Technical Operations Manual (TOM)

The Michael J. Fox Foundation for Parkinson’s Research

Systemic Synuclein Sampling Study (S4)

Study Number: S4-001
Phase: IV Observational
Investigational Product: N/A
Indication: Parkinson’s Disease and Healthy Volunteers
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Technical Operation Manual (TOM)
Systemic Synuclein Sampling Study (S4)

Approval & Signature Page

I acknowledge and approve the Systemic Synuclein Sampling Study (S4) Technical Operations Manual (TOM), version Final V1.0, dated 10-August-2015. Any revisions made to the TOM will require it to be re-versioned with signatures.

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1 INTRODUCTION

This Technical Operations Manual (TOM) describes the technical components of single photon emission computed tomography (SPECT) Imaging used in the clinical study protocol titled, “Systemic Synuclein Sampling Study (S4)” and includes, but not limited to, submitting test images, approval to scan process, information about imaging time points, subject safety and adverse event monitoring, subject naming convention, documentation, radiopharmaceutical administration and image acquisition, image reconstruction, image transfers, imaging and documentation archival, imaging and data query process, and imaging center quality control will be described in detail.

*For more information about the clinical study, please request a copy of the current clinical study protocol from your respective clinical study site team.

1.1 Imaging Core Lab

The Imaging Core Lab (ICL) is the Institute for Neurodegenerative Disorders (IND) based in New Haven, Connecticut, USA. In conjunction with the study sponsor the ICL will provide the imaging center with any technical support necessary to ensure optimal imaging is achieved for transfer to the ICL. IND will be responsible for imaging center evaluation, qualification, and training as well as, receipt, quality control (QC), query, and data management of imaging data and corresponding scan acquisition documentation.

2 SUBMITTING TEST IMAGES

Each imaging center needs to transfer a de-identified “test” DICOM image (preferably a brain SPECT scan or a Striatal Phantom) 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. Each imaging center will be provided with a username and password to access IND’s PACS Web DICOM Upload Utility with detailed instructions on how to electronically transfer images and the corresponding Data Transfer Document. If IND is receiving data from an imaging center and the method of transfer is well established, the requirement to transfer “test” images may be waived.

3 IMAGING CENTER APPROVAL

3.1 Pre-Approval to Scan First Subject

Following the on-site or teleconference technical visit, an ‘Approval to Scan’ notification and a detailed technical site set-up report summarizing the radiopharmaceutical dose, technical acquisition and reconstruction parameters, image archival, and the approved method of image transfer will be sent to the imaging center, with a copy to the clinical site and sponsor designees. The approval notification and technical report should be kept in the Technical Binder.

*Please note, this ‘Approval to Scan’ notification indicates that the imaging center is now ready to scan their first study subject only.

3.2 Approval to Scan All Subsequent Subjects

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 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).
*Please note the clinical coordinator should NOT schedule a second subject for imaging until IND has reviewed the first subject and it has passed quality control.

4 TECHNICAL BINDER

Each imaging center will receive a technical binder containing all essential imaging study documents including, but not limited to, a copy of this TOM, acquisition document, image transfer document, fax cover sheet, Scanner QA Event Log, key IND contact information, and a CD containing the site setup PowerPoint presentation, PDF copies of all essential imaging study documents, and a copy of the Investigators Brochure (IB) as applicable. Additionally, there will be sections to archive all study documents that have been submitted, and all study related communications (e.g. emails, faxes, etc.).

*Please note, study related documents may be updated throughout the trial and subsequently distributed to imaging centers. The imaging center should appropriately update the technical binder.

5 SPECT IMAGING TIME POINTS

5.1 DaTscan™ (123I-Ioflupane)

Subjects will have a DaTscan™ at screening for eligibility

**Time Point / Visit**

During screening for eligibility*

*IMPORTANT – Specific to Screening Scan’s: The screening DaTscan™ scan report will be used by the clinical site to assess a subject’s eligibility for entry into the study. It is therefore paramount that the imaging data and corresponding imaging documents are transferred to IND within 24 hours of image acquisition.

A visual interpretation of all screening DaTscan™ images will be performed at the ICL by a qualified Nuclear Medicine Specialist. The clinical site study coordinators will receive a report indicating whether the DaTscan™ images demonstrate evidence of a dopamine transport deficit.

