

Fox Investigation for New Discovery of Biomarkers (BioFIND)
Sponsor: Michael J. Fox Foundation For Parkinson's Research
Collaborator: National Institute of Neurological Disorders and Stroke
BioFIND Operations Manual



BioFIND

OPERATIONS

MANUAL

TABLE OF CONTENTS

SECTION 1	GENERAL INFORMATION	
	Study Contacts	2
	Study Personnel	3
	CTCC Office Closings	4
SECTION 2	PROTOCOL	
SECTION 3	ENROLLMENT	
	General Information	2
	Subject ID Assignment	2
	CTCC Unique ID	2
	Activities Prior to Enrollment.....	3
	Protocol Deviation Codes.....	3
	Electronic Enrollment Process	4
	Subject Identification Code List	6
SECTION 4	SOURCE DOCUMENTS WORKSHEETS AND eCRFs	
	eClinical Training Manual.....	2
	Access to EDC and Portal	2
	Electronic Signatures	2
	Source Document Worksheets	3
	General Directions for eCRF Completion.....	3
	Directions for BioFIND eCRF Pages.....	6
SECTION 5	ASSESSMENTS	
	MDS-UPDRS with Hoehn & Yahr.....	2
	Modified Schwab & England Activities of Daily Living.....	3
	Montreal Cognitive Assessment (MoCA).....	4
	REM Sleep Behavior Disorder Questionnaire	10
SECTION 6	REPORTABLE EVENTS	
	Incident Reporting	2
	Notification Reporting	3
	Reporting of Adverse Events.....	3
SECTION 7	LABORATORY SPECIMEN MANAGEMENT	
	Research Biomarkers Lab Manual	

BioFIND Operations Manual

SECTION 8	SOURCE DOCUMENTATION	
	Instructions for Source Documentation	2
	APPENDIX 8 – Source Document Worksheets.....	4
SECTION 9	MONITORING	
	Study Initiation.....	2
	Site Visit.....	2
	Interim Monitoring	3
	Telephone Closeout Visit	3
	Contents of Regulatory Binder	3
SECTION 10	REPORTS	
	Enrollment Report	2
	Cumulative Enrollment.....	2
	Enrollment By Diagnosis, Gender, Age	2
	Incident Report	2
	Notification Report	2
	Pending Queries Report.....	3
	Missing Pages Report.....	3
	Missing Inv eSignature Report.....	3
	Missing Completion Status Report	3
	Site Performance Report	3

SECTION 1

GENERAL INFORMATION

Study Contacts

Study Personnel

Clinical Trials Coordination Center (CTCC) Office Closings

CLINICAL TRIALS COORDINATION CENTER (CTCC) STUDY CONTACTS

Whom to Call	Reason to Call
<p>Lead Project Manager Alice Rudolph Phone: 585-275-0556 Cell: 585-520-6266 Fax: 585-461-3554 Email: alice.rudolph@chet.rochester.edu</p>	<p>Protocol or day-to-day study operational questions Reportable events (Incidents and Notifications) SAEs</p>
<p>Information Analyst Nichole McMullen Phone: 585-273-4234 Fax: 585-461-4594 Email: nichole.mcmullen@chet.rochester.edu</p>	<p>CRF questions Data queries</p>
<p>Site Monitor Carol Zimmerman Phone: 585-341-7517 Fax: 585-341-7510 E-mail: carol.zimmerman@chet.rochester.edu</p>	<p>Audit and regulatory concerns</p>
<p>eClinical System Support Phone: 585-275-3893 (Monday-Friday 8:30 a.m. – 9:00 p.m. ET) Website: http://support.chet.rochester.edu/</p>	<p>Assistance with accessing eClinical (user name/password), navigation issues within the system Website support for FAQs, information about eClinical training, training manual and contacts</p>
<p>Michael J. Fox Foundation Vanessa Arnedo Phone : 212-509-0995 Fax: 212-509-2390 Email : varnedo@michaeljfox.org</p>	<p>Subcontract Payment issues Recruitment materials</p>

STUDY PERSONNEL

Please note the importance of consistency of study personnel. Each site has identified **one primary investigator** and **one primary coordinator** on record. It is essential to maintain consistency as much as possible throughout the study for the same investigator and coordinator to follow the same subject from the Baseline Visit/Visit 01 to the Final visit/Visit 02.

All key site personnel (e.g., investigator, coordinator and data entry staff) involved in the conduct of the study, including conducting assessments and/or entering data in EDC, will require a staff code assigned by the CTCC, and must be listed on the Delegation Log provided by the CTCC. Additional staff who are involved in the study (e.g., physician performing LP only, neuropsychologist, individual responsible for regulatory documents, etc.) do not require a staff code, however, they must be listed on the Delegation Log. The Delegation Log must be updated whenever there is a change to the study team staff. A copy of this log is to be submitted to the CTCC prior to study start up, when modified during the study, and at study completion.

Notify the CTCC Project Manager in advance of the need to change investigator or coordinator. Change in Investigator must be approved by the BioFIND Principal Investigator and MJFF, and change in coordinator will be reviewed by the project team. Any new staff that does not currently have a staff code should complete the *New/Change Staff Form* (see Portal Administrative folder for a copy) and fax it to the CTCC (fax number and instructions are provided on the form).

A BioFIND *Address List* is located in the eClinical Portal Administrative folder and will be updated as changes in staffing are made. Please notify the BioFIND Project Manager if there are any changes in address, email, fax, telephone number, or staffing.

CLINICAL TRIALS COORDINATION CENTER (CTCC)

CTCC OFFICE WILL BE CLOSED ON THE FOLLOWING DAYS

Office Closings through May 2015

The CTCC will be closed on the days listed below. If you have an emergency on a day we are closed, please call 585-275-7311 and you will be instructed whom to contact. Please distribute this information to the appropriate people in your office.

All day Monday, September 3, 2012

All day Thursday and Friday, November 22-23, 2012

All day Monday and Tuesday, December 24-25, 2012

All day Tuesday, January 1, 2013

All day Monday, May 26, 2014

All day Friday, July 4, 2014

All day Monday, September 1, 2014

12 PM ET Wednesday, November 26, 2014

All day Thursday and Friday, November 27-28, 2014

All day Wednesday and Thursday, December 24-25, 2014

All day Wednesday, December 31, 2014

All day Thursday, January 1, 2015

All day Monday, May 25, 2015

SECTION 2

PROTOCOL

(Insert a copy of the protocol and any amendments)

SECTION 3

ENROLLMENT

General Information
Subject ID Assignment
CTCC Unique ID
Activities Prior to Enrollment
Protocol Deviation Codes
Electronic Enrollment Process
Subject Identification Code List

GENERAL INFORMATION

A subject will be considered to have enrolled into the study if the subject consented to participation and met all eligibility criteria. Subject withdrawals will be monitored by the study team and the need to replace a subject who withdraws will be evaluated as the study progresses. Once 120 PD and 120 Control subjects have enrolled into the study, sites will be notified that enrollment is closed.

