Manual of Operations

S4: Systemic Synuclein Sampling Study

Version 2.0

23 March 2016

Version 2.0 of the S4 Manual of Operations is to be used in conjunction with Version 2.0 of the S4 Protocol

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### 1.0 GLOSSARY OF ABBREVIATIONS

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<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>α-syn</td>
<td>Alpha-synuclein</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CTSDMC</td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
<tr>
<td>DAT</td>
<td>Dopamine Transporter</td>
</tr>
<tr>
<td>DCC</td>
<td>Data Coordinating Center</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HC</td>
<td>Healthy Control</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HSPP</td>
<td>Human Subject Protection Program</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IND</td>
<td>Institute for Neurodegenerative Disorders in New Haven, CT</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IXRS</td>
<td>Interactive Voice/Web Response System</td>
</tr>
<tr>
<td>LP</td>
<td>Lumbar Puncture</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MDS-UPDRS</td>
<td>Movement Disorder Society Unified Parkinson Disease Rating Scale</td>
</tr>
<tr>
<td>MJFF</td>
<td>The Michael J. Fox Foundation for Parkinson’s Research</td>
</tr>
<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the Counter</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PT/PTT</td>
<td>Prothrombin Time/Partial Thromboplastin Time</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cell</td>
</tr>
<tr>
<td>S4</td>
<td>Systemic Synuclein Sampling Study</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SC</td>
<td>Steering Committee</td>
</tr>
<tr>
<td>UPSIT</td>
<td>University of Pennsylvania Smell ID Test</td>
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</table>
2.0 MOP CONTENTS AND ORGANIZATION

2.A Protocol
A summary of the protocol is abstracted here for quick reference. The current approved protocol is available in online study documents. A print copy is retained in the site regulatory binder.

Objectives:

The primary objective is:

To characterize the distribution of alpha-synuclein (α-syn) pathology through evaluation of quantitative and semi-quantitative outcomes for α-syn (total, phosphorylated, oligomeric and other α-syn species) in multiple tissues and body fluids in individual subjects with clinically typical Parkinson’s disease (PD) and healthy controls (HC). The primary objectives are:

- To evaluate the α-sync markers as potential surrogate markers for patient selection/enrichment that would be useful in future clinical trials.
- To compare α-syn load and pattern in the biofluids and tissues in PD subjects versus HC subjects.

The secondary objectives are:

- Evaluate the feasibility and safety of obtaining multiple tissues and biofluids in an individual with PD.
- Establish standardized protocols for biopsies of various tissues and methodology for α-syn staining and pathological analysis.
- Establish standardized protocols for various biofluid acquisition and assays for quantifying total α-syn and other α-syn species (once assays are available).
- Establish a bank of tissues and biofluids from a cohort of HC subjects and well-characterized subjects with typical PD for use for the future development and testing of biomarker assays.
- Compare the α-syn load among the tissues and fluids in the PD cohort subdivided by the clinical stage of disease (early PD not requiring dopamine replacement therapy, moderate PD on dopamine replacement therapy without motor fluctuations, advanced PD with motor fluctuations).
- Compare the α-syn load among the tissues and fluids with dopamine transporter (DAT) integrity based on striatal uptake measured by DAT imaging among the PD groups in addition to comparing PD versus HC.

Study Design:

This is a multi-center, cross-sectional, observational study to evaluate α-syn pathology in multiple tissues and biofluids in individual subjects with PD and HC at a single time point. Each subject’s participation will be approximately 16 weeks. The total duration for sample collection for this study will be approximately 24 months.

Current Version:

The current version of the study protocol is available online for download by study staff on the study website (www.s4study.org), managed by the Clinical Trials Statistical Data Management Center (CTSDMC). Previous protocol versions are also available on the website. As each new version of the protocol is released to sites, it will be distributed as an electronic pdf version.

Protocol version control is extremely important, especially in multi-center trials, to ensure that all sites and all regulatory authorities receive identical documents. During protocol development, the CTSDMC maintains version control of the protocol documents. Before a protocol is considered “final” and actionable, it must undergo a formal review and approval by the Principal Investigators (PI), the Steering Committee, the Sponsor, the clinical and regulatory staff at the Institute for Neurodegenerative Disorders (IND), and staff at the CTSDMC. After approval, the CTSDMC is responsible for obtaining all required approvals prior to finalizing the protocol.
document. Once the document is finalized, the CTSDMC labels it as an actionable version and releases it for distribution as an electronic .pdf copy to all participating sites.

2.B Communications Plan

Routine administrative communications with clinical sites, such as scheduling meetings and training sessions and addressing other site issues will be managed by the CTSDMC. Information that needs to be circulated to all study sites will be distributed by email released by the CTSDMC Lead Coordinator. Such communications, both regulatory and non-regulatory, will also be hosted on the study website for access by study staff.

In order to assure ongoing communication between study leadership, the Steering Committee, and site investigators, teleconferences will be scheduled regularly and on an as needed basis. A regular teleconference will be offered for the clinical site coordinators in order to build camaraderie, share best practices, discuss issues, and share strategies for success. The communications will be developed and led by the CTSDMC staff.

The Steering Committee will also participate in routine bi-weekly calls to discuss progress, issues, and potential solutions.

Routine reports for study progress will be generated by the CTSDMC and be made available to the Steering Committee through regular updates to the study general reports file hosted on the study website.

These reports will include:

- Activation of study sites
- IRB approval status
- Accrual of study subjects
- Withdrawal or conclusion of participation of study subjects
- Age, ethnicity, race, and gender of study subjects
- Compliance by site with study procedures (deviations)
- Data completeness
- Adverse Events
<table>
<thead>
<tr>
<th>Study Management Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Questions Regarding:</strong></td>
</tr>
</tbody>
</table>
| Urgent medical management questions | Danna Jennings, MD  
Senior Clinical Research Director  
Institute for Neurodegenerative Disorders  
60 Temple St, Ste 8B  
New Haven, CT 06510  
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Lead CTSDMC Coordinator/Monitor  
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Email: holly-riss@uiowa.edu  
Alternate contact for database questions:  
Trevis Huff  
Lead Data Manager  
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Iowa City, IA 52242  
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Email: trevis-huff@uiowa.edu |
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Tel: 203-401-4337  
Email: lcortina@indd.org |
2.C Screening and Eligibility Criteria
To assure that clinical sites accrue participants with the same characteristics, this section provides a detailed discussion of the screening procedures utilized to identify and determine participant eligibility. Frequently, there is a pre-screening phase during which the study coordinator responds to initial telephone inquiries from physicians or potential study subjects.

If the individual meets the pre-screening criteria (e.g. age, apparent diagnosis) then the patient will attend a screening visit, provide informed consent, and complete the initial screening procedures that can confirm individual eligibility. Prior to administering any of these procedures, the study staff must provide a detailed description of the study and must obtain the individual’s informed consent (see Section 2.D)

2. C.1 Eligibility Criteria
The study eligibility is determined by a set of protocol-specific inclusion and exclusion criteria that are outlined in the protocol in sections 3.3.2-3.3.6. Potential study participants must meet all entry criteria prior to enrollment. This section defines the criteria for both PD subjects and HC subjects.

2. D Informed Consent and HIPAA
Once a clinical site coordinator, investigator, or other site staff member identifies an individual that appears to meet pre-screening criteria, the informed consent is initiated and the individual must sign an informed consent form prior to undergoing a physical examination, medical history, laboratory procedures, or other eligibility assessments. This section describes the specific instructions regarding the process of obtaining informed consent. The study investigator or study coordinator typically provides a detailed explanation of the study and informed consent procedures.
consent form a prospective participant. Additionally, the study staff member must discuss the nature of the study, study procedures, visit obligations, and importance of compliance, potential risks and benefits, and study duration. The process should provide for ample time for the prospective participant to read the informed consent form.

An individual must be informed that he/she is not obligated to participate in the study. The informed consent process should ensure that there is no penalty for not participating in a clinical trial and that treatment will not be compromised if individuals do not participate or if they cease participation at any time. Adequate time should be allowed for the prospective participant to ask questions. The participant’s signature/legal representative and the investigator or the person actually obtaining the consent must sign the informed consent. A copy of the signed informed consent must be provided to the participant.

The informed consent form is to be retained in the subject source binder, along with the completed informed consent process note documenting the consenting process.

2.D.1 Informed Consent Document
The current approved informed consent document is available in the online study documents. A print copy of each original approved document is retained in the site regulatory binder.

If there is a change in any of the study procedures that may affect the participant, the informed consent document will be revised and again approved by the IRB. Any participants enrolled in the study prior to such changes will be presented with the revised consent and be asked to review and sign the amended consent form prior to participating in the study further. All subjects participating in study procedures must sign the current approved version of the informed consent document prior to participating in any study procedures.

Submission of the informed consent process note into the electronic Case Report Form (eCRF) generates a unique subject identification number.

2. D.2 HIPAA Procedures
A HIPAA form will be incorporated into the Informed Consent Form or provided separately, per institutional policy. The HIPAA form describes participant and data confidentiality associated with the study.