6 SUBJECT SAFETY AND ADVERSE EVENTS

Each subject needs to be monitored for adverse events while they are at the imaging center. An adverse event is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

The clinical site principal investigator (PI) is responsible for reporting AE’s to the study sponsor. Although adverse events related to the DaTscan™ injection are not anticipated, other things can happen during the subject’s time at the imaging center (i.e. subject falls, injection site reaction, nausea, dizziness, etc.). Therefore, it is very important for the imaging centers to contact their respective clinical study site personnel immediately (i.e., principal investigator or study coordinator) if they become aware of any adverse events during the imaging procedures, whatever the cause may be. The clinical study coordinator should be contacted by phone and the time of that call documented along with specific information related to the adverse event.
7 SUBJECT IDENTIFICATION (NAMING CONVENTION)

It is very important that the imaging center uses a standard file naming convention so that all scans can be easily identified by IND. The subject ID will be provided by the Clinical Site Personnel when scheduling the DaTscan™ visit. The subject ID will be utilized in the naming convention for each DaTscan™.

- 2-digit site number – 4 digit subject number (e.g., 10-1123)

The subject identifier (naming convention) should be populated in both the Patient Last Name Field and the Patient ID Field with the Date of Birth arbitrarily populated with 01-Jan-1970 when setting up an acquisition or during the de-identification.

*Please note, the above subject identifier (naming convention) should also be populated in the appropriate fields on the corresponding SPECT Acquisition Document and Image Transfer Document.

8 IMAGING DOCUMENTATION

During the imaging visit the technologist will document imaging specific data on the SPECT Acquisition Document that includes, but is not limited to, subject and site specific data, radiopharmaceutical dose and administration data, and SPECT acquisition and reconstruction data. The technologist will also maintain a Scanner QA Event Log that will be completed each day a subject is scanned, at ad-hoc when routine quality control is performed, or when preventive maintenance is performed. An Image Transfer Document will be completed with information regarding image file names and the method of transfer.

*Please note, all three documents will be completed with regards to Good Clinical Documentation Practices and all three documents will be submitted to IND at the time of image transfer. The completed and submitted documents will be archived in the appropriate space in the technical binder.

9 RADIOTRACER & IMAGING

The radiopharmaceutical DaTscan™ (123I- Ioflupane Injection) will be used to provide assay of striatal dopamine transportation using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). Because DaTscan™ is commercially available; imaging centers will order DaTscan™ doses according to their center’s standard operating procedures. Imaging centers are responsible for ensuring their RAM license and/or other applicable licenses are in order to allow for the center to accept DaTscan™. Imaging center staff should be aware of days of availability and approximate time of dose delivery to facilitate scheduling with the clinical staff. DaTscan™ is an FDA approved imaging agent, and the full prescribing information can be found by visiting http://us.datscan.com/wp-content/uploads/2014/06/prescribing-information.pdf.

9.1 SPECT Radiotracer Administration (DaTscan™)

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 injection.
- Administration of a thyroid protecting agent (potassium perchlorate, potassium iodide oral solution or Lugol’s solution) at least 1 hour prior to the patient receiving injection.
Approximately 3-5 mCi (111-185 MBq) of DaTscan™ will be administered as a slow intravenous injection (over approximately 20 seconds) through an indwelling catheter followed by an infusion line flush of 15-20mls of normal saline. Do not exceed a dose of 5 mCi (185 MBq) and do not use when the activity is below 3 mCi (111 MBq).

For accurate determination of the amount of activity injected, the syringe is assayed prior to and immediately following injection (the residual syringe should be refilled with saline to the same volume as the initial injection volume) with the assay amounts and times recorded on the SPECT Acquisition Document.

9.2 SPECT Imaging

Images will be acquired using a dedicated gamma scanner that is capable of performing SPECT imaging approximately 4 hours (+/- 30 minutes) post DaTscan™ injection. The patient should be informed about the total acquisition time and positioned for maximum comfort. The patient’s head should be placed in the appropriate head holder and the field of view (FOV) should encompass the entire head to include the brain from most superior cortical regions through the inferior portion of the cerebellum. Since routine viewing software allows correction of minor obliquities of head orientation, the patient’s comfort (which reduces the probability of motion during acquisition) is more important than perfect alignment of the head. The patient should be told of the necessity to avoid (voluntary) movements of the head and asked for her/his active cooperation and be immobilized per standard procedures for brain imaging.