SUBJECT ID ASSIGNMENT

- A series of consecutive 4 digit subject IDs will be provided to each site by the CTCC at the time a site is activated (approved to enroll).
- Each potentially eligible person who signs consent will be assigned a subject ID from the list in sequential order by the site.
- The subject ID will be used throughout the study and will be included on all data forms and labs for all visits.

CTCC UNIQUE ID

If willing, the subject will also be identified with a CTCC Unique Identification number. Refusing the CTCC Unique ID is not a protocol deviation. The CTCC Unique ID system was designed and implemented in response to the desired ability to track individual subjects across multiple studies conducted at the Clinical Trials Coordination Center without storing any personally identifiable information. The information captured is the subject's information, so make sure to document prior to completion of the subject's study visit. This number is only captured once and is not used throughout the study. It is a separate number from the assigned Subject ID described above.

NOTE: To avoid duplicate Unique ID's assigned to a subject, only collect the subject's information. Do not use information about other individuals to generate the number. If a subject at your site already has a Unique ID, there is no need to re-enter the information. Use the same number as previously generated.

Once the subject has signed the consent form, collect the following data elements about the subject that will be entered into the secure website

<https://www.ctcc.rochester.edu/uniqueid/> to generate the Unique ID number:

- Last Name at birth
- First Name at birth
- Gender at birth
- Day, Month, Year of birth
- City and Country of birth
- Mother's Maiden Name

Record the number on the CTCC Unique ID page and keep a copy of the subject's CTCC Unique ID number in the site records. If at any point the subject forgets his or her CTCC Unique ID number, you or the subject can go back to the website and enter the 9 data elements again. These 9 data elements **must be identical to those entered before** (i.e., if no middle initial was used the first time data was entered, there should be no middle initial used when re-entering the data) to obtain the same unique ID number. The computer program will create the same fingerprint and return the same unique ID number each time the subject's data elements are entered.

ACTIVITIES PRIOR TO ENROLLMENT

Before a subject is considered enrolled into the study (i.e., an eligible subject who counts towards the total enrollment goal), the site investigator and coordinator should review the Inclusion/Exclusion forms to assess that the subject meets all eligibility criteria and complete the Inclusion/Exclusion page in EDC. Any uncertainty regarding the subject's eligibility should be referred to the CTCC Project Manager **prior to** the subject's Baseline/V01 Visit.

What Information Must Be Available to Enroll a Subject?

- Required data to be entered
 - Screening/Demographics Page
 - MoCA Page
 - Inclusion/Exclusion Page

Note: If all Baseline/V01 pages are not completed, any unopened pages will appear on a site's Missing Pages report 5 days after the visit has passed.

- Staff Code (investigator/coordinator reporting enrollment)
- Enrollment Date (date of Baseline/V01)
- Subject's Initials
- Subject's Date of Birth
- Subject's Gender
- Date Consent Form was Signed
- Protocol Deviation Code (if applicable)

PROTOCOL DEVIATION CODES

In the event a subject does not meet specific protocol eligibility criteria, yet the site investigator believes the subject should be allowed to enroll, the CTCC Project Manager must be contacted immediately. The Project Manager, in consultation (if necessary) with the Principal Investigator, will determine if a subject will be allowed to deviate from the specified protocol criteria to enroll in the study. In this case, the Project Manager will provide the site with a **Protocol Deviation Code** to use for the subject. This unique alphanumeric code will be entered into EDC on the Inclusion/Exclusion page identifying the subject as having been allowed to

enroll. The relevant eligibility statement should be answered accurately and use of the code will allow the enrollment.

NOTE: If a Protocol Deviation Code is not provided for a given subject not meeting eligibility criteria, the subject should not be enrolled into the study.

ELECTRONIC ENROLLMENT PROCESS IN eCLINICAL

Subjects will be enrolled via the web-based electronic data entry server protected by 128-bit SSL server certificates. Authenticated accounts will be created and maintained by the CTCC for each of the sites participating in the study once appropriate training has been completed by assigned site staff.

Use of the EDC system will allow **24/7** access to the module, providing additional flexibility, which may be especially useful for sites outside the Eastern Time zone.

NOTE: The eClinical system is down for routine maintenance every Sunday from 8 am to 12 pm (noon) Eastern Time. The eClinical system is also unavailable during a daily restart at 12 am (midnight) Eastern Time.

Site staff with user access will be directed to a page where they will enter their assigned **User ID** and **Password** in order to access the system. Once these have been validated, there will be options for entering a new subject into the system.

NOTE: A MAC computer cannot be used for this process.

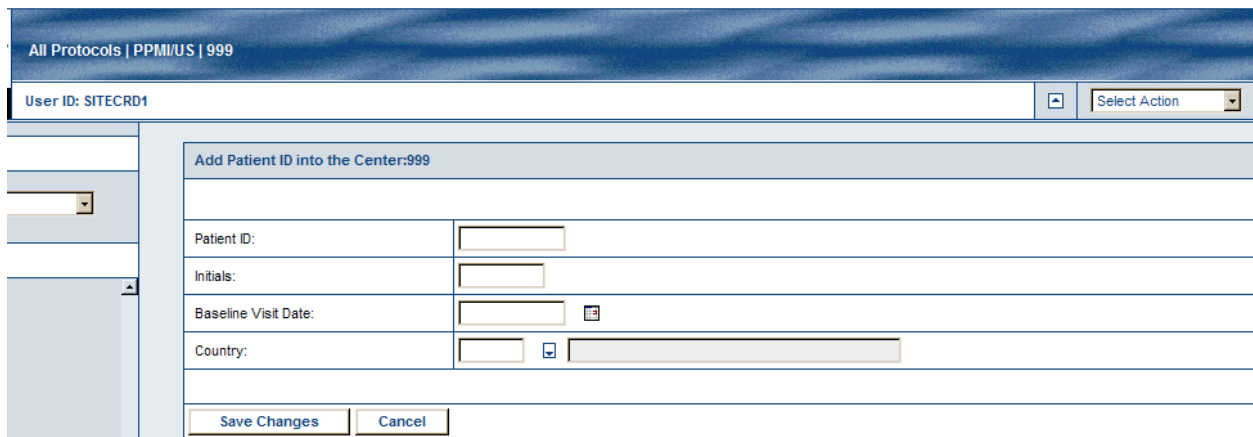
In the event of system difficulties with the enrollment process, the eClinical Help Desk should be contacted (585-275-3893). Hours of operation are Monday - Friday from 8:30 a.m. – 9:00 p.m. ET.