2.E Subject ID
The unique Subject ID is 6 characters in length and unique to each subject. The format of the unique Subject ID is as follows:

XX-YYYY

The number is broken down as follows:

- XX = 2-digit site number
- YYYY = 4-digit number assigned sequentially based on site enrollment
### 3.0 DESCRIPTION OF VISITS

#### 3. A Screening Visit

The patient will be identified as a potential study subject and will go through a screening process prior to enrollment in the S4 study. The procedures for the screening visit may take up to 8 hours and may occur over multiple days. The screening visit will include the following:

<table>
<thead>
<tr>
<th>Assessment/Procedure</th>
<th>Location of Source Documentation</th>
<th>Enter into Electronic Data Capture System (EDC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain Informed Consent</td>
<td>IRB Approved Informed Consent signed</td>
<td>Informed Consent eCRF</td>
</tr>
<tr>
<td>Review subject’s medical and family history</td>
<td>Medical Record or Subject Research Binder</td>
<td>Medical History and Medical History of PD eCRF</td>
</tr>
<tr>
<td>Review of concomitant meds</td>
<td>Medical Record or Subject Research Binder</td>
<td>Con Meds eCRF</td>
</tr>
<tr>
<td>Vital Signs (blood pressure, heart rate, respiratory rate, and temperature)</td>
<td>Vital Signs CRF</td>
<td>Vital Signs eCRF</td>
</tr>
<tr>
<td>Physical Exam including height and weight</td>
<td>Physical Exam CRF</td>
<td>Physical Exam eCRF</td>
</tr>
<tr>
<td>Neurological Exam</td>
<td>Neurological Exam CRF</td>
<td>Neurological Exam eCRF</td>
</tr>
<tr>
<td>MDS-UPDRS Parts I-IV (Part IV will not be done for healthy controls or early PD subjects. This assessment can be done at any visit) <em>See 3.A.1</em></td>
<td>Combination of MDS-UPDRS and CRF. The patient portion of MDS-UPDRS and the CRF portion that are completed by site/investigator</td>
<td>MDS-UPDRS eCRF</td>
</tr>
<tr>
<td>Hoehn and Yahr (all subjects)</td>
<td>This is part of the MDS-UPDRS</td>
<td>MDS-UPDRS eCRF</td>
</tr>
<tr>
<td>Modified Schwab &amp; England (PD Subjects only)</td>
<td>Schwab &amp; England CRF</td>
<td>Schwab &amp; England eCRF</td>
</tr>
<tr>
<td>PD Stage Assignment</td>
<td>Medical Record or Subject Research Binder</td>
<td>Informed Consent eCRF</td>
</tr>
<tr>
<td>MoCA (all subjects)</td>
<td>MoCA</td>
<td>MoCA eCRF</td>
</tr>
<tr>
<td>Scales for Outcomes in Parkinson’s Disease Autonomic (SCOPA-AUT) (all subjects)</td>
<td>SCOPA-AUT CRF</td>
<td>SCOPA-AUT eCRF</td>
</tr>
<tr>
<td>UPSIT (all subjects)</td>
<td>UPSIT</td>
<td>UPSIT eCRF</td>
</tr>
<tr>
<td>Clinic lab assessments</td>
<td>Medical Record or Subject Research Binder</td>
<td>Clinical Safety Assessments eCRF</td>
</tr>
<tr>
<td>DAT SPECT Imaging</td>
<td>DAT SPECT Imaging</td>
<td>DaTSCAN Imaging eCRF</td>
</tr>
<tr>
<td>Review AEs after SPECT Imaging</td>
<td>Procedural Follow Up CRF and AE CRF</td>
<td>Procedural Follow Up eCRF and AE eCRF</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Medical Record or Subject Research Binder and CRF</td>
<td>Eligibility eCRF</td>
</tr>
</tbody>
</table>

#### 3.A.1 MDS-UPDRS

The full 30 page MDS-UPDRS, including Hoehn and Yahr Stage, and Score Sheet has been provided to sites 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 and indicate this responsibility on the Delegation of Responsibility (DOR) log.

**Part Ia** – Assessed by site investigator or sub-investigator (coordinator may conduct Part Ia if training and certification is completed and indicated on the DOR log)

**Part I (Patient Questionnaire)** – Completed by the subject and/or caregiver

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

**Part III** – Assessed by site investigator or sub-investigator

**Part IV** – Assessed by site investigator or sub-investigator. (Part IV will not be done for healthy controls or early PD subjects)

**Hoehn and Yahr Stage** – Assessed by site investigator or sub-investigator

### 3.A.2 MDS-UPDRS (Post-Dose)

PD subjects who have started levodopa or dopamine agonist will have an assessment of MDS-UPDRS Part III and Hoehn and Yahr stage in a “practically defined off” state. The repeat post-dose motor exam is NOT conducted in subjects who have started other types of PD medications (e.g. amantadine, rasagiline (Azilect®), selegiline (Eldepryl®, Zelapar®)).

- Definition of practically defined off = Subject has not taken PD meds since last regularly scheduled dose the night before the visit (at least 6 hours before evaluation).

Steps for assessing:

1. Subject should be reminded to hold medication for the in-person visit when this will be conducted.
2. Conduct full MDS-UPDRS.
3. Give subject appropriate PD medication dose.
4. **Approximately one hour** after the subject receives PD medication, repeat Part III only (Motor Exam) and Hoehn and Yahr Stage. Complete the *MDS-UPDRS Post Dose* source worksheet.

The MDS-UPDRS can be done at any visit.

### 3.A.3 Modified Schwab & England Activities of Daily Living

This 0-100 scale is used to rate a subject’s current overall function. 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.

3.A.4 Montreal Cognitive Assessment (MoCA)
The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for 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.

1. Alternative 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:

- 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 sound.

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, 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 to 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 = the 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 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.
3.A.5 SCOPA-AUT

The SCOPA-AUT is a 26 item self-report questionnaire of autonomic function. There are questions covering upper and lower gastro-intestinal function, urinary function, cardio-circulatory function, sexuality, and other miscellaneous autonomic problems (e.g. sweating, light sensitivity).

Instructions for Administration and Scoring:

1. Ask the subject to answer the questions by placing a cross in the box that best reflects their situation. If they wish to change an answer, fill in the ‘wrong’ box and place a cross in the correct one.

2. If they have used medication in the past month in relation to one or more of the problems mentioned, then the question refers to how the subject was while taking this medication. They can note the use of medication on the last page.

3. It is permissible to have input from a spouse or other knowledgeable informant when completing the SCOPA-AUT.

4. If appropriate, reinforce that that subject should answer all items, including those (like sexual function) that are potentially sensitive. Responses to these questions will not be disclosed without permission from the subject.

5. Do not calculate a total score. Scoring will be done centrally.
A. Source of Information: 1 = Patient, 2 = Caregiver, 3 = Patient and caregiver

SCOPA-AUT

By means of this questionnaire, we would like to find out to what extent in the past month you have had problems with various bodily functions, such as difficulty passing urine, or excessive sweating. Answer the questions by placing a cross in the box which best reflects your situation. If you wish to change an answer, fill in the ‘wrong’ box and place a cross in the correct one. If you have used medication in the past month in relation to one or more of the problems mentioned, then the question refers to how you were while taking this medication. You can note the use of medication on the last page.

1. In the past month have you had difficulty swallowing or have you choked?
   - never
   - sometimes
   - regularly
   - often

2. In the past month, has saliva dribbled out of your mouth?
   - never
   - sometimes
   - regularly
   - often

3. In the past month, has food ever become stuck in your throat?
   - never
   - sometimes
   - regularly
   - often

4. In the past month, did you ever have the feeling during a meal that you were full very quickly?
   - never
   - sometimes
   - regularly
   - often

5. Constipation is a blockage of the bowel, a condition in which someone has a bowel movement twice a week or less.
   In the past month, have you had problems with constipation?
   - never
   - sometimes
   - regularly
   - often

6. In the past month, did you have to strain hard to pass stools?
   - never
   - sometimes
   - regularly
   - often
3.A.6 Clinical Safety Labs
Blood for routine clinical labs will be collected at the screening visit and at subsequent visits as needed and sent to each site’s designated local laboratory. This will include whole blood for Chem-20 panel (8.5 mL red top/marble top), PT/PTT analysis (2.7 ml light blue top Sodium Citrate tube) and whole blood for CBC and platelets analysis (10 ml lavender top EDTA tube). Each site will be responsible for ordering these supplies, send the samples for analysis, and receiving the results. These results are for the site to review to ensure the subject is medically stable to proceed with the study procedures. The results from these labs will not be entered into the clinical database, but will be signed off by the investigator and placed in the subject’s study chart.

3.A.7 University of Pennsylvania Smell Identification Test (UPSIT)
The University of Pennsylvania Smell Identification Test (UPSIT) is a forced-choice test (i.e., subject must choose one of the four choices, even if no smell is identified) in which subjects identify an odor among four response alternatives. The test has four booklets containing ten odorants each, one per page, for a maximum score of 40. The stimuli are embedded in scratch and sniff microcapsules fixed and positioned on strips at the bottom of each page. Lower scores indicate reduced odor identification.

