices, documentation of the IRB/IEC composition, and all IRB/IEC correspondence including notification/approval of protocol amendments, notification of serious adverse events to the IRB/IEC, and IRB/IEC notification of study termination
iii. IRB/IEC approved consent form (sample) and advertisement
iv. Signed protocol (and amendments, where applicable)
v. Signed subject consent forms

vi. Copies of the completed CRF worksheets (and subject diary cards, if applicable)
vii. Delegation Log with names, signatures, initials, and functional role of all persons completing protocol assessments, providing back-up to the site investigator and coordinator, if applicable, as well as staff entering data to the EDC system.
viii. Copies of laboratory reports/printouts
ix. Any source data/records not kept with the subject's hospital/medical records
x. Laboratory accreditation and relevant laboratory reference ranges
xi. Signed and dated receipt of supplies
xii. Record of all monitoring visits made by personnel
xiii. Copies of correspondence to and from CTCC
xiv. Certificate for Human Subject Protection Program (HSPP) for each individual named on the Delegation Log who has direct subject contact
xv. Copy of professional licensure/registration, as applicable, for each individual named on the Delegation Log, who has direct subject contact ensuring licensure is in the state in which the study will be conducted
xvi. A Note to File indicating the assessments that will be considered source documents
xvii. Any other documentation as required by the CTCC (e.g., Conflict-of-Interest/Financial Disclosure)

The investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each subject. This documentation, together with the subject's hospital/medical records, is the subject's source data for the study.

17.2. Maintenance and Retention of Records

It is the responsibility of the 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 the MJFF and CTCC and the federal regulations in a secure and safe facility with limited access until notified by the MJFF or the CTCC.

The investigator will be instructed to consult with the CTCC before disposal of any study records and to notify the 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 Section 17.5). At the conclusion of the study a PDF (portable document format) file depicting the eCRFs for each site will be provided on electronic media for record keeping. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

17.3. QA Audits/Site Visits

During the course of the study and after it has been completed one or more study site visits may be undertaken by authorized representatives of the Sponsor or CTCC.

The purpose of the audit 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. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

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

17.4. Regulatory Inspections

The study may be inspected by regulatory agencies, such as the Food and Drug Administration (FDA). 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.

17.5. Data Management

Utilizing Electronic Data Capture (EDC) An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. This system is protected by 128-bit server certificates and utilizes authenticated, password-protected accounts for each site. The EDC 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. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

Data management staff at the CTCC will be responsible for all data collection procedures.

Utilizing Electronic Data Capture (EDC) Data review, coding and query processing will be done through interaction with the CTCC, site personnel and the Study Monitor. Queries will be generated in real-time as the data is entered. Once the data are submitted to the EDC system, it is immediately stored in the central study database located at the CTCC and are accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail. As data recorded by sites in eCRFs are received, narrative text of adverse experiences and concomitant medications will be periodically coded using established coding mechanisms.

Utilizing Electronic Data Capture (EDC) The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

Data will be securely transferred to the Laboratory for Neuro Imaging (LONI) in Los Angeles, California. Once LONI and the 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) the database are removed at this time.

18. INVESTIGATOR/SITE

Each site investigator is responsible for providing a copy of the protocol, which was furnished to him/her, to all physicians and other study personnel responsible to him/her who participate in this study. The site investigator will discuss this information with study personnel to assure that they are adequately informed regarding the conduct of the study. The site investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.

19. STUDY MONITORING

19.1. Study Committees

19.1.1 Steering Committee

The SC is composed of the lead PI, CTCC PI, the PIs from each clinical trial site, and representatives from MJFF and NIH. The SC is responsible for the operational logistics and data management for the study. Specific responsibilities include advising on final project protocol(s) and amendments, helping to define standard practices for data and sample collection, developing policies and guidelines for publication of analyses generated by the study sites, advising and collaborating on development of applications for use of repository biological specimens.

A representative of the SC will be a member of Biospecimen Review Committee (BRC) that will review scientific proposals and advise on data resulting from analyses of the biospecimens collected as part of the BioFIND cohort to ensure proper representation of the sample and clinical characteristics.

