

QIBA Profile: Quantifying Dopamine Transporters with 123Iodine Labeled Ioflupane in Neurodegenerative Disease

(Short Title: SPECT dopamine transporters)

Stage: A. Draft

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| --- |
| **Notation in this Template** |
| **Template Element** | **Appears as** | **Instructions** |
| Boilerplate text | Plain black text | Don't change. Should appear in all profiles. |
| Example text | Plain grey text | Provides an example of content and wording appropriate to that location.Rewrite it to your needs and change the text color back to Automatic (which will make it black). |
| Placeholder | <text in angle brackets> | Replace text and <> with your text.Use Find/Replace for ones that appear frequently. |
| Guidance | Comment with "GUIDANCE" at the top.  | Delete it when you've followed it and don't need it anymore. |

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# Change Log:

This table is a best-effort of the authors to summarize significant changes to the Profile.

|  |  |  |
| --- | --- | --- |
| **Date** | **Sections Affected** | **Summary of Change** |
| 2016.01.18 | All | Distribute first rough draft |
| 2016.01.19 | phantoms | To be upgraded on Tuesday telecon |
| 2016.01.22 | 2 (Claims)3 (Requirements) | More sections to be assigned during “big” BC meeting - Mozley |
| 2016.01 | 3.6 Acquisition | Yuni |
| 2016.02.16 | 3.1-3.6moved later | Brian Zimmerman & John Dickson |
| 2016.02.17 |  | Nancy Obuchowski delivers stats for claims |
| 2016.02.19 | all | BIG BC meeting |
|  |  |  |
| 2016.03.08 | 3.10 | Robert Miyoaka & John Seibyl lead task force meeting to change text |
| 2016.03.15 | 3.10 | Robert Miyoaka delivers revised version |
| 2016.03.14 | 3.9 | Pierre Tervé et al compose the first draft |
| 2016.03.16 | all | line editing & tracked changes clean up (Mozley) detritus |
| 2016.03.16 | 3.6 | CT att. & localization parameters replaced by Image Wisely (Yuni) |
| 2016.03.18 |  |  |
| 2016.03.22 | references | John Seibyl adds first draft |
| 2016.04.14 | 3 & 4 | F2F meeting moves much of Section 3 to 4 |
| ? | 3.1 | Patrick Cella |
| 2016.04.15 | 3.1 | Revisions by Johannes of Siemens with copies to Cella of GE |
| 2016.04.? | 3 | Edits by Eric Frey and start to Recon section |
| 2016.04.26 | all | Edits/additions by John Seibyl |
| 2016.04.28 | all | Clean up by Yuni |
| 2016.05.03 | 3.7 Reconstruction | Eric Frey added Discussion & parts of Table 3.7.2 |
| 2016.05.05 | 3.7.2 | Yuni updated Table 3.7.2 based on May 03 Telecon |
| 2016.05.10 | All | Robert Miyaoka changed ROI to VOI and pixel to voxel |
| 2016.05.10 | 3.10 Image Analysis | Robert Miyaoka incorporated changed discussed during 2016.05.10 conference call |

# Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage.