Instructions for Administration and Scoring:

1. This is a self-administered assessment. Instructions provided on the face page of Booklet 1 of 4 should be reviewed with the subject before beginning the test. DO NOT COMPLETE the address and other personal information requested on the back of Book 1.
2. Emphasize the importance of providing a response to every question, even if no odor is perceived. Subjects should understand it is necessary to complete each item in order to make their test valid and reassure subjects that they may not smell each of the odors. Remind the subject not to seek help from other people to identify the odors.
3. The subject should understand the correct procedure for releasing the odors and should be encouraged to sniff the label immediately after it has been scratched. Be careful not to mark the test strip too thoroughly, for it is possible to eliminate the odor if this is done.
4. If a subject has difficulty scratching the label or reading the multiple choice responses, the coordinator may assist in releasing the odor and/or reading the responses aloud while the subject is sniffing the strip.
5. Responses should be recorded for each item on the columns provided on the last page of each booklet. Note that the number for each question corresponds with the number on the scoring cards.
6. If a subject has difficulty completing all 4 booklets at one time (e.g., short attention span or unwillingness to cooperate), it is permissible to spread the testing out over the period of the study visit.
7. Once all 40 items are completed, the total number of correct responses is established using the scoring key. Record the total number correct for each booklet in the EDC on the UPSIT page.
**3.A.8 DatSCAN™**

**Administration of a DatSCAN™**

DatSCAN™ should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides within a designated clinical setting. More detailed instructions are provided in the Imaging Technical Site Binder.

The following procedures will be performed for all patients prior to administration of the radiotracer:

- For women of child-bearing potential, a negative urine (HCG) pregnancy test must be observed prior to the patient receiving the injection. (Note: This is typically completed at the imaging center).
- Administration of a thyroid blocking agent (potassium perchlorate, potassium iodide oral solution or Lugol’s solution) according to the imaging center’s standard operating procedures prior to the patient receiving the injection.

DatSCAN™ is a 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. Clinical efficacy has been demonstrated across the range from 111 to 185 MBq. Do not exceed 185 MBq and do not use when the activity is below 110 MBq.

To minimize the potential for pain at the injection site during administration, a slow intravenous injection (about 15 to 20 seconds) via an arm vein is recommended.

The dose should be assayed in a 10 ml syringe filled to a standard volume of 6 ml. In order to avoid geometry effects on determination of actual injected dose following injection of DatSCAN™, the syringe should be reassayed. Subjects should be pretreated with saturated iodine solution (10 drops in water) or perchlorate (1000 mg) prior to DatSCAN™ injection. Subjects are to be imaged 4 ± 0.5 hours after injection with a total scanning time of 30-35 minutes. Total time at imaging center is approximately 5.5-6.0 hours. Specifically-bound activity washes out from striatal binding sites slowly, but not negligibly, hence effort should be made to maintain a consistent imaging time post injection of DatSCAN™.

Scheduling of an Imaging Visit:

Each imaging center needs to first transfer a de-identified “test” DICOM image prior to the site set up using the approved method of image transfer. This “test” DICOM image transfer between the imaging center and IND serves as an opportunity to discover any potential DICOM image transfer issues.

The site (clinical and imaging) will then receive an approval to scan notification indicating that the imaging center is now ready to scan their first subject only. After the first subject has been imaged, the imaging center will be instructed to promptly transfer the images to IND for quality control review. Once the subject images have passed quality control the imaging center and the clinical coordinator will be notified via email that they have been approved to continue imaging additional subjects. Sites will be notified within approximately 3 business days of receipt of the first subject data (barring no queries). It is important to note:

- The clinical coordinator should NOT schedule a second subject for imaging until IND has reviewed the first subject scan and it has passed quality control
- The requirement for first subject data approval prior to imaging additional subjects is waived for sites already participating in other DaTscan™ protocols with IND.

Upon completion of the Screening SPECT scan, the imaging core will complete a Visual Interpretation Report. DaTscan™ results will be communicated by a Visual Interpretation report sent to the clinical site (for PD subjects only). For the HC subjects, the Visual Interpretation Report will not be provided to the site since it does not impact eligibility.

Study Coordinator will need to arrange the DaTscan™ visit with the designated imaging center. It is important to provide the imaging center with the subject ID and remind them that this is a research study. Ordering
DaTScan™ Dose:

- DaTScan™ doses should be ordered following the process outlined below:
- Orders should be placed by contacting the closest GE pharmacy by phone or fax unless other arrangements are in place (please contact your GE pharmacy for the fax order form).
- If you are unaware of the closest GE pharmacy, please contact GE Customer Service directly by phone (508-683-3701 or 508-683-2396)
- Please note, DaTScan™ orders must be placed by 11am at a minimum of TWO DAYS before required delivery date whether or not being placed through a local GE pharmacy or through GE Healthcare Customer Services. Cancellations: doses should still be cancelled at least 2 business days prior to delivery.
- When ordering the dose, please provide the pharmacy with the Subject ID and indicate that the dose is for S4 (pharmacists will be instructed not to ask for the subject name for S4 doses as this is a research study).

The Imaging Core lab should be made aware of any DaTSCAN™ orders placed via datscan@indd.org and the email should include the protocol # in the “Subject” heading of the email.

3. B Biofluid Collection and Skin Biopsy Visit

The activities of this visit will be completed within 120 days of the Screening Visit (based on date Informed Consent was signed if screening activities occur on more than one day). The Biofluid Collection and Skin Biopsy Visit will include the following activities and will take about 4 hours to complete. The procedures for this visit may occur over multiple days. The site coordinator will accompany the subject throughout the visit and will be responsible for collecting and processing biofluid and skin biopsy samples once the procedures are complete. Please see the biologics manual for details regarding the biofluid and skin biopsy procedures.

<table>
<thead>
<tr>
<th>Assessment/Procedure</th>
<th>Location of Source Documentation</th>
<th>Enter into Electronic Data Capture System (EDC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of concomitant meds</td>
<td>Con Meds CRF</td>
<td>Con Meds eCRF</td>
</tr>
<tr>
<td>Blood draw for research samples (whole blood, serum, plasma) for analyses of a-syn species and other biomarker analysis</td>
<td>Blood Sampling CRF</td>
<td>Blood Sampling eCRF</td>
</tr>
<tr>
<td>Blood sample for DNA genomic analyses and RNA for gene expression analyses</td>
<td>Blood Sampling CRF</td>
<td>Blood Sampling eCRF</td>
</tr>
<tr>
<td>Saliva Samples collection</td>
<td>Saliva Sampling CRF</td>
<td>Saliva Sampling eCRF</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Lumbar Puncture CRF and Skin Biopsy CRF</td>
<td>Lumbar Puncture eCRF and Skin Biopsy eCRF</td>
</tr>
<tr>
<td>Lumbar Puncture</td>
<td>Lumbar Puncture CRF</td>
<td>Lumbar Puncture eCRF</td>
</tr>
<tr>
<td>Skin Punch Biopsies</td>
<td>Skin Biopsy CRF</td>
<td>Skin Biopsy eCRF</td>
</tr>
<tr>
<td>Review of AEs related to LP and skin biopsies</td>
<td>Procedural Follow Up CRF and AE CRF</td>
<td>Procedural Follow Up eCRF and AE eCRF</td>
</tr>
</tbody>
</table>

3. B.1 Saliva Samples

Please refer to the biologics manual for details regarding the saliva collection procedure.

3. B.2 Lumbar Puncture

Please refer to the biologics manual for details regarding the lumbar puncture procedure.
3. C Colon Tissue Collection Visit
The activities of this visit will be completed within 120 days of the Screening Visit (based on date Informed Consent was signed if screening activities occur on more than one day). The Colon Tissue Collection Visit will include the following activities and take about 1 hour to complete. Please see the biologics manual for details related to the colon biopsy procedure.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Review of concomitant meds</td>
<td>Con Meds CRF</td>
<td>Con Meds eCRF</td>
</tr>
<tr>
<td>Vital signs (blood pressure, heart rate, respiratory rate, and temperature) prior to initial of the colon biopsy and at the end of the colon biopsy</td>
<td>Colon Biopsy CRF</td>
<td>Colon biopsy eCRF</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy and collection of sigmoid colon biopsies under optional conscious sedation for colon tissue collection and staining for a-syn and other biomarker analysis</td>
<td>Colon Biopsy CRF</td>
<td>Colon biopsy eCRF</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Colon Biopsy CRF</td>
<td>Colon biopsy eCRF</td>
</tr>
<tr>
<td>Review of AEs related to colon biopsy</td>
<td>Procedural Follow up CRF and AE CRF</td>
<td>Procedural Follow Up eCRF and AE eCRF</td>
</tr>
</tbody>
</table>

3. D Submandibular Gland Tissue Collection Visit
The activities at this visit will be completed within 120 days of the Screening Visit (based on date Informed Consent was signed if screening activities occur on more than one day). The Submandibular Gland Tissue Collection Visit will include the following activities and will take about 1 hour to complete. This visit will be completed on a single day. The biopsies will take place in a procedure room or facility utilized by an Otolaryngologist. Please see the biologics manual for details related to the submandibular gland biopsy procedure.