Sample eClinical Login Page:



Sample EDC New Patient Page:

NOTE: 'Subject Number' is called 'Patient ID' in the system.



Patient ID = The 4 digit subject number assigned to the person who signed consent. This number is assigned consecutively from the block of numbers provided from the CTCC.

Initials = Insert the initials of the subject.

Baseline Visit Date = Leave this field blank. This will be auto-populated once the subject is enrolled.

Country = Leave this field blank. We are not collecting Country at the present time.

Enrollment will require the site coordinator, in consultation with the site investigator, to verify that the subject meets study inclusion/exclusion criteria after all Baseline/V01 activities have been completed. In the event that a subject does not meet all eligibility criteria, a Protocol Deviation Code must be entered if approved by CTCC.

Enrollment Verification:

Once the subject is entered into the eClinical system the site will receive an automatic email verifying the enrollment/entry into the study, date and patient ID number. This email will act as the enrollment verification. The coordinator should file the report in the subject's study binder.

SUBJECT IDENTIFICATION CODE LIST

The Subject Identification Code List is a confidential record of all subjects enrolled into the study. This list containing individuals' names and addresses is maintained only at the site and should remain in a safe, secure location. DO NOT DISTRIBUTE A COPY TO SPONSOR OR THE CTCC. The original must be retained at the site and may not be destroyed until notified by sponsor or the CTCC that the document is no longer needed. A copy of this form may be obtained from the ePortal "Source Document Worksheets" folder.

SECTION 4

**SOURCE DOCUMENT WORKSHEETS AND
eCRFs**

eClinical Training Manual
Access to EDC and Portal
Electronic Signatures
Source Document Worksheets
General Directions for eCRF Completion
Directions for BioFIND eCRF Pages

eClinical TRAINING MANUAL

The electronic data capture tool within the eClinical suite of applications is Data Review/Capture (EDC). A complete set of guidelines for the eClinical system including EDC basics and the query management process are detailed in the *eClinical Portal and Electronic Data Capture Training Guide*. Please refer to the *training guide* for expanded topic discussions as well as step-by-step procedures. The guide is located in the ePortal Training folder.

ACCESS TO EDC AND Portal

After successful completion of all training requirements, protocol (study) personnel will be assigned a permanent User ID and temporary password. Access to the BioFIND protocol is based upon the user's role. Users may be limited to "read only" or may be given permits to enter and update data, provide resolutions to queries and apply electronic signatures.

Users are responsible for maintaining the security of their access to the applications. The eClinical application requires each user to change their password every 60 days.

NOTE: The EDC application will automatically time out after 30 minutes of inactivity. Data must be saved as each eCRF page is entered. You will be prompted to save the page if you attempt to move to the next page without saving data. However, if the system times out, unsaved data is lost.

ELECTRONIC SIGNATURES

The definition of an electronic signature is "a computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual's handwritten signature". The FDA and Clinical Trials Coordination Center consider electronic signatures to be the equivalent of handwritten signatures. Please refer to the eClinical Portal and Electronic Data Capture Training Guide for directions to apply electronic signatures.

An electronic signature (eSignature) is required to be personally applied by the Site Investigator or delegated Sub-Investigator who conducted the visit. An eSignature is required on the following eCRFs:

- Signature Form (for each visit)
- Adverse Event Log (at the subject's conclusion of participation)
- Adverse Event Follow-up Log (when AE ongoing at 7-10 day LP follow-up call is resolved/stabilized or 30 days after LP, whichever occurs first)

SOURCE DOCUMENT WORKSHEETS

Sites are supplied with 10 packets of source document worksheets (SDWs) for 6 PD subjects and 4 Control subjects. Once a site has enrolled 6 PD and 4 Control subjects, additional SDWs will need to be printed from the ePortal “Source Document Worksheet” folder. (Sites entering the study after the initial five sites must print all SDWs from ePortal.)

NOTE: Prior to the first study visit, print off a blank set of the source document pages from the ePortal “Source Document Worksheets” folder and keep the blank set in your study binder as back-up. Should you experience any issues with accessing the internet to enter data or download source worksheets, you will have a blank set to copy and use as needed.

GENERAL DIRECTIONS FOR eCRF COMPLETION

An eCRF is an auditable electronic record designed to record data required by the clinical trial protocol. eCRFs may have special display elements, electronic edit checks, and other properties or functions and are used for both capture and display of the data.

Sites will be provided source document worksheets to capture data onto the eCRF page, while other eCRF pages are completed from separate source notes. See Section 8 “Source Documentation” for details. Data should be entered within 2 days of a completed visit. Once the subject is enrolled, any missing pages will appear on the Missing Pages Report for data not entered within 5 days of a visit. Once data is entered and saved, it is securely transmitted to the CTCC central database and stored on a secure server.

Range and edit checks run concurrently with data entry. Sites should develop a practice of immediately checking the Query Management Module to review and resolve any queries that may have been generated from these checks. The Information Analyst (IA) will also routinely run consistency checks, which review the data for consistency within a page and across multiple pages and/or multiple events. The IA will also run automated programs to code Medical History and Concomitant Medications.

REMEMBER: Queries are generated as soon as a page is opened and saved. If an assessment is not complete or information is pending, it is advised that you only open the page and enter the data once the information is complete. For example, entering only the drug name on the ConMed Log will produce queries for each of the numerous other items in that row.

Sites are responsible for logging into EDC (at least weekly) to review and resolve additional queries that may have been generated or applied manually. Sites may also reference the Pending Queries Report to determine what requires resolution in the database.

When all data for a page has been entered, the Entry Complete box in the bottom left corner must be checked. This is necessary so that the page can be transferred to LONI in the nightly data feed.

When data for all pages in an event are “clean” (no queries pending resolution and no missing pages), the event can be *Secured* by the CTCC Information Analyst. Pages in a secured status can be viewed by all, but no updates or changes to data can be made by the site users. Should changes to data be required, the site staff must contact the CTCC Information Analyst and request that a page or pages be un-secured.

The EDC system audit trail tracks all the required elements:

- Initial entry of data: by whom and when;
- Updates to data: by whom, when, the old and new values, and why the change was made to the data.

Abbreviations

Sites are discouraged from abbreviating, but abbreviation is acceptable when the meaning is unambiguous.