As a general protocol, raw projection data, with each head rotating 360 degrees, will be acquired with parallel hole collimator using a step and shoot mode into a 128 x 128 matrix with each step moving 3 degrees for a total of 120 projections with an energy window centered on 159 KeV +/- 10% with a total scan duration of approximately 30 – 35 minutes. Specific scan parameters including collimation and acquisition mode will be selected for each center on the basis of an assessment during the technical set up visit.

9.3 SPECT Reconstruction

The imaging center will reconstruct the SPECT images using their standard clinical DaTscan™ scan reconstruction. The ICL will also reconstruct the images using a standard iterative reconstruction algorithm and then correct them for attenuation.

10 ARCHIVAL OF IMAGES

Imaging centers are required to archive both the raw projection data and the reconstructed images for this study as this is considered to be the source data. The method of archiving should follow the imaging center’s specific Standard Operating Procedures.

*Please note that both raw projection data and the reconstructed images will be transferred to the ICL.

11 IMAGE TRANSFER

Prior to transferring the raw projection data and the reconstructed SPECT images to IND, please be sure to assess the images for completeness, artifact and/or patient motion and document it accordingly. All imaging data must be de-identified and labeled with the appropriate naming convention. Images will be transferred to IND using the approved method of transfer that has been previously established and tested during site setup.
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The preferred method of image transfer is IND’s secure Web DICOM Upload Utility. Please refer to the notification sent with the username, password, and instructions for performing a web upload. During the web upload the images will automatically de-identify the data and label it according to the study naming convention.

*Please note, a Data Transfer document needs to be completed and submitted at the time of image transfer.

12 SUBMITTING DOCUMENTS

At the time of image transfer the SPECT Scan Acquisition Document, Imaging Data Transfer Document, and the Camera QA Log should all be submitted to IND. Please be sure all documents are complete and legible. Documents should be either emailed to corelab@indd.org or faxed to +1-203-401-4303.

*Please remember to transfer images and submit documents within 24 hours of acquisition for screening scans used for eligibility purposes.

13 RECEIPT NOTIFICATION

Once the raw projection data and the reconstructed SPECT images and corresponding documents are received at IND, the imaging center will be sent an email indicating that the data and documents have been received and that they are under review. This email should be printed and filed in the Technical Binder.

14 QUERIES

IND will review the data transfer document against what was received to verify all expected files were submitted. All documents will be reviewed for accuracy and completeness using a standard quality assurance procedure. Image will undergo a two step quality assurance check, including review of the file naming, ensuring image headers are de-identified, energy windows, movement artifacts, scanner based artifacts, timing of the acquisition relative to injection, among other checks.

If there is a problem with the documents or images a query may be generated. There are two types of queries you may receive:

1) **Data Clarification Form (DCF)** – DCFs are sent to imaging centers if there is missing information or if there is a clarification needed from study documents.

2) **Technical Issue Clarification Form (TIC)** – TICs are sent if there are technical issues found with SPECT scans, such as problems with acquisition procedures or reconstruction, or image quality in general.

*Please note: it is expected that all queries generated be to be completed, signed, and returned to IND within 24 hours of receipt for screening SPECT scans.

15 ARCHIVAL OF DOCUMENTS

All imaging documents, data receipts, email communications, adverse event documentation, and camera quality control documents must be retained in the appropriate section of the Technical Binder.
16 QUALITY CONTROL AND CALIBRATIONS

Quality control measures are to be performed according to the center and the scanner manufacturer’s standard procedures as implemented in the center’s quality control program for the gamma SPECT scanner and dose calibrator.

The SPECT scanner should have and maintain up-to-date flood uniformity corrections (intrinsic and extrinsic) and center of rotation (COR) corrections. IND recommends calibrations are to be completed on a schedule based on manufacturer recommendations and requirements. In addition a daily $^{57}$Co flood scan should be done at the beginning of the day the scanning is to be completed. The $^{57}$Co flood scan should be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the quality of the SPECT scan the study should be rescheduled. Verification that the daily QC scan has been performed should be documented on the Scanner QA Event Log provided in the binder.

Quality control of the dose calibrator should be performed throughout the course of the study. This typically will include daily constancy, quarterly linearity and annual accuracy tests.