<table>
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<th>Enter into Electronic Data Capture System (EDC)</th>
</tr>
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<tbody>
<tr>
<td>Review of concomitant meds</td>
<td>Con Meds CRF</td>
<td>Con Meds eCRF</td>
</tr>
<tr>
<td>Vital signs (blood pressure, heart rate, respiratory rate, and temperature) prior to initial of the colon biopsy and at the end of the colon biopsy</td>
<td>Submandibular biopsy CRF</td>
<td>Submandibular biopsy eCRF</td>
</tr>
<tr>
<td>tissue collection and staining for a-syn and other biomarker analysis</td>
<td>Submandibular biopsy CRF</td>
<td>Submandibular biopsy eCRF</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Submandibular biopsy CRF</td>
<td>Submandibular biopsy eCRF</td>
</tr>
<tr>
<td>Review of AEs related to colon biopsy</td>
<td>Procedural Follow Up CRF and AE CRF</td>
<td>Procedural Follow Up eCRF and AE eCRF</td>
</tr>
</tbody>
</table>
4.0 DATA FLOW
The clinical site is responsible for ensuring that all forms are complete, intact, and are transmitted to the CTSDMC through direct entry into the EDC. The timelines for completion of study forms is:

- Source: day of visit, or phone call
- eCRF: 14 business days of visit
- Adverse Events: within 5 days of becoming aware of event
- Serious Adverse Events: within 24 hours of becoming aware of event

Missing Forms:
The data validation process will prompt for missing data forms. The data system will issue a monthly report to each site, detailing forms that are missing and/or forms that have not yet been completed. If a form is overdue by more than a month or has been incomplete for more than a month, the CTSDMC staff will call the site to encourage them to enter the data and complete entry of the form. In the event that data cannot be obtained, the CTSDMC will mark the form as missing in the data system and the site will not be reminded again that the form is missing and/or incomplete.

Missing Values and Data Anomalies:
The purpose of data QC and missing forms checks is to minimize data anomalies and missing data. However, the data system will allow both missing values and logical inconsistencies after they have been reviewed by the CTSDMC data manager and verified as accurate by the site. Algorithms for handling missing data will be described in detail in the statistical analysis plan (SAP).

Retention of Study Documentation:
The length of time all study files are to be maintained is specified as three years from the notification of the investigator by the principal investigator of the conclusion of the study, unless the site is required by local regulatory agencies to retain study records for a longer period of time.

Individual IRBs, institutions, and states may have differing requirements for record retention; investigators should adhere to whichever requirements are most rigorous.

If the responsible investigator retires, relocates, or for other reasons withdraws responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of study documents before having obtained written approval from the sponsor.

Investigators should retain forms and all other study documents before having obtained written approval from the sponsor.

External Study Data:
All external data will be retained in the subject’s source binder. Key data elements will be reported in the eCRF in a summary format.

Quality Control Procedures:
Data integrity and study credibility depend on factors such as ensuring adherence to the protocol, obtaining complete follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality. The study quality control plan includes study training, data validity checks of the eCRF (which are built into the EDC); online reviews of the eCRF by study monitoring staff, and periodic monitoring visits. Issues identified through monitoring will be brought to the attention of the site investigator and the site study staff for correction or remediation.
Site compliance issues, which are identified and not brought into adherence, will be discussed at the Steering Committee level. Recommendations for site retraining or site discontinuation will be determined by this group in consultation with the study monitoring and audit staff.

**Data Form Checks:**

Data and form checks depend upon data flow design of the data capture in the eCRF. Data quality control checks may specify the following types of review:

- All data received from participating clinical centers
- No missing forms or data
- Unique identification (ID) number for each study participant is consistent across all forms and visits
- Correct numbers in the site ID and participant’s ID number
- Legible source data
- Consistent and logical dates over time
- Data within acceptable ranges
- Data consistent across forms and visits
- All fields of a ‘complete form’ actually completed or reason for no data noted
- All required forms completed or reason for no data noted

**Reports:**

At the beginning of enrollment, routine study reports will be prepared by the CTSDMC staff, and reported through the online study website for review by appropriate study staff. These routine reports prepared for the Principal Investigator by the CTSDMC are an important quality control tool. Weekly reports will describe participants enrolled by site and in aggregate. Enrollment reports will describe participants screened, enrolled, refused participation, completed, discontinued study, and lost to follow-up. Monthly reports will also describe adverse events and serious adverse events. Administrative reports can enumerate the study compliance with eCRF forms completed, entered, and missing and/or erroneous data and forms.

**Policies:**

The Manual of Operations (MOP) contains the study’s policies, such as confidentiality and publication policies.

**Confidentiality Procedure:**

It is the responsibility of the study Steering Committee to outline and enforce participant confidentiality and data security guidelines for the study. Study staff should be instructed in the responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals before they are allowed access to any study data.

The following is a list of study participant confidentiality safeguards:

- **Data flow procedures**- participants identifying information should not be transmitted from the research sites to the CTSDMC, the Biorepository Core or the Imaging Core
- **Electronic files**- participant identifying information stored electronically will be maintained in an encrypted form or in a separate file
- **Forms**- forms or pages containing personal identifying information should be separated from other pages of the source data forms
- **Data listings** – participant name, name code, hospital chart or record number, or other unique identifiers, such as Social Security number, will not be included in any published data listing
- **Data distribution** – internally utilized data listings that contain participant name, name code, or other identifiers easily associated with a specific participant will not be distributed
• **Data disposal**- computer listings that contain participant identifying information will be disposed of in an appropriate manner
• **Access**- participant records stored in the data center will not be accessible to persons outside of the center without the express written consent of the participant
• **Storage**- study forms and related documents retained both during and after study completion will be stored in a secure, fireproof location

Computers will be used to store and/or analyze clinical data. The CTSDMC and site investigator will address the following elements of computer security to ensure that the data remain confidential.

• **Passwords**- Passwords provide limitations on general access to the systems and to the functions individuals can use on the system. Passwords will be changed on a regular basis
• **User Training**- Study staff with access to clinical computer systems should be trained in their use and in related security measures. Training should include explanations of how to access the system and a discussion of the need for, and importance of, system security
• **System Testing**- Prior to the use of the study EDC, and if it is modified, the system will be validated to verify that it performs as expected. Testing will also verify that the password approach to system access performs as intended
• **System Backups**- Backup copies of the studies EDC will be made at daily intervals. Backups should be stored in remote locations and secure areas with limited access. Storage areas have controlled temperature and humidity so that they backups are not damaged

**Publications:**

Investigators have a responsibility to the public to make study results available as soon as possible. The study publication policy requires that requests for data queries from study investigators be routed to the Steering Committee for review. Study data will not be released inappropriately. Authorship of the study results will be predetermined by the Steering Committee. Manuscripts regarding the study results or methods will be subjected to rigorous review before they are submitted for publication.

**5.0 S4 STUDY WEBSITE, DATA ENTRY, AND ECRF INSTRUCTIONS (APPENDIX A)**

The study website, data entry guide, and eCRF instructions can be found in Appendix A of the MOP.

**6.0 SAFETY REPORTING**

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE). Adverse events will be reported from the time of enrollment into the study (signed informed consent) through the end of study.

Relevant definitions include the following:

• **Adverse Event (AE)** - An AE is any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as dictated by physical signs or symptoms occurring in any phase of the clinical study whether or not associated with the study procedures. This definition includes an exacerbation of pre-existing medical conditions or events, historical conditions not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug interaction, or the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form (CRF). Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

• **Serious Adverse Events (SAE)** – Any untoward medical occurrence that:
  • Death
  • Life threatening
  • Hospitalization-Initial or Prolonged
Disability
Congenital anomaly
Required intervention to prevent permanent impairment/damage
Important medical events as determined by the Site PI or Designee

Adverse Event Reporting:

All AEs are collected, analyzed, and monitored using an Adverse Event Form (instructions for filling out the eCRF can be found in Appendix A). AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety must be reported. All AEs experienced by participants during the study time frame specified in the protocol are to be reported.

Site investigators and coordinators will be instructed to assess for AEs at in-person study visits when DaTSCAN™, LP, skin biopsies, colon biopsies, and submandibular gland biopsies are performed. AEs will be collected throughout the study and followed until the final follow-up phone call at 7 days (+2 days) following the procedure for DaTSCAN™, skin biopsies, LP, colon biopsies, and submandibular gland biopsies, but not more than 30 days following study participation. If the AE is continuing at the end of the subject’s participation in the study, the event will be resolved with sequelae and the date recorded is the last contact with the subject.

Adverse Event Intensity Grading:

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be used to grade the AE that is reported for the study procedure. This information can be located on the www.s4study.org website and can be found under the Study Materials Tab. The levels are as follows:

- Mild/Grade 1-Aware of event, but easily tolerated
- Moderate/Grade II-Discomfort, enough to cause interference with usual activity
- Severe/Grade III-Incapacitating, subject is unable to work or perform usual activities
- Life Threatening/Grade IV
- Death/Grade V

Relationship to Study Procedure:

The relationship to the study procedure will need to be determined.