Misspellings

Misspellings by site staff are corrected in the database by CTCC staff as long as there is no ambiguity in the meaning. If the meaning is unclear, the site is queried for clarification.

Numeric Data

All numbers will be auto justified and do not require any leading zero fills. If a response requires a decimal point, the decimal point must be entered into one of the answer boxes.

Dates

Dates are recorded in the MMDDYYYY format. If an exact date is not known, you will be prompted to identify which part of the date is estimated.

BioFIND Operations Manual

Time

Time is recorded in the hours:minutes (HH:MM) format using military time. For example: 13:31 (1:31 pm). The EDC application requires entry of the colon.

Data Entry Errors

Errors due to incorrect data entry ('keypunch error') are to be corrected in the database and assigned 'site entry error' as reason for change.

Corrections or Updates to Saved Data

If a change is made to an eCRF after it is saved in the database, the correction will require the Site Coordinator or Site Investigator to indicate the reason for change within the audit dialog box. If a change was made to a page that required an eSignature, the eSignature will need to be reapplied. If a correction is necessary after the data have been *secured*, the CTCC IA must be contacted. All changes are documented via the audit trail.

Missing Data

Unexpected blanks are queried unless accompanied by a note to explain the reason for leaving the item blank (see the training guide for instructions on entering notes).

Missing Assessments/Pages

If part of an assessment is not performed, an explanatory note should be added to the respective data field(s). If the entire assessment is missed, do not open and/or save the page (this could generate unnecessary queries). A comment should be added to the Signature Page to document why the assessment was missed or not done.

REMEMBER: Missing pages will appear on the Missing Pages Report and will be included in site metrics regarding data entry compliance.

Missed Visits

If a visit is not performed, it should be noted on the visit Signature page. No other eCRFs from the visit should be opened. If the final visit is missed, the site must complete the Signature page, Conclusion of Study Participation page and all logs.

Unscheduled Visits/Unscheduled Phone Visits

If a subject calls to report an adverse event, the site investigator must determine whether a clinical visit is required. If an unscheduled visit is necessary, the site should pull in (add) the U0x event (see the training guide for instructions on pulling in an unexpected event) and refer to

BioFIND Operations Manual

the schedule of activities to determine which assessments and eCRFs should be completed for an unscheduled visit.

If a blood, saliva, urine, or CSF sample is not usable due to a problem in collection, processing, or shipping, or it fails quality control procedures at the central repository, and the subject returns to the site to provide another sample(s), then pull in (add) the U0x event and the relevant page(s) for the sample(s) being repeated.

Evaluation Dates

Visit date refers to the actual date that visit activities were conducted. Typically, the date is consistent on all eCRFs for the visit. If, for any reason, a visit stretches across several days, record the actual date the given task was performed, and indicate the latest date that activities were completed as the visit date on the Signature Page. In Comments on the Signature Page, state that the visit was conducted over multiple days.

Subject Identification Number (Subject ID)

All subjects who are potentially eligible and who have signed an informed consent should be assigned a 4-digit Subject Identification Number (provided by CTCC to sites). Subject ID Numbers should be assigned consecutively, beginning with the first number in the Subject ID Number list provided to each site.

NOTE: The EDC system refers to the Subject Number as Patient ID.

DIRECTIONS FOR BIOFIND eCRF PAGES

SCREENING/DEMOGRAPHICS FORM

- Data will be captured about any subject who has signed consent
- Information provided is also used to describe recruitment efforts in reports to the sponsor and IRB annual reports
- Typically in BioFIND the consent form is signed at Baseline/V01, and therefore, the projected enrollment date (item 5) is the same as the visit date. However, if that is not the case, please be sure to indicate a projected enrollment date (i.e., date of Baseline/V01). If this is unknown at the time of data entry, it is acceptable to estimate; however, please update the page once the visit is scheduled.
- Each subject should be asked how s/he learned about the study so that the Referral Source (item 6) can be recorded accurately.

- If between signing consent and completing Baseline/V01, a subject declines further participation or is excluded, be sure to return to the Screening/Demographics Form to complete item 7 or 8 respectively.

INCLUSION/EXCLUSION

- Ensure the correct form is used; there is a separate form for PD subjects and for Control subjects. Also be sure to use the correct Inclusion/Exclusion page if content has been modified due to a protocol amendment.
- This page must be completed in order to enroll a subject. (See Section 3 regarding Protocol Deviation Code.)

PD FEATURES

- Completed for PD subjects only to capture symptom onset and date of diagnosis. Question 3 – capture the symptoms that were present at the time of PD diagnosis.

FAMILY HISTORY OF PD

- Completed only at Baseline/V01.
- If response is “None” then a zero (0) should be used.
- Note that Control participants should have no first degree relative with PD indicated (i.e., response to question 1, 2,3, or 9). (Per AM2, PD subjects are no longer excluded by having a first degree relative with PD.)

PRIMARY DIAGNOSIS

- Form is to be completed by the Investigator.
- Included for both PD and Control subjects.
- In order to be eligible for participation, PD subject response to Q2 should be “01 = Idiopathic PD” and Control subject response to Q2 should be “17 = No PD nor other neurological disorder”.

GENERAL NEUROLOGICAL EXAM

- Form is to be completed by the Investigator.

USE OF PD MEDICATION

- Completed for PD subjects.
- Used to track whether a PD subject has started medication for treating symptoms of PD.
- If subject is on multiple PD medications, answer items regarding date and time of most recent dose based on the most recent dose of medication that is of highest priority

BioFIND Operations Manual

according to this list (with 1 being the highest): 1) levodopa; 2) dopamine agonist; 3) amantadine; 4) MAO-B inhibitor.

MDS-UPDRS

- Form, including Hoehn and Yahr, is to be completed by the Investigator or Sub-investigator (unless Principal Investigator has granted Coordinator permission to administer some/all parts).
- Only Part III is administered for Controls at Baseline/V01; no part is administered at V02.
- Parts I, II, III and IV are administered for PD subjects at Baseline/V01.
 - Part III should be administered 1-3 hours after the last PD medication of highest priority (see list under “Use of PD Medication” above).
 - All PD subjects are to be administered Part IV regardless of the type of PD treatment medication they are taking.
- At V02, only Part III is administered for PD subjects.
 - Part III should occur early in the morning before any PD medication dose.

MODIFIED SCHWAB & ENGLAND ADL

- Form is to be completed by the Investigator.

MOCA

- This test is administered to both PD and Control subjects, but it is an eligibility criterion for Controls only.
- The test administration worksheet is considered source and totals may be entered directly into the database from the worksheet.