|  |
| --- |
| **Q. Measurand: cross sectional or longitudinal**A. start with cross sectional only; added longitudinal Jan 2016 |
| **Q. Measurand: striatal binding ratio or percent injected dose per gram**A. start with striatal binding ratio; launch absolute quant by 3Q2016 |
| **Q. Acquisition: need method for determining minimal acceptable counts**A. in progress; might require new ground work |
| **Q. standards: solid (e.g., Cobalt 57) or fillable**A. in progress |
| **Q. Narrow and broad beam linear attenuation coefficient values used in I-123 publications seem to be highly variable. For narrow beam 0.143 to 0.16 and for broad beam 0.10 to 0.12****JNM 2012;53:154-163 , EJNMMI 2010;37:443-450; EJNMMI 2011;38:1529-1540, JNM 2010;51:1624-1631, Lange et al PLoS ONE sept 2014** |
| **Q. Section 3.6 CT parameters differ from Imaging Wisely guidelines** |
| **Q. Concerns raised regarding collimator resolution requirements** **What do you mean by ‘Accurate separate definition of caudate and putamen’****FWHM < 10 mm : Manufacturer specified planar resolution vs. on-site measurement with I-123 test object** |
| **Q. Dr. Klein suggested the need to tie the collimator resolution requirement to the SBR accuracy requirement in the phantom study specified in the profile. But difficult to do as there are several other factors that contribute to SBR accuracy.** |
| **Q. 3.6.2 (Ancillary Equipment) and 3.6.3 (Phantom Imaging) that Brian Zimmerman and John Dickson added to the Acquisition section (3.6) might be in the wrong place, and possibly should be moved to 3.8 which is defined in the Table of Contents as Image QA.** |
|  |
| **Scalar value of bias is currently uncertain** |
| **We cannot agree on a method for distinguishing the anterior from the posterior putamen, but we note that there are several software systems that do this; however, their groundwork data is not available** |
|  |
|  |
|  |

# Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

|  |
| --- |
| **Q. Is this template open to further revisions?**A. Yes.This is an iterative process by nature.Submit issues and new suggestions/ideas to the QIBA Process Cmte. |
| **Q.** A. |

# 1. Executive Summary

Parkinsonism is a major health problem. Distinguishing Parkinson’s disease (PD) and its related disorders from other movement disorders that can mimic it has important implications for prognosis and clinical management. The goal of this QIBA Profile is to optimize the performance of Iodine-123 (123I) ioflupane single photon emission computed tomography (SPECT) for quantifying the concentration of regional cerebral dopamine transporters (DaT) in patients who are being evaluated for neurodegenerative disorders.

The **Claims** (Section 2): This profile claims that compliance with its specifications will (1) produce cross sectional measurements of DaT that can distinguish patients with PD from matched controls, and (2) distinguish true biological change from measurement noise in clinical trials of patients with PD who will be studied longitudinally with 123I-ioflupane. Both claims are founded on observations that idiopathic PD is associated with dopminergic neuronal degeneration, which is particularly pronounced in the subtantia nigra, whose degenerating axonal projections to the basal ganglia manifest a loss of DaT activity. In most clinical imaging contexts, the loss is first observed in the most posterior aspect of the putamen, and then seems to march anteriorly, with left and right sides showing asymmetric changes. As a result, quantifying DaT in the posterior putamen can distinguish patients with PD from matched controls.

The **Activities** (Section 3) describe what needs to be done to make measurements that reliably distinguish patients from controls with confidence. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim.

**The Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.
This QIBA Profile, “Quantifying Dopamine Transporters with 123Iodine Labeled Ioflupane in Neurodegenerative Disease”, addresses quantitative SPECT imaging, which is often used as a diagnostic, as well as a longitudinal biomarker of disease progression or response to treatment. It places requirements on Acquisition Devices, Technologists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis.

The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of the DaT measurements to distinguish patients with PD from matched controls.

The clinical performance target is to achieve a 95% confidence interval for the striatal binding ratio with both a reproducibility and a repeatability of +/- 10%.

This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints.

Note that this document only states requirements to achieve the claim, not “requirements on standard of care.” Conformance to this Profile is secondary to properly caring for the patient.

QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

# 2. Clinical Context and Claims

Clinical Context

Parkinson’s disease (PD) is a major health problem. The prevalence is increasing as the population ages. Onset can be insidious, which can make the diagnosis challenging on clinical grounds alone. A number of radiopharmaceuticals that can quantify several different components of the pre-synaptic dopamine system have been shown to help distinguish between idiopathic PD and movement disorders like essential tremor that mimic it. This profile focuses on a marketed radiopharmaceutical for this use, Iodine-123 (123I) labeled ioflupane (methyl (1R,2S,3S,5S)- 3-(4-iodophenyl)- 8-(3-fluoropropyl)- 8-azabicyclo[3.2.1]octane- 2-carboxylate).