No will be answered if:

- Not Related-Improbable temporal relationship and is plausibly related to concomitant drugs or underlying disease
- Unlikely-Occurred within a reasonable timeframe after study procedure, but there is a likely association of an intercurrent/underlying medical condition or concomitant drugs

Yes, will be answered if:

- Possible-Occurred within a reasonable timeframe after study procedure, but could be related to concomitant drugs or underlying disease
- Probably-Occurred within a reasonable timeframe after study procedure, is unlikely to be attributable to concomitant drugs or underlying disease, and there is a plausible mechanism to implicate the study procedure
- Definite-Occurred within a reasonable timeframe after study procedure and cannot be explained by concomitant drugs or underlying disease

Time Period for Adverse Event and Serious Adverse Event Reporting:

The time period for reporting adverse events is within 5 business days of becoming aware of the event.
The time period for reporting serious adverse events is within 1 business day of becoming aware of event.

### 7.0 PROTOCOL DEVIATION

A protocol deviation is defined as a variation from the protocol-directed conduct of a clinical trial. Any non-compliance with the study protocol, GCP, ICH Guidelines, or a protocol specific MOP requirement, is considered a protocol deviation.

It is imperative that the protocol be followed exactly as written whenever possible. If a deviation from protocol-specified procedures is necessary in the interest of ensuring subject safety, the site should treat the subject as clinically necessary and report the deviation to the CTSDMC as described below.

A protocol deviation is defined as an occurrence that:

- Refers to an Informed Consent deviation
  - Failure to obtain informed consent
  - No documentation of informed consent
  - Incomplete documentation of informed consent
  - Informed consent obtained after initiation of study procedures
  - Informed consent obtained by someone other than individuals authorized by IRB to obtain consent
  - Missing signed and dated consent form
  - Subject signed expired or incorrect version of the consent form
- Refers to Protocol Compliance deviation
  - Enrollment of a subject who did not meet all inclusion/exclusion criteria
  - Failure to conduct a study visit
  - Failure to complete all study procedures at a study visit as specified
  - Study procedures/visits conducted out of window
  - Protocol-specified study therapy not administered as directed

All deviations, regardless of rationale, must be recorded on the Protocol Deviation eCRF immediately upon the site’s awareness of the deviation.

**THE CTSDMC STAFF WILL MAKE A DETERMINATION IN CONCERT WITH THE PRINCIPAL INVESTIGATORS REGARDING WHETHER A DEVIATION IS A REPORTABLE EVENT THAT REQUIRES PROMPT REPORTING TO THE IRB AS AN UNANTICIPATED PROBLEM, OR IF THE EVENT MAY BE REPORTED AT THE TIME OF CONTINUING REVIEW. IF THE DETERMINATION IS MADE THAT A REPORTABLE EVENT HAS OCCURRED, THEN THE SITE STUDY STAFF AND THE SITE INVESTIGATOR WHERE THE EVENT OCCURRED WILL BE CONTACTED AND REQUIRED TO SUBMIT THE REPORTABLE EVENT URGENTLY.**

### 8.0 MONITORING

Site monitoring will occur through periodic site visits conducted during the course of the study by comparison of the data listings to the source documentation and review of the site regulatory file. Details are provided in the monitoring plan. The plan includes intensive remote review of the first subject visit including review of source data and eCRF from a site from Screening Visit. A plan is in place for annual monitoring visits. The first monitoring visit will occur prior to having five subjects enrolled and then again at the end of the study. The frequency of visits may be revised based upon site performance and the number of participants enrolled.

The purpose of monitoring visits is to:

- Assure the rights and safety of participants
- Confirm that study conduct follows the guidelines of Good Clinical Practice (GCP)
• Assure maintenance of required documents
• Verify adherence to the protocol
• Monitor the quality of data collected
• Assure accurate reporting and documentation of all adverse events

During the monitoring visits, the data recorded on the study eCRF are reviewed and verified against source documents to assure:

• Informed consent has been obtained and documented
• Adverse Events have been identified and recorded
• The information recorded on the forms is complete and accurate
• There are no omissions in the reports of specific data elements
• Missing examinations are indicated on the forms
• Participant disposition at study exit is accurately recorded

Site investigators must allow the clinical monitor access to all study documents, including informed consent forms and source documents, including pertinent hospital or medical records.

Once the site visit is complete, a site monitoring report will be drafted and presented to the site to provide feedback regarding any problems or issues that may have been uncovered during the visit. The format used for this study is straightforward, stating any problems, and describing recommendations for corrections. A time line for corrections will be presented to the site staff and included in the report to ensure that follow-up of the issues is completed and implemented into the study conduct procedures.

9.0 STUDY COMPLETION AND CLOSEOUT PROCEDURES:
Study closeout activities will be performed to confirm that the site investigator’s study obligations have been met and post study obligations are understood. Closeout activities include, but are not limited to, the following:

• Verification that study procedures have been completed, data collected, and study supplies are returned to the responsible party or prepared for destruction
• Review of investigator’s correspondence and study files against the CTSMDC’s records for completeness
• Assurance that all data queries have been completed
• Assurance the correspondence and study files are accessible for internal audit
• Reminder to investigators of the ongoing responsibility to maintain study records and to report any relevant study information to the sponsor
• Meeting in person or by teleconference with the site investigators to ensure that they are aware of regulatory obligations and requirements for record retention
• Assurance that the investigator will notify the IRB of study completion and obtaining a copy of the notification
• Preparation of a report summarizing study conduct
Appendix A:  
S4 Study  
Website and Data Entry  
User Manual  

09/08/2015
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I. Website

A. Logging In

The S4 Study website is a secure site that requires users to log in with a user ID and password. Functions exist that allow the user to change his/her password or retrieve a forgotten password.

Typically, the system requires users to change their passwords each year.

If a user forgets his/her password, s/he can submit the “Forgot Password?” form. An email will be sent to the address specified in the user’s account profile. The email includes a link to the study website that authenticates the user and allows the user to set a new password.
B. Events Calendar

An events calendar is available on the main website and can be accessed through the “Collaboration” tab. Buttons are available on the left and right of the calendar header to navigate between continuous months. Links to all months with scheduled events are available at the bottom of the page. To access the details of particular events, click on the day number or the list of events displayed within each calendar cell.

Please use landscape mode when printing.
A list of the events scheduled on the selected day is displayed. When the user selects an event from the list, the details appear on the right side of the page.

If the user is assigned to the same group as the event, s/he can also access any documents (e.g. agenda, minutes) attached to the event.
C. Network Directory

Users can look up contact information using the directory available on the main website. To access the directory page, click on the “Collaboration” tab and you will see the menu link labeled “Directory”. On the directory page, the user first selects the type of organization: site, group, or protocol (study). This will display a list from which the user may select any or all of the checkboxes on the left. The user then clicks the “Show Members” button to view a list of the individuals associated with the selected organization(s). A textbox is also available to search for a particular individual by name.
When the list of individuals is displayed, two options are available. The user selects the required individuals using the checkboxes on the left and either clicks the “Show Details” button to view more complete details or the “Send Email” button to send an email to the selected individuals.

<table>
<thead>
<tr>
<th>Select All</th>
<th>Name</th>
<th>Phone</th>
<th>Email</th>
<th>Center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bosch, Michael</td>
<td>319-353-3041</td>
<td><a href="mailto:michael-bosch@uiowa.edu">michael-bosch@uiowa.edu</a></td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
<tr>
<td></td>
<td>Coffey, Chris</td>
<td>000</td>
<td><a href="mailto:christopher-coffey@uiowa.edu">christopher-coffey@uiowa.edu</a></td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
<tr>
<td></td>
<td>Costigan, Michele</td>
<td>319-384-4183</td>
<td><a href="mailto:michele-costigan@uiowa.edu">michele-costigan@uiowa.edu</a></td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
<tr>
<td></td>
<td>Cozzie, Elizabeth</td>
<td>319-384-2751</td>
<td><a href="mailto:elizabeth-cozzie@uiowa.edu">elizabeth-cozzie@uiowa.edu</a></td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
<tr>
<td></td>
<td>Ecklund, Dixie</td>
<td>319-335-8446</td>
<td><a href="mailto:dixie-ecklund@uiowa.edu">dixie-ecklund@uiowa.edu</a></td>
<td>Clinical Trials Statistical and Data Management Center</td>
</tr>
</tbody>
</table>
On the page of complete details, the user can return to the previous list of individuals by clicking the “Show Details” button. (Note: the “<<” button returns to the initial page listing sites, groups, or protocols.)

Checkboxes for each individual and the “Send Email” button are also available on the details page.
II. Data Entry

A. eCRF Status

eCRFs exist with three different statuses: Incomplete, Complete, and Unobtainable. The status of the eCRF is indicated by a label located next to the eCRF link.

Users can save data an eCRF as “Incomplete” if all the data is not available to enter at that time. A “Save/Exit” button is available at the top of the eCRF data entry page.

When all the data is entered and finalized, the user must click the “Save/Review” button to validate the eCRF. This initiates logic checks that are run to insure the accuracy of the data and notifies the user of any errors. Once all the errors have been resolved, the data is displayed for a final review and the user must click the “Submit” button to submit the eCRF as “Complete”. eCRFs are not included in reports and statistical analysis until they have been submitted and the status has changed to complete. In addition, some eCRFs do not become available until other eCRFs have been submitted.
In some cases, data for an eCRF (or an entire visit) cannot be obtained (e.g. subject did not show up, unable to schedule, refused/missed assessment). Study coordinators should contact the DCC if this situation occurs. For tracking purposes, the visit or eCRF will be marked as “Unobtainable” by a DCC staff member.