19.1.2 Biospecimen Review Committee

The BRC will be comprised of scientific advisors that may rotate over the duration of BioFIND.

BRC members will evaluate proposals for access/use of BioFIND biospecimen according to agreed upon criteria. Following evaluation, the BRC will make a recommendation on whether a proposal should be accepted or declined.

The BRC decisions regarding biospecimen distribution shall be advisory to the NINDS and MJFF, and the final decision regarding distribution shall be that of the NINDS and the MJFF jointly. In case of disagreement between MJFF and the NINDS regarding distribution, the recommendation of the BRC will stand as the final decision.

19.2. Case Report Forms

Utilizing Electronic Data Capture (EDC) Sites will enter subject information and data into an electronic case report form (eCRF) in the Electronic Data Capture (EDC) application. The eCRFs are used to record study data and are an integral part of the study and subsequent

reports. Therefore the eCRFs must be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled at their site. ***Data should be entered into the EDC system within 1-2 business days of a subject's visit.***

Sites will be supplied with a set of source document worksheets that correspond to the eCRF. The worksheets will serve as source documents and are required to be used to enter data into the eCRFs. Sites will initially enter all data into the subject's medical chart and/or onto source documentation worksheets prior to entering data into the eCRFs via computer stations connected remotely to the central server through an Internet browser.

Electronic Signatures:
An electronic signature from the site investigator is required on the following eCRFs:

- Signature Form
- AE Form
- AE Follow-up Log

It is the site investigator's responsibility to ensure that entries are proper and complete. During entry of data, error checks will be performed by the EDC that will immediately flag problematic data (i.e., missing, out of range, inconsistent) allowing for sites to correct the data at that time. Error checks will be implemented in the EDC based upon specifications defined in the data management plan.

The data entered from the eCRFs will be securely transmitted to a central database stored on a secure server located at the CTCC. Upon completion of a subject's visit or the study, sites have the option to print the completed eCRFs depicting the data that were entered.

At the conclusion of the study, the site will be provided a PDF (portable document format) file on electronic media depicting eCRFs for their site. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

19.4. Monitoring Visits

To ensure compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements, the monitor or representative is responsible for monitoring that sites conduct the study according to the protocol, standard operating procedures, and other written instructions and regulatory guidelines.

Monitoring visits by a Study Monitor will be arranged in advance, at a mutually-acceptable time, with site personnel. The site personnel must allow sufficient time for the Study Monitor to review CRFs and relevant source documents and queries. The site coordinator and/or investigator(s) should be available to answer questions or resolve data clarifications.

19.5. Primary Source Documents

The investigator must maintain primary source documents supporting significant data for each subject in the subject's medical notes. These documents, which are considered 'source data,' should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's consent to participate in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of adverse events, and changes in medication usage Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse experiences
- Original, signed informed consent forms for study participation

The investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study (e.g., laboratory reports). Laboratory reports from the site's laboratory will be signed and dated by the investigator following review and filed with the subject's source documents. This documentation, together with the subject's hospital/site medical records, is the subject's 'source data' for the study. During monitoring visits the Study Monitor will need to validate data in the CRFs against these source data.

CRF Worksheets

Sites will be supplied with a set of worksheets that correspond to the eCRF for this study. The worksheets will serve as source documents for study observations and assessments and should be used to enter data into the eCRF. Additional source documentation for information not specifically included on the source document worksheets may be recorded on a separate document.

19.6. Closeout Visit

Following the completion of the study, Study Monitor(s) may conduct a closeout visit to ensure that all data queries have been resolved, any protocol deviations are documented appropriately, all relevant study data has been retrieved, and clinical supplies have been/will be properly returned or destroyed and that the investigator has copies of all study-related data/information on file.

20. REFERENCES

1. Mollenhauer B, Cullen V, Kahn I, et al. Direct quantification of CSF alpha-synuclein by ELISA and first cross-sectional study in patients with neurodegeneration. Exp Neurol 2008;213:315-325.

2. Shi M, Bradner J, Hancock AM, et al. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. Ann Neurol 2010;69:570-580.