LABORATORY PROCEDURES

- Centrifuge rates are to be recorded in **g force**, not in RPM.
- The worksheet is considered source, and all responses may be entered into the database from the worksheet.

SALIVA AND URINE SAMPLES

- Centrifuge rates are to be recorded in **g force**, not in RPM.
- The worksheet is considered source, and all responses may be entered into the database from the worksheet.

CLINICAL LABS

- The Site must retain the actual results reports from its local clinical laboratory as source documentation.
- Reports are to be reviewed and dated/initialed by the Investigator.

BioFIND Operations Manual

- Results are to be entered onto the worksheet and then into the database.

LUMBAR PUNCTURE

- Centrifuge rates are to be recorded in **g force**, not in RPM.
- This worksheet will contain information based on the LP conducted by the site and results regarding cell counts, protein, and glucose reported by the local clinical laboratory.
- The Site must retain the actual results reports from its local clinical laboratory as source documentation.
- Reports are to be reviewed and dated/initialed by the Investigator.

VISIT STATUS

- A Visit Status form is required for each expected in-person and telephone study visit whether or not the visit was actually performed.

SIGNATURE FORM

- A Signature Form is required for each expected in-person and telephone study visit whether or not the visit was actually performed.
- Site payment for each visit is processed based on completed data entry and completed Signature Form, the eSignature applied by the Investigator.
- This form certifies that the investigator or designated sub-investigator who conducted the visit has reviewed all data points for the visit and determined that they are complete, accurate and compatible with source documents.
- **This form must be signed AFTER all data for the visit have been reviewed and entered.**

CONCOMITANT MEDICATION LOG

- Record medications the subject is taking at the time of the Baseline/V01 Visit.
- At subsequent visits record new meds, and changes/discontinuation of previously listed medications.
- Medication: Whenever possible, use generic name. If generic name cannot be determined, use brand name.
- Dose: The total dose the participant takes for one administration. Enter only the numerical portion. For example, 2 tablets of 300 mg each should be entered as TOTAL of 600 mg.
- Units: The unit of measurement by which the drug is being measured (e.g. mg, IU, tabs).
- Frequency: How often the drug is being given (e.g. QD, BID, QID).
- Route: Record route of administration using key options 1-9.

BioFIND Operations Manual

- Start/Stop Dates: The start date of medication should be the date the participant first began taking the medication. Enter in MMDDYYYY format; if the exact date is unknown, an **estimated date** should be used.
- Date estimation key: Record date estimation using key options 1-4 following start and stop dates.
- Ongoing: If medication is continuing, leave blank until the study is over or subject ends participation. If a medication has stopped, answer should be 0 (No) and a valid stop date must be provided.
- Indication: Purpose for which the medication is taken (e.g. hypercholesterolemia, general health).
- PD Medication: If medication is a PD med then response of 1=Yes should be used.

If a subject is receiving botox injections for drooling, record the date of the most recent injection as the start and stop dates.

ADVERSE EVENT LOG

- Used to record adverse events that may be reported within 7-10 days of a lumbar puncture only. Record these adverse events whether or not they are thought to be related to the LP.
- Record diagnosis if known rather than symptoms.
- See the Protocol for the definition of serious adverse event, severity, and relationship to study.

ADVERSE EVENT FOLLOW-UP LOG

- This form is required if subject has an ongoing AE at 7-10 day LP follow-up call.
- For each ongoing AE, transcribe the row number and AE term from the Adverse Event Log.
- This form should be finalized when all AEs recorded have been followed for 30 days from LP or until resolved or stabilized (whichever occurs first).

CONCLUSION OF STUDY PARTICIPATION

- Used for subjects who withdraw participation before the study is completed, as well as for subjects who complete the study.

SECTION 5

ASSESSMENTS

MDS-UPDRS with Hoehn & Yahr
Modified Schwab & England Activities of Daily Living
Montreal Cognitive Assessment (MoCA)
REM Sleep Behavior Disorder Questionnaire

MDS-UPDRS

The full 30 page MDS-UPDRS, including Hoehn and Yahr Stage, and Score Sheet is posted on ePortal for use as source documentation for this assessment. Instructions for administration are contained within the MDS-UPDRS packet. In addition, Investigators and Sub-investigators must receive training and certification through the MDS website prior to administration.

Part Ia – Non-motor experiences of daily living assessed by site Investigator or Sub-investigator (coordinator may conduct as approved by CTCC).

Part Ib (Patient Questionnaire) – Completed by the subject and/or caregiver.

Part II (Patient Questionnaire) – Completed by the subject and/or caregiver.

Part III – Motor examination conducted by site Investigator or Sub-investigator.

- Note: Questions 3a, 3b, and 3c will not be captured in the database. See Use of PD Medication data form to capture and record information for subjects on medication for treating symptoms of PD.

Part IV – Motor complications assessed by site Investigator or Sub-investigator.

Hoehn and Yahr Stage – Assessed by site Investigator or Sub-investigator.

- 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.

Modified Schwab & England Activities of Daily Living

This 0-100 scale is used to rate a subject's current overall function and reflects the speed, ease, and independence with which an individual performs daily activities, or personal chores, such as eating, toileting, and dressing. Scores should be in increments of 5 points (e.g., 100, 95, 90, 85, etc.) based on a consensus rating of the investigator, subject and/or caregiver.

- 100% Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
- 90% Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
- 80% Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
- 70% Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
- 60% Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
- 50% More dependent. Help with half, slower, etc. Difficulty with everything.
- 40% Very dependent. Can assist with all chores but few alone.
- 30% With effort, now and then does a few chores alone or begins alone. Much help needed.
- 20% Nothing alone. Can be a slight help with some chores. Severe invalid.
- 10% Totally dependent, helpless. Complete invalid.
- 0% Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden.

Consensus rating
(Investigator, patient, other sources)

1.

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Montreal Cognitive Assessment (MoCA) (version 7.1)

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) was designed as a rapid screening instrument more sensitive to patients with mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. Less than 26 is exclusionary for Control subjects.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern:

1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: "Copy this drawing as accurately as you can, in the space below".

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: "Draw a **clock**. Put in all the numbers and set the time to 10 after 11".

Scoring: One point is allocated for each of the following three criteria:

BioFIND Operations Manual

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. **Naming:**

Administration: Beginning on the left, point to each figure and say: "Tell me the name of this animal".

Scoring: One point each is given for the following responses: (1) lion, (2) rhinoceros or rhino, (3) camel or dromedary.

5. **Memory:**

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them". Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time." Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "I will ask you to recall those words again at the end of the test."

Scoring: No points are given for Trials One and Two.