**B. “Deleting” Radio Buttons**

Radio buttons exist in groups that only allow one option to be selected at a time. In order to remove the selection from a radio button, click on the selected option and press the “delete” key.

![Radio Buttons](image)

**C. The Date Picker**

Date fields are equipped with a date picker that allows the user to select a date from a pop-out calendar that appears when the user clicks inside the text field.

![Date Picker](image)
This control has several features:

- **Decrement (subtract) month** – click the arrow to the left of the month, year header
- **Increment month** – click the arrow to the right of the month, year header
- **Select today’s date** – click the label indicating today’s date located below the calendar
- **Navigate to a non-adjacent month** – click the month, year header; this will display a table of months in the current year (see below). The year can be
incremented or decremented by clicking on the arrows located on either side of the year header.

Navigate to another year – click the year header; this will display a table of years (see below). The decade can be incremented or decremented by clicking on the arrows located on either side of the header.

D. Unavailable Items

Some items are not applicable depending on the option selected in a preceding item. In this case, the irrelevant item(s) will be disabled when that option is selected.
In the example below, “No” is selected for the Skin body system indicating that no abnormality is present and the items requesting information describing the abnormality are disabled (unavailable). The same is true for the Eyes body system where “Not Done” is selected. Conversely, because “Yes” is selected for the Head/Neck/Lymphatic body system, these items are enabled for that system.

<table>
<thead>
<tr>
<th>Body System</th>
<th>a) Abnormality Present?</th>
<th>b) Describe Abnormality</th>
<th>c) Is Abnormality Clinically Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Skin</td>
<td>✔️ Yes ● No ● Not Done</td>
<td></td>
<td>Disabled ● Yes ● No</td>
</tr>
<tr>
<td>2. Head/Neck/Lymphatic</td>
<td>✔️ Yes ● No ● Not Done</td>
<td></td>
<td>Enabled ● Yes ● No</td>
</tr>
<tr>
<td>3. Eyes</td>
<td>✔️ Yes ● No ● Not Done</td>
<td></td>
<td>Disabled ● Yes ● No</td>
</tr>
</tbody>
</table>

This type of design may sometimes be referred to as a “skip-out” by DCC personnel.

E. Overruling an Error

Some error messages can be overruled by the user. DCC personnel may refer to this capability as an “Override”. In this case, a function is available below the error message that allows the user to indicate that the data is in fact correct. There are two types of overrides:

- Comment only – user must select the checkbox and enter a comment in the text field before the system will accept the override

> The range for Item 10.b is 35 to 150, you entered 600.

   Override this item Reason: __________________________

- Required item – user must select the checkbox and choose one of the radio button options before the system will accept the override; if the
“Other” option is selected; the user must also enter a comment in the text field.

<table>
<thead>
<tr>
<th>Item B.2. is required.</th>
<th>Override this item</th>
<th>Refused</th>
<th>Missing</th>
<th>Other</th>
</tr>
</thead>
</table>

F. Changing Submitted Data

Sometimes it is necessary to modify a data item after the eCRF has been submitted. For most eCRFs, a “Make Post Complete Change” link is available for each record that allows the user to change the data remotely.

This link opens the eCRF in “post-complete change mode” where the user can correct the data and re-submit the eCRF. Prior to re-submission, however, the user must enter a comment for each item that was modified. This creates an audit trail that is used to track changes.
Some eCRFs do not allow data to be changed remotely. For these eCRFs, the study coordinator must complete a Data Change Request form. Contact the DCC for further details if this becomes necessary.

G. Keeping a Log

Some data (such as Concomitant Medications) is entered in a log which allows the user to track the status of the data as needed. The source data may be reviewed at each visit but a link to the log is available under the “Event Driven” visit option.

The link navigates to a page that allows the user to add, edit, and delete records as needed based on changes observed in the source data.

As with other eCRFs, records can be saved as incomplete but must eventually be reviewed and submitted. After submission, a “Change” option is available to the left of the record that allows the user to modify the data as described in section F.

H. Subject IDs

An “Enroll New Subject” link is available above the subject list that allows the user to create a new subject ID.
The link opens an informed consent eCRF. When the user submits this eCRF, a new subject ID is created and is added to the list of subjects consented at the user’s site. Subject IDs in S4 Study are assigned sequentially across sites so the IDs at any given site may not be consecutive.

The subject ID is divided into two parts. The first two digits indicate the site ID and the last four digits indicate the unique ID of the subject. DCC staff may refer to this second number as the PID or Participate ID. After selecting a subject from the list, the user must confirm the selection by reentering the PID before proceeding to the data entry screens.
B. eCRF Instructions

The headers in the eCRFs are all the same:

- The visit date is a 2-digit month, 2-digit day, and a 4-digit year.
- The visit name will be:
  - Screening Visit
  - Biofluid Collection and Skin Biopsy Visit
  - Colon Biopsy Visit
  - Submandibular Gland Biopsy Visit
- Subject ID and Subject Initials

The footers in the eCRFs are all the same:

- Recorder’s Initials
- Date

B.1 Form 1 Informed Consent eCRF (Screening)

General Instructions: It is important to collect the date of certain milestones, such as informed consent, study enrollment from both an administrative and human subject’s protection standpoint.

Specific Instructions: Document that the informed consent was conducted and sign the source document and record the date consent was obtained. The coordinator may not check ‘not applicable’ for both version number and date (A2 and A3).

A1: Date the subject signed the informed consent (2-digit month/2-digit date/4digit year)

A2: Version Number of Consent form: Not all IRBs will assign a version number. If your IRB does not assign one, check N/A

A3: Version Date of Consent Form: This is the date that is in the footer of the consent document being signed (2-digit month/2-digit date/4digit year).

B: Only one answer maybe be checked regarding the stage of Parkinson’s Disease or Healthy Control

*If the consent is revised while the subject is still enrolled in the study, the subject should be re-consented and a new informed consent process note should be completed for source documentation.*

This consent is found under the Events Driven Tab.

B.2 Form 2 Demographics eCRF (Screening)

General Instructions: This form contains data elements that are collected to describe the demographics of the study population. The items are used to compare baseline characteristics among study group and to identify confounding variables.

Responses to categories are obtained from self-report when possible or obtained from legal guardian interview.
Specific Instructions:

Question 2: Choose Female or Male.
Question 3: This data element can be used to calculate the subject’s age when the data are analyzed.
Question 4: Choose only one response in which the subject most closely identifies.
Question 5: Choose all responses in which the subject identifies.
Question 6: Report the highest obtained level of education
Question 7: Choose one response that best describes how the subject learned about the S4 Study.

B.3 Forms 3A and 3B Eligibility for HC and PD Subjects eCRF (Screening)
General Instructions: The study inclusion and exclusion criteria specify the characteristics of potential study subjects that must be met prior to enrollment.

If “no” is selected for any inclusion item, or “yes” is selected for any exclusion item, the form can be submitted without completing the entire form. The form may be incomplete for screen failures.

Specific Instructions:

All Inclusion Criteria must be answered YES and all Exclusion Criteria must be answered NO in order for the subject to be considered eligible for study participation.

Investigator Signature: The Investigator must review, sign, and date this form.

B.4 Form 4A Medical History PD eCRF (Screening)
General Instructions:
Medical History data are collected at the Screening Visit to verify the inclusion and exclusion criteria (e.g., no history of other significant neurological disorders) and to describe the study population. Typically, the Medical History Form captures conditions that are reported by the subject.

The form should focus on significant medical history of all problems or conditions other than those related to the focus of the study and are presented in the order typically used during a patient visit.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year
Question 2: Enter the 2-digit month and 4-digit year the first symptoms were confirmed by history obtained by the physician.
Question 3: Enter the 2-digit month and 4-digit year of initial diagnosis
Question 4: Results of the clinical assessment – only one answer per feature
Question 5: Only one answer is allowed
Question 6: If yes is checked, answer a, b, and c

If no is checked, no other answers are needed. Section a, b, and c will grey out
B.5 Form 4B Medical History HC eCRF (Screening)

General Instructions:

Medical History data are collected at the Screening Visit to verify the inclusion and exclusion criteria (e.g., no history of other significant neurological disorders) and to describe the study population. Typically, the Medical History Form captures conditions that are reported by the subject.

The form should focus on significant medical history of all problems or conditions other than those related to the focus of the study and are presented in the order typically used during a patient visit.