Quality assurance data, software upgrades, changes in hardware and any other manipulations or changes to the imaging scanner will be recorded on a Scanner QA Event Log which will be provided to the imaging centers during the technical set-up visit. This monthly log records any QC, software or other changes to the scanner and acquisition computer. The Scanner QA Event Log(s) up to and including the date of each subject scan should be emailed or faxed with other documents at the time of the electronic transfer of the image data.

17 SPECT SCANNER REPLACEMENT OR UPGRADES

If your center will be replacing or upgrading your SPECT scanner or acquisition software, it is critical that you inform IND prior to the replacement or upgrade occurring, so that IND can take the necessary steps to ensure the continuity of the imaging outcome measures in this longitudinal research study. IND may need to revisit the imaging center to acquire another phantom.

18 REVISION HISTORY

This document will be considered draft until final form and a signature page are signed and dated by representatives of the trial Sponsor and by MNI. Subsequent changes to the final TOM resulting from protocol amendments, and analysis plan or methodology changes will be documented in this section.

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Version Date</th>
<th>Reason for Changes</th>
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19 IMPORTANT CONTACTS

For all questions related to queries, documentation, or need additional study supplies please contact;

Emily Virden  
Senior Data Coordinator & QC Associate  
+1-203-401-4354 voice  
+1-203-401-4304 fax  
evirden@indd.org

For all technical questions related to SPECT protocol setup or image quality control please contact;

Nick Sandella  
Imaging Services Programs Manager  
+1-203-401-4356 voice  
+1-203-401-4304 fax  
nsandella@indd.org

For all questions related to image transfer, PACS web upload, or sFTP account issues please contact;

Dennis Colclough  
System Support Administrator  
+1-203-401-4344 voice  
+1-203-401-4304 fax  
dcolclough@indd.org

For all other study related questions please contact;

Lisa C. Cortina  
Director, Project Manager  
+1-203-401-4337 voice  
+1-203-401-4304 fax  
lcortina@indd.org
EXAMPLE OF SPECT ACQUISITION DOCUMENT

SPECT Scan Information Source Document

Site Number:  
Scan Acquisition Date:  
Imaging Center Name:  
Clinical Site Name:  
Visit Number:  
Age At Time Of Scan:  
Gender:  
Radiochemical:  
Thyroid Blockade Method:  
Time Blockade Administered:  
Injection Time:  
Initial Activity:  
Residual Activity Post Injection:  
Actual Dose:  
Subjection Acquisition:  
Scan Identifier:  
Camera:  
Acquisition Protocol Used:  
Start Time:  
Step Time:  
Technical Comments:

**Ones completed, please fax this form to IND at (603) 681-4303 or email to consilta@indd.org**
### Example of Image Transfer Document

#### IND SPECT Subject Imaging Data Transfer Information Source Document

<table>
<thead>
<tr>
<th>Site Number:</th>
<th>Subject ID Number:</th>
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<tbody>
<tr>
<td>Scan Acquisition Date:</td>
<td>MM MMM YYYY</td>
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<tr>
<td>Imaging Center Name:</td>
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<tr>
<td>Clinical Site Name:</td>
<td></td>
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</tbody>
</table>

**Visit Number:**
- [ ] Screening
- [ ] Previously Acquired

**PPMI Subject ID Number:**
- [ ] PPMI Site Number
- [ ] PPMI Subject Number

#### Transfer Information (Not Required for Previously Acquired Scans):

- **Transfer Mode:**
  - [ ] DICOM
  - [ ] FTP
  - [ ] Web Upload
  - [ ] Other: [ ]

- **Data Format:**
  - [ ] DICOM
  - [ ] Intartle
  - [ ] Native System File

#### Scans Sent:
- [ ] Raw Projection Data
- [ ] Reconstructed Data

**Date Data Sent to IND (DD-MM-YYYY):** [ ] [ ] [ ] [ ]

**Time Sent (24 hour clock):** [ ] [ ]

**Files Verified and Transferred By:** [ ]

**Comments:**

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**MNIID1019**

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**Once completed, please fax this form to IND at (203) 481-4303 or email to corelab@indd.org**
## Example of Scanner QA Event Log

<table>
<thead>
<tr>
<th>Scan Date</th>
<th>Scan Day QC Floods</th>
<th>Pass/Fail</th>
<th>Date</th>
<th>Software upgrades, hardware changes, any other manipulations or changes to the imaging camera, etc.</th>
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