6. **Attention:**

Forward Digit Span: Administration: Give the following instruction: "I am going to say some numbers and when I am through, repeat them to me exactly as I said them". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”.

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A)

Serial 7s: Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: **I only know that John is the one to help today.**” Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: **The cat always hid under the couch when dogs were in the room.**”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.” Record the subject’s responses on the “MoCA Fluency: Letter F” response sheet.

Scoring: On the MoCA worksheet, 11 or more correct responses = 1; 10 or less = 0. On the MoCA page in EDC, also enter the total number of correct responses for “F” phonemic fluency as recorded on the response sheet.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification.

After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of traveling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember. Make a check mark for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues.**

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "Which of the following words do you think it was, NOSE, FACE, or HAND?" Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE: category cue: part of the body multiple choice: nose, face, hand

VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet

CHURCH: category cue: type of building multiple choice: church, school, hospital

DAISY: category cue: type of flower multiple choice: rose, daisy, tulip

RED: category cue: a color multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: "Tell me the [year, month, exact date, and day of the week]." Then say: "Now, tell me the name of this place, and which city it is in."

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all sub-scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

BioFIND Operations Manual

MONTREAL COGNITIVE ASSESSMENT (MOCA) SUBJECT ID _____ VISIT NO _____

VISUOSPATIAL / EXECUTIVE		Copy cube	Draw CLOCK (Ten past eleven) (3 points)	POINTS																		
				<input type="checkbox"/> Contour <input type="checkbox"/> Numbers <input type="checkbox"/> Hands ___/5																		
NAMING																						
				___/3																		
MEMORY																						
Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		<table border="1"> <thead> <tr> <th></th> <th>FACE</th> <th>VELVET</th> <th>CHURCH</th> <th>DAISY</th> <th>RED</th> </tr> </thead> <tbody> <tr> <td>1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial						2nd trial							No points
	FACE	VELVET	CHURCH	DAISY	RED																	
1st trial																						
2nd trial																						
ATTENTION																						
Read list of digits (1 digit/ sec). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2				___/2																		
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] F B A C M N A A J K L B A F A K D E A A J A M O F A A B				___/1																		
Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt				___/3																		
LANGUAGE																						
Repeat: I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []				___/2																		
Fluency / Name maximum number of words in one minute that begin with the letter F [] _____ (N ≥ 11 words)				___/1																		
ABSTRACTION																						
Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler				___/2																		
DELAYED RECALL																						
Has to recall words WITH NO CUE		<table border="1"> <thead> <tr> <th></th> <th>FACE</th> <th>VELVET</th> <th>CHURCH</th> <th>DAISY</th> <th>RED</th> </tr> </thead> <tbody> <tr> <td></td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> </tr> </tbody> </table>		FACE	VELVET	CHURCH	DAISY	RED		[]	[]	[]	[]	[]		Points for UNCUED recall only						
	FACE	VELVET	CHURCH	DAISY	RED																	
	[]	[]	[]	[]	[]																	
Optional Category cue Multiple choice cue																						
ORIENTATION																						
[] Date [] Month [] Year [] Day [] Place [] City				___/6																		
© Z.Nasreddine MD Version November 7, 2004 www.mocatest.org		Normal ≥ 26 / 30		TOTAL ___/30 Add 1 point if ≤ 12 yr edu																		

REM Sleep Behavior Disorder Questionnaire

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) is a 10 item, subject self-rating instrument assessing sleep behavior with short questions that have to be answered either “yes” or “no”. Questions are framed to gather information about current behaviors. For purposes of BioFIND, “current” is defined as within 6 months of the Baseline/V01 study visit.

Instructions and scoring:

- 1) Since subjects do not always have a long-time companion, the bed partner’s input is encouraged, but not required.
- 2) Subjects should respond to each question. If they are not certain, they should choose the response (either yes or no) that is most likely.
- 3) For question 10, more than one nervous system disease may be recorded. All PD subjects should record “parkinsonism”.
- 4) Questions 6.1 to 6.4 should be marked “yes” if any of the phenomena described in the appropriate line is present.
- 5) Scoring will be performed centrally.

REM SLEEP DISORDER QUESTIONNAIRE

- A. Source of Information: 1 = Patient, 2 = Caregiver, 3 = Patient and caregiver A.
1. I sometimes have very vivid dreams. (0 = No, 1 = Yes) 1.
2. My dreams frequently have an aggressive or action-packed content. (0 = No, 1 = Yes) 2.
3. The dream contents mostly match my nocturnal behaviour. (0 = No, 1 = Yes) 3.
4. I know that my arms or legs move when I sleep. (0 = No, 1 = Yes) 4.
5. It thereby happened that I (almost) hurt my bed partner or myself. (0 = No, 1 = Yes) 5.
6. I have or had the following phenomena during my dreams:
- 6.1 speaking, shouting, swearing, laughing loudly (0 = No, 1 = Yes) 6.1
- 6.2 sudden limb movements, "fights" (0 = No, 1 = Yes) 6.2
- 6.3 gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes, falls off the bed (0 = No, 1 = Yes) 6.3
- 6.4 things that fell down around the bed, e.g., bedside lamp, book, glasses (0 = No, 1 = Yes) 6.4
7. It happens that my movements awake me. (0 = No, 1 = Yes) 7.
8. After awakening I mostly remember the content of my dreams well. (0 = No, 1 = Yes) 8.
9. My sleep is frequently disturbed. (0 = No, 1 = Yes) 9.
10. I have/had a disease of the nervous system: (0 = No, 1 = Yes)
- 10a. stroke 10a.
- 10b. head trauma 10b.
- 10c. parkinsonism 10c.
- 10d. RLS 10d.
- 10e. narcolepsy 10e.
- 10f. depression 10f.
- 10g. epilepsy 10g.
- 10h. inflammatory disease of the brain 10h.
- 10i. other, specify: _____ 10i.