Specific Instructions:

Section A: Date is collected as 2-digit month/2-digit date/4-digit year

Section B:

Answer Yes or No if there are any medical history problems/conditions. If no form is complete. If yes:

- Click on Enter a Medical History Record
  - Body System: Choose the correct system and write the corresponding numeric code in the box
  - Medical History Term: Write the medical term that correlates to the numeric value. Enter only one term per line.
  - Start Date: Date is collected as 2-digit month/2-digit date/4-digit year
  - Still Present: Mark yes or no
  - End Date: Date is collected as 2-digit month/2-digit date/4-digit year

B.6 Form 5 Family History of PD eCRF (Screening)

General Instructions:

Family History of PD data are collected at the Screening Visit. Typically, the Family History of PD Form captures information that is reported by the subject.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year

Questions 2-7: An answer must be recorded yes or no

Questions 8-15: This is a text box that you will write in and enter into the database

B.7 Form 6 Neurological Exam eCRF (Screening)

General Instructions:

The neurological exam is administered at the Screening Visit. The neurological exam is to be conducted by the site investigator.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year

Questions 2-5: For each sub question check one for a) Assessment Result:
• Normal
• Abnormal—Fill in Description
• Unable to Test
• Not Tested

Section b) Description will populate if Abnormal is checked. Provide the description

**Question 6:** For each sub question check one for a) Assessment Result:

• Absent—Fill in Description
• Normal
• Hyperactive clonus—Fill in Description
• Hypoactive—Fill in Description
• Hyperactive, no clonus—Fill in Description
• Unable to test
• Not Tested

Section b) Description will populate if Absent, Hyperactive clonus, Hypoactive, Hyperactive, no clonus is checked. Provide the description

**Question 7:** For each sub question check one for a) Assessment Result:

• Flexor
• Indeterminate
• Extensor
• Unable to Test
• Not Tested

Section b) Description will populate if Flexor, Indeterminate, or Extensor checked. Provide the description

**B.8 Form 7 Physical Exam eCRF (Screening)**

**General Instructions:**
The physical exam is administered at the Screening Visit and is to be conducted by the site investigator or sub-investigator

**Specific Instructions:**

**Question A:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question B:**
For each sub question check one for a) Abnormality Present:

• Yes
• No
• Not Done
Section b) and section c) will populate if yes is marked for abnormality present

**Question C:** If any additional comments are needed, fill in the text box

**B.9 Form 8 Vital Signs eCRF (Screening)**

**General Instructions:**
The vital signs CRF are administered at the Screening Visit.

**Specific Instructions:**

**Question 1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Questions 2-5:** These are numerical fields

**Question 5a:** Pick one answer

**Questions 6-7:** These are numerical fields

**B.10 Form 9 MDS-UPDRS eCRF (Screening)**

**General Instructions:** MDS-UPDRS is a test that is done by the site investigator or sub-investigator on all subjects.

**Specific Instructions:**

**Question A:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question B:** Is the subject taking medication for their Parkinson’s? If Yes answer:

- **B.1** If so was the subject able to abstain from taking their medication before coming in for their visit?
  - If Yes answer B.2 and continue
  - If No answer B.2 and SKIP Part III Off Medication
- **B.2** Date is collected as a 2-digit month/2-digit date/4-digit year. Time is collected as a 24-hour clock
- **Part I:** Indicate answers for all questions that the subject provided information for
- **Part II:** Indicate answers for all questions that the subject provided information for
- **Part III (On Medication):** Indicate answers for all questions that the subject provided information for
- **Part III (Off Medication):** Indicate answers for all questions that the subject provided information for
- **Part IV:** Indicate answers for all questions that the subject provided information for

**B.11 Form 10 Modified Schwab & England Activities of Daily Living eCRF (Screening)**

**General Instructions:** This 0-100 scale is used to rate a subject’s current overall function. 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.
Specific Instructions:

**Question 1:** Choose 1 answer

**B.12 Form 11 SCOPA-AUT-EN eCRF (Screening)**

General Instructions: The SCOPA-AUT is a 26 item self-report questionnaire of autonomic function. There are questions covering upper and lower gastro-intestinal function, urinary function, cardio-circulatory function, sexuality, and other miscellaneous autonomic problems (e.g. sweating, light sensitivity).

Specific Instructions:

**Questions 1-21** 1 answer is allowed for these questions:

- Never
- Sometimes
- Regularly
- Often

**Questions 22-23** 1 answer is allowed for these questions and only MEN answer them:

- Never
- Sometimes
- Regularly
- Often
- Not Applicable

**Question 23a:** 1 answer is allowed for this question and only MEN answer it:

- Yes – Answer which medication if Yes is checked
- No

**Questions 24-25** 1 answer is allowed for these questions and only WOMEN answer them:

- Never
- Sometimes
- Regularly
- Often
- Not Applicable

**Question 26:** 1 answer is allowed for a, d, e, f:

- No
- Yes—Answer which medication if Yes is checked
**B.13 Form 12 UPSIT eCRF (Screening)**

**General Instruction:** The University of Pennsylvania Smell Identification Test (UPSIT) is a forced-choice test (i.e., subject must choose one of the four choices, even if no smell is identified) in which subjects identify an odor among four response alternatives. The test has four booklets containing ten odorants each, one per page, for a maximum score of 40. The stimuli are embedded in scratch and sniff microcapsules fixed and positioned on strips at the bottom of each page. Lower scores indicate reduced odor identification.

**Specific Instructions:** A score will be recorded from each booklet.

**B.14 Form 13 Montreal Cognitive Assessment (MOCA) eCRF (Screening)**

**General Instructions:** The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for 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.

**Specific Instructions:**

**Question A:** Date is collected as 2-digit month/2-digit date/4-digit year

**Questions A1-A7:** This is a text field and a number will be assigned based on the range. Enter that number into the eCRF.

**B.15 Form 14 Clinical Safety Assessment eCRF (Screening)**

**General Instructions:** The clinical safety assessments that are done at screening will be documented in this eCRF.

**Specific Instructions:**

**Question A:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question B:**

For each sub question check one for a) Abnormality Present:

- Yes
- No
- Not Done

Section b) and section c) will populate if yes is marked for abnormality present.

**Question C:** If not collected, then comments are needed, fill in the text box.

**B.16 Form 15 Pregnancy Test eCRF (Screening)**

**General Instructions:** Pregnancy tests are to be administered at the Screening Visit for any female of child bearing potential.
Specific Instructions:

**Question 1:** Indicate if the subject is male, female but not of child bearing potential, or female of child bearing potential:

- If subject is male – STOP
- If the subject is female but not of child bearing potential – STOP
- If the subject is female of child bearing potential- Go to Question 2

**Question 2:** Indicate how the specimen was collected:

- Blood
- Urine
- Not Collected

**Question 3:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 4:** Time is collected as a 24-hour clock

**Question 5:** Indicate Test Result:

- Pregnant
- Not Pregnant

**B.17 Form 16 DaTSCAN Imaging eCRF (Screening)**

General Instructions: The DaTSCAN will be administered to all subjects.

Specific Instructions:

**Question 1:** Indicate Yes or No if the scan was collected. If yes advance to 1a and 1b

**Question 1a:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 1b:** Indicate which study the scan was collected for

**Question 2:** ONLY FOR PD SUBJECTS, HC SUBJECTS THIS DOES NOT APPLY:

- From the interpretation report mark, the 1 of the 2 choices

**B.18 Form 17 Blood Sampling eCRF (Biofluid Collection and Skin Biopsy Visit)**

General Instructions: Blood drawn for the Biofluid Collection and Skin Biopsy Visit will be captured.

Specific Instructions:

**Question 1-2:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 3:** Time is collected as a 24-hour clock
Question 4: Choose 1 answer

Question 5: Choose 1 answer. If no is checked then skip to Question 6. If yes is checked answer:

Question 5a: Date is collected as 2-digit month/2-digit date/4-digit year

Question 5b: Time is collected as a 24-hour clock

Question 6: Choose 1 answer. If no is checked then skip to Question 7. If yes is checked answer:

Question 6a: Time is collected as a 24-hour clock

Question 6b: Date is collected as 2-digit month/2-digit date/4-digit year

Question 6c: Time is collected as a 24-hour clock

Question 6d-6e: This is a numeric field

Question 6f: Choose 1 answer

Question 6g: This is a numeric field

Question 7: Choose 1 answer. If no is checked then skip to Question 8. If yes is checked answer:

Question 7a-7b: Time is collected as a 24-hour clock

Question 7c-7d: This is a numeric value

Question 7e: Choose 1 answer

Question 7f-7g: This is a numeric value

Question 7h: Time is collected as a 24-hour clock

Question 7i: This is a numeric value

Question 8: Choose 1 answer. If no is checked then skip to Question 9. If yes is checked answer:

Question 8a: This is a 24-hour clock

Question 8b: Choose 1 answer

Question 8c: This is a 24-hour clock

Question 8d: This is a numeric value

Question 9: Choose 1 answer. If no is checked then skip to Question 10. If yes is checked answer:
**Question 9a:** This is a 24-hour clock

**Question 10:** Choose 1 answer. If no is checked then skip to Question 11. If yes is checked answer:

**Question 10a-10b:** Time is collected as a 24-hour clock

**Question 10c-10d:** This is a numeric value

**Question 10e:** Choose 1 answer

**Question 10f-10g:** This is a numeric value

**Question 10h:** This is a 24-hour clock

**Question 10i:** This is a numeric value

**Question 11:** Choose 1 answer. If no is checked then this form is complete. If yes is checked answer:

**Question 11a:** This is a 24-hour clock

**Question 11b:** This is a numeric value

**Question 11c:** Choose 1 answer

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**B.19 Form 18 Saliva Sampling eCRF (Biofluid Collection and Skin Biopsy Visit)**

**General Instructions:** Blood drawn for the Biofluid Collection and Skin Biopsy Visit will be captured.

**Specific Instructions:**

**Question 1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 2:** Choose 1 answer. If “Current” or “Former” is chosen answer 2a

**Question 3:** Choose 1 answer. If “Current” or “Former” is chosen answer 3a

**Question 4:** Choose 1 answer. If not done is answered, no other answers are required. If any of the other choices are collected answer a-o

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**B.20 Form 19 Lumbar Puncture eCRF (Biofluid Collection and Skin Biopsy Visit):**

**General Instructions:** The lumbar puncture eCRF is to be done at the Biofluid Collection and Skin Biopsy Visit.

**Specific Instructions:**

**Question 1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 2:** 1 answer is expected for this question:
- Not Done—Fill in 2a if this is checked
  - Collected
  - Partial Collection
  - Attempted, no collection—Fill in 2a if this is checked

**Question A1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question A2:** Time is collected as a 24-hour clock

**Question A3:** 1 answer is required:
- Fasted
- Low Fat Diet
- Not Fasted, No low fat diet

**Question A4:** 1 answer is required

**Question A4a:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question A4b:** Time is collected as a 24-hour clock

**Question A5-A8:** This is a numerical field

**Question B1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question B2:** 1 answer is expected for what size needle was used

**Question B3-B5:** 1 answer is required

**Question B6:** Answer yes or no. If no answer B6a.

**Question B6b-d:** Record values and units

**Question B7-B8:** Answer yes or no and record date. Date is collected as 2-digit month/2-digit date/4-digit year

**Question B9:** Time is collected as a 24-hour clock

**Question B10-11:** This is a numeric field

**Question B12:** Choose 1 answer

**Question B13:** Time is collected as a 24-hour clock

**Question B14-B15:** This is a numeric field

**Question B16:** Choose 1 answer
Question B17: Time is collected as a 24-hour clock

Question B18: This is a numeric field

Question C1-C4: These are numeric fields

B.21 Form 20 Skin Biopsy Procedure eCRF (Biofluid Collection and Skin Biopsy Visit)
General Instructions: The skin biopsy procedure eCRF is to be done at the Biofluid Collection and Skin Biopsy Visit.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year

Question 2: 1 answer is expected for this question:
- Not Done—Fill in 2a if this is checked
- Collected
- Partial Collection
- Attempted, no collection—Fill in 2a if this is checked

Question 3: 1 answer is expected for this question

Question 4: This is a numeric field

Question 5: This is a text field

Question 6: This is a numeric field

Question 7: Please answer yes or no. If another device was used answer 7a

Question 8: This is a text field

B.22 Form 21 Colon Biopsy Procedure eCRF (Colon Biopsy Visit)
General Instructions: The colon biopsy procedure eCRF is to be done at the Colon Biopsy Visit.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year

Question 2: 1 answer is expected for this question:
- Not Done—Fill in 2a if this is checked
- Collected
- Partial Collection
- Attempted, no collection—Fill in 2a if this is checked
B. 23 Form 22 Submandibular Gland Biopsy eCRF (Submandibular Gland Biopsy Visit)

General Instructions: The submandibular gland biopsy procedure eCRF is to be done at the Submandibular Gland Biopsy Visit.

Specific Instructions:

Question 1: Date is collected as 2-digit month/2-digit date/4-digit year

Question 2: 1 answer is expected for this question:

- Not Done—Fill in 2a if this is checked
- Collected
- Partial Collection
- Attempted, no collection—Fill in 2a if this is checked

Question A (1-4): These are numeric fields

Question B1: Choose 1 answer

Question B2: This is a text field

Question B3: This is a numeric field

Question B4: Choose yes or no, if yes answer 4a
**Question B5:** Choose 1 answer, if no is chosen answer 4a

**Question B6:** Time is collected as a 24-hour clock and then answer as a numeric field

**Question B7:** These are numeric fields

**Questions B8:** This is text field

**Questions 9 and 10:** Time is collected as a 24-hour clock

**Question C (1-4):** These are numeric fields

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**B.24 Form 23 Procedural Follow Up eCRF (All Biopsy Visits)**  
**General Instructions:** The procedural follow up eCRF is to be completed after each biopsy is done. This will be completed within a window of 7 days’ post procedure ± 2 days.

**Specific Instructions:**

**Question 1:** Choose which visit this relates to (can check more than 1)

**Question 2:** Choose yes or no, if no complete 2a

**Question 3:** Choose yes or no, if yes complete 3a; Date is collected as 2-digit month/2-digit date/4-digit year

**Question 4:** Choose yes or no. If subject answers yes to Adverse Event, fill out Form 25 Adverse Event

**Question 5:** Choose yes or no. If any additions or changes to Concomitant Medications, fill out Form 24A or 24B Con Meds

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**B.25 Form 24A Concomitant Medications eCRF (Event Driven)**  
**General Instructions:** The concomitant medications eCRF is found under the Event Driven tab. This is to be completed any time there is an addition or change in reported concomitant medication.

**Specific Instructions:**

**Click Add New Record**

**Question 1 and 2:** These are text fields

**Question 3:** This is a numeric field

**Question 4:** This is a drop down menu. If OTH (Other) is selected, Specify Dose Unit will open and it becomes a text field

**Question 5:** This is a drop down menu. If OTH (Other) is selected, Specify Dose Frequency will open and it becomes a text field. If PRN is selected it will open **Question 6** which is a numeric field
Question 7: This is a drop down menu

Questions 8 and 9: Date is collected as 2-digit month/2-digit date/4-digit year

Question 10: Check if there is not an end date and the medication is ongoing

If a change is needed to an existing entry on the Concomitant Medication Form, click on “CHANGE”. This will bring up a review page for you to enter the reason why the entry has been changed.

If an existing entry on the Concomitant Medication Form needs to be deleted, click on “DELETE”. A pop-up box will appear asking if you are sure you want to delete the entry. Click OK or CANCEL depending on what action should be taken.

B.26 Form 24B Concomitant Medications for PD eCRF (Event Driven)
General Instructions: The concomitant medications for PD eCRF is found under the Event Driven tab. This is to be completed any time there is an addition or change in reported concomitant medication.

Specific Instructions:

Click Add New Record

Question 1: This is a drop down menu

Question 2: This is only available if a combination drug is selected in Question 1. This is a numeric field

Question 3: This is only available if a non-combination drug is selected in Question 1. This is a numeric field

Question 4: This is a drop down menu. If OTH (Other) is selected, Specify Dose Unit will open and it becomes a text field

Question 5: This is a drop down menu. If OTH (Other) is selected, Specify Dose Frequency will open and it becomes a text field. If PRN is selected it will open Question 6 which is a numeric field

Question 7: This is a drop down menu

Questions 8 and 9: Date is collected as 2-digit month/2-digit date/4-digit year

Question 10: Check if there is not an end date and the medication is ongoing

If an existing entry on the Concomitant Medication Form needs to be deleted, click on “DELETE”. A pop-up box will appear asking if you are sure you want to delete the entry. Click OK or CANCEL depending on what action should be taken.
B.27 Form 25 Adverse Event eCRF (Event Driven)

**General Instructions:** The Adverse Event eCRF is found under the Event Driven tab. This is to be completed any time an Adverse Event (AE) or Serious Adverse Event (SAE) is reported.

**Specific Instructions:**

Click Enter New Initial Adverse Event/Serious Adverse Event

**Questions 1 and 2:** Date is collected as 2-digit month/2-digit date/4-digit year

**Questions 3 and 4:** These are text fields

**Questions 5:** Choose 1 answer

**Questions 6 and 7:** These are text fields

**Question 8:** Check all that apply

**Question 9:** Choose only 1 answer

**Question 10:** Choose yes or no, if yes is chosen answer which procedure this is related to. If other is chosen, fill in the Other field

**Question 11:** Choose 1. If choosing Resolved or Resolved with sequelae, then answer 11a by entering a date. Date is collected as 2-digit month/2-digit date/4-digit year

**Question 12:** Choose 1 answer

B.28 Form 26 Protocol Deviation eCRF (Event Driven)

**General Instructions:** The Protocol Deviation eCRF is found under the Event Driven tab. This is to be completed any time a protocol deviation is reported.

**Specific Instructions:**

**Questions 1 and 2:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 3:** Choose 1:
- If Informed Consent is chosen, skip to Item 4
- If Protocol compliance is chosen, skip to Item 5
- If Other is chosen fill in Specify and skip to Item 6

**Questions 4 and 5:** Choose 1. If Other is chosen, fill in the text box

**Questions 6-8:** These are text boxes

**Question 9:** Choose 1 answer
B.29 Form 27 Study Termination eCRF (Event Driven)

General Instructions: The Study Termination eCRF is found under the Event Driven tab. This is to be completed any time the subject comes off the study.

Specific Instructions:

**Question 1:** Date is collected as 2-digit month/2-digit date/4-digit year

**Question 2:** Choose 1 answer. If lost to follow up is chosen, enter the date as 2-digit month/2-digit date/4-digit year. If other is chosen, specify the reason

**Question 3:** This is a text field