SECTION 6

REPORTABLE EVENTS

Incident Reporting
Notification Reporting
Reporting of Adverse Events

INCIDENT AND NOTIFICATION REPORTING

When notifying the CTCC of an event, please have the following information available:

- Caller's staff code
- Subject ID Number (if applicable)
- Date of notification/event
- Details surrounding the event

INCIDENT REPORTING

(See Protocol Section 12)

The objective of the incident reporting process is to alert key personnel overseeing the study regarding all experiences that may influence the safety of individual subjects or the subjects in the study as a whole. Incidents may be reported by the Site Investigator or Coordinator. The following events are considered incidents and must be reported to the CTCC Project Manager within 24 hours of the time they occur or become known to site staff:

- **Change of Diagnosis**
 - Although each subject is enrolled into the study with a clinical diagnosis of PD or as a control with no current or active neurological disorder, it is understood that further evaluations or changes may occur to a subject that may result in a new or different diagnosis. However, this is highly unlikely within the short duration of a subject's participation in BioFIND.
- **Participation in Another Clinical Trial or Study**
 - Use of investigational drugs or devices within 60 days prior to Baseline/V01 is exclusionary in BioFIND, and should not be started within the short duration of a subject's participation in BioFIND. However, if it becomes known that a subject did begin participating in another clinical trial or observational study during BioFIND, we would like to track this information. If the subject is participating in a clinical trial, be sure to indicate the study drug information (if known) on the Concomitant Medication Log.
- **Withdrawal**
 - Regardless of the reason, whether investigator initiated or subject request, all withdrawals must be reported and the Conclusion of Participation CRF completed.
- **Serious Adverse Event (SAE)**
- **Death**

The incident will be entered into an on-line module and immediately distributed by email to the Principal Investigator, Steering Committee, and study team members.

The site will also receive an e-mailed report for review after the call. This report should be kept with the subject's source binder.

NOTIFICATION REPORTING

The purpose of the notification process is to detail all noteworthy and relevant clinical or data management decisions that might influence the interpretation of the study data. The Coordinator, Investigator or Site Monitor may report notifications.

The following events are examples of issues requiring notification and should be reported to the CTCC Project Manager:

- Eligibility issues
 - Site must report any questions or issues regarding eligibility as soon as possible before enrolling the subject in EDC. If any eligibility criteria are not met, you must obtain a protocol deviation code from the CTCC to be used on the Inclusion/Exclusion form.
- Issues with any protocol procedures
- Site specific issue(s)

The final Notification Report describing the event will be emailed to the site. The Site Coordinator should review the content of this report for accuracy. The CTCC should promptly be notified if any additional information or corrections are needed. This report should be kept with the subject's source binder.

REPORTING OF ADVERSE EVENTS

Definitions and techniques for assessing Adverse Events (AEs) and Serious Adverse Events (SAEs) are described in Section 11 of the protocol.

For the purposes of reporting SAEs in BioFIND, the study period is defined as the time period from the lumbar puncture until the 7-10 day follow-up call. If an SAE does occur within this time period, it must be reported to the Project Manager and a MedWatch form must be completed.

The CTCC must be notified within 24 hours of site's awareness of any SAE, including death. The SAE reported by phone will be entered into an Incident Module and will be sent to the Principal Investigator and Steering Committee, and other study staff via e-mail.

Notifying the IRB/EC and Subjects

Institutional guidelines should be followed in notifying a site's IRB/EC of SAE's (safety reports) and in communicating relevant information to subjects. The site must maintain a copy of IRB/Ethics

BioFIND

notification and of the IRB/Ethics acknowledgement of receipt of any serious adverse event or safety report that is submitted.

SECTION 7

LABORATORY SPECIMEN MANAGEMENT

Research Biomarkers Laboratory Manual
[Insert Copy]

SECTION 8

SOURCE DOCUMENTATION

Instructions for Source Documentation

APPENDIX 8

Source Documentation Worksheets

[Insert blank set of unique forms]

INSTRUCTIONS FOR SOURCE DOCUMENTATION

Per FDA and ICH guidelines, source documents include the first record of any subject data, regardless of the medium used to record the data. These documents may include subject's medical records, progress notes, lab reports, and so on.

The BioFIND study uses electronic data capture (EDC). Sites are responsible for maintaining adequate source documents for this study. Sites must keep visit and subject correspondence notes in addition to use of the Source Document Worksheets (SDWs). Subject study charts must be made available to the site monitor for review. SDWs for all of the eCRFs that will be used in this study are located in the ePortal "Source Document Worksheets" folder. Sites will be provided with an initial set of source worksheet binders (6 PD and 4 Control) that will contain SDWs for visits baseline-final. Photocopy or print extra worksheets as your needs require. (Sites entering the study after the initial five sites must print all SDWs from ePortal.)

The Investigator or Coordinator may record directly on the SDWs and supplement with additional information as needed. Any written or dictated note must, at a minimum, contain information specified in the worksheet.

You should carefully record the process used by your site when consenting an individual subject. Include in your source that the subject was given a copy of the signed consent.

The following SDWs will be considered source for data entered into EDC:

- Confidential Subject Identification Code List (Note: Source only – not entered in the database)
- Delegation Log (Note: Source only – not entered in the database)
- Screening/Demographics
- Socio-Economics
- CTCC Unique ID
- PD Features
- Primary Diagnosis
- Family History (PD)
- Inclusion/Exclusion
- Medical History (General)
- Smoking and Alcohol Questionnaire
- General Neurological Exam
- Vital Signs
- Fasting Status
- Use of PD Medication
- Modified Schwab & England Activities of Daily Living

BioFIND Operations Manual

- REM Sleep Disorder Questionnaire
- Laboratory Procedures
- Saliva and Urine Samples
- DNA Sample
- Clinical Labs
- Lumbar Puncture
- Conclusion of Study Participation
- Visit Status
- Investigator Signature
- Concomitant Medication Log
- Adverse Event Log
- Adverse Event Follow-up Log

The following worksheets/booklets will be considered source for data entered into EDC:

- MDS-UPDRS packet
- Montreal Cognitive Assessment (MoCA) worksheet

The progress notes/source documentation/medical records should contain information about whatever has happened to the subject during the course of the study, especially if it is not captured on the CRF worksheet or visit notes. Please keep your source documents either with your CRF worksheets or in a subject binder, available at the time of the site monitoring visit.

APPENDIX 8

Source Documentation Worksheets

[Insert blank set of unique forms]

SECTION 9

MONITORING

Study Initiation

Site Visit

Interim Monitoring

Telephone Closeout Visit

Contents of Regulatory Binder

MONITORING

Study Initiation

Attendance at the Investigator/Coordinator Orientation Meeting was required for staff of the initial five sites. The objective of the orientation was to ensure that study site personnel understand the protocol and their individual responsibilities, as well as all of the regulatory requirements. During the site orientation meeting, the following items were reviewed:

- Protocol and Data Forms
- AEs and SAEs
- Biological samples, storage and shipment
- Investigator obligations
- Record keeping
- Study files
- Source documentation
- Advertisement for enrollment

For staff and/or sites joining BioFIND after the Orientation Meeting, protocol and biologics training will be provided via webinar.

Site Visit

The Project Manager at the CTCC will work closely with the site monitors to provide consistent answers to investigators and coordinators regarding their protocol questions during monitoring visits.

After each monitoring visit, the study monitor will produce a site monitoring report that is reviewed at the CTCC. The study monitor will send a follow up letter to the site reiterating any discussions that occurred at the monitoring visit and listing any action items.

Per agreement of the sponsor, Principal Investigator, and CTCC, each site will have one on-site monitoring visit during the study. This visit will occur after a site has enrolled at least 2 subjects, one of which must be a PD subject. At this visit, the Investigator, Coordinator, and any other key staff members involved in the study should be available (or easily reachable). During this visit, the following will be reviewed:

- Adequacy of study facilities
- Ensuring that the study staff has a good understanding of the protocol and proper procedures for CRF completion and data entry

BioFIND Operations Manual

- Regulatory binder, protocol, case report form worksheets, adverse event reporting, medical record (source) documentation, and informed consents (to assure that the inclusion/exclusion criteria have been properly met, that data forms are completed correctly, and the documentation adheres to the Good Clinical Practice (GCP) requirements)
- eCRFs of at least one PD and one Control who have completed the study will be reviewed for completeness and accuracy and compared to the source documentation
- Signed consent forms for all other currently enrolled subjects.
- Study correspondence, including correspondence between the Investigator and the site's IRB, and between the site staff and the CTCC

Interim Monitoring

On a quarterly basis after this on-site visit, sites will be requested to send to the monitor a copy of the signed consent form and Screening/Demographics source document worksheet for each subject newly consented during the previous quarter. The monitor will compare these documents and will verify that the Screening/Demographics data have been completely and accurately entered into the database.

Telephone Closeout Visit

The monitor is responsible for a clinical site close out visit when all subjects have completed the study at a site, the monitor will hold a conference call with the coordinator to verify that the site's regulatory binder and the CTCC file contain all regulatory documents pertaining to the study for that site. Record retention requirements will also be discussed.

Contents of the Regulatory Binder

The site must maintain a Regulatory Binder (also referred to as the Investigator's file or study file). This binder will be reviewed at the in-person monitoring visit and by telephone at the end of the study and should therefore be kept up-to-date.

The Investigator's Regulatory Binder should contain the following:

- Current CV's and licenses (if applicable)
- Protocol and Amendments (when applicable)
- Protocol Investigator Agreement Signature Page
- IRB Communication
 - Approval letter(s) for protocol, consent forms, recruitment materials, amendments
 - Approved consent forms
 - Approved recruitment and subject materials

BioFIND Operations Manual

- IRB Membership Inquiry Form
- Correspondence to/from IRB
- Study closeout letter to IRB
- General Correspondence
- SAE's (if applicable)
 - Completed SAE forms
 - Correspondence regarding SAE forms
- Incident Reports (if applicable)
- Notifications (if applicable)
- Confidentiality Agreements
- Monitoring Log
- Delegation Log
- Notes to File
- Blank of each unique CRF Worksheet (in Regulatory Binder or Operations Manual)
- Lab documentation and CLIA waiver certification (if applicable)
- Human Subject Education certifications
- MDS-UPDRS certification (for Investigators and Sub-investigators)

SECTION 10

REPORTS

Enrollment Report
Cumulative Enrollment
Enrollment By Diagnosis, Gender, Age
Incident Report
Notification Report
Pending Queries Report
Missing Pages Report
Missing Inv eSignature Report
Missing Completion Status Report
Site Performance Report

BIOFIND STUDY REPORTING

Described below are some of the reports generated for the BioFIND study to help the Operations Team manage the project and ensure sites are meeting expectations and goals of the study. In addition, some reports are generated to assist sites in keeping track of what may be missing as a result of all the data that needs to be entered.

ENROLLMENT REPORT

- A summary for each site and the whole study of the number of PD and Control subjects consented, excluded/declined, enrolled, withdrawn, and completed, in addition to the number of subjects for whom CSF samples were collected.
- Distributed on a weekly basis to site Investigators and Coordinators and the Operations Team.

CUMULATIVE ENROLLMENT

- A graph depicting actual and projected enrollment across time, and a pie chart indicating the percent of targeted enrollment met to date.
- Distributed to site Investigators and Coordinators and Operations Team on meeting days.

ENROLLMENT BY DIAGNOSIS, GENDER, AGE

- A summary of total enrollment at each site, as well as for the whole study, separated out by subject group, gender and age.
- A subject appears on this report once they are enrolled into the study.
- This report will be used by the Operations Team to monitor the overall study population, particularly in regard to age and gender balance for subjects enrolled, as discussed in Section 4.6 of the protocol.

INCIDENT REPORT

- Generated when a site notifies CTCC of any protocol specified reportable event as outlined in Section 12 of the protocol. (Also see Section 6 of this manual.)
- This report is a summary of the event that occurred and is distributed to the site Investigator and Coordinator.
- The Coordinator is to review the report to ensure accuracy and file a copy in the study binder.

NOTIFICATION REPORT

- Generated when a site informs the CTCC of any relevant clinical or data management issues that should be noted (see Section 6 of this manual).

BioFIND Operations Manual

- A summary of the event that occurred is distributed to the site Investigator and Coordinator.
- The Coordinator is to review the information to ensure accuracy and file a copy in the study binder.

PENDING QUERIES REPORT

- Generated when a query is left unresolved 5 days beyond the creation date.
- Distributed to site Coordinator on a weekly basis or more frequently during close out.

MISSING PAGES REPORT

- A page is listed as missing when an expected page is not entered within 5 days of the visit for an individual subject.
Missing pages start to be reported once a subject is enrolled. The Missing Pages Report is emailed to the Coordinator on a weekly basis.

MISSING INV eSIGNATURES REPORT

- An Investigator's signature is listed as missing for any completed visit that does not have the electronic signature of the Investigator applied to the Signature Form.
- The Investigator or Sub-investigator who conducted the visit should sign off on the visit.
- The Missing INV eSignature Report is sent only to the primary designated Investigator at each site (and copied to the Coordinator) on a weekly basis.

MISSING COMPLETION STATUS

- The Entry Complete box must be checked on a page once all the data on that page has been entered.
- The Missing Completion Status Report is sent to the Coordinator on a weekly basis.

SITE PERFORMANCE REPORT

- Tracks expected forms received (data entered) and the timeliness of data entry (i.e., within 5 days of the visit).
- Tracks how many queries are generated at each site and how timely the site addresses queries (i.e., timely is a comparison of origination date to the resolution date)
- This report will be used by the study team to ensure timely entry of data, as well as accurate and clean data, which is essential to this project. Any significant issues will be addressed directly with a site.