**Conformance to this Profile by all relevant staff and equipment supports the following claim(s):**

**Claim 1:** **Cross sectional.** For a striatal binding ratio (SBR) of Y, a 95% confidence interval for the true SBR is Y ± (1.96 **×** Y **×** 0.106 ). For example, if a patient’s measurement of SBR=4, then 1.96x4x0.106=0.83. So the 95% CI for the true SBR is [4 -0.83] to [4+0.83], or [3.17 to 4.83].

During the initial presentation of newly symptomatic patients, a diagnosis of Parkinson’s disease (PD) is consistent with a finding of a SBR in the posterior putamen that is 50% or less than the value in aged-matched controls, or 80% or less than the value in the whole striatum.

Claim 2: Longitudinal. A measured change in SBR of $∆\%$ indicates that a true change has occurred with 95% confidence if $∆\%$ is larger than rc (10%). If Y1 and Y2 are the SBR measurements at the two time points, a 95% confidence interval for the true change is $\left(Y\_{2}-Y\_{1}\right)\pm 1.96\sqrt{(Y\_{1}×0.036)^{2}+(Y\_{2}×0.036)^{2}}$.

**These claims hold when:**

* **Anatomical imaging, such as magnetic resonance imaging (MRI), has already ruled out other causes of parkinsonism, such as stroke;**
* **The patient has not been taking drugs or nutritional supplements that can transiently influence the measurements;**
* **The patient does not have a deformity or condition that prevents proper positioning in the scanner;**
* **The patient can tolerate the imaging procedures well enough to prevent motion from confounding the acquisition;**
* **The administration of the radiopharmaceutical is not confounded by infiltration of the dose;**
* **Et cetera**

**Discussion**

The primary measurand, or outcome measure, is the specific binding ratio (SBR) obtained in the striatum, and usually divided into separate values for the caudate, anterior putamen, and posterior putamen. While research studies sometimes include the SBR for other structures, such as the substantia nigra pars compacta, the thalamus, amygdala, and hippocampus, these regions are beyond the scope of this profile.

The SBR is defined as the count density in a striatal volume of interest (VOI) divided by a reference region count density minus 1, and is roughly equivalent to the binding potential (BPnd) using a reference region as estimate of non-displaceable uptake in basal ganglia.

The reference region is ideally the cerebellum, as it contains no known dopaminergic proteins or messenger RNA for these proteins. Acceptable alternatives include the occipital cortex, particularly when the axial field of view is limited.

An alternative outcome measure is the fraction of the injected dose per unit volume in a VOI expressed in units of kBq/mL. This measure is an estimate of transporter number, rather than transporter density.

These claims are based on estimates of the within-subjects coefficient of variation (wCV) for SBRs in the basal ganglia. In the claim statement, the CI is expressed as Y ± 1.96 × Y × wCV. The claim assumes that the wCV is constant for each component of the basal ganglia (e.g., head of caudate and anterior putamen) in the specified size range, and that there is negligible bias in the measurements (i.e., bias < 5%). For estimating the critical % change, the % Repeatability Coefficient (%RC) is used: 2.77 × wCV × 100.

The +/- 10% boundaries can be thought of as “error bars” or “noise” around the measurement of SBR change. If an operator measures change within this range, it cannot be certain that there has really been a change. However, if a SBR changes beyond these limits, then an observer can be 95% confident there has been a true change in the SBR, and the perceived change is not just measurement variability. Note that this does not address the biological significance of the change, just the likelihood that the measured change is real.

Clinical interpretation with respect to the magnitude of true change:
The magnitude of the true change is defined by the measured change and the error bars (+/- 15%). If an operator measures the SBR to be 3.0 at baseline and 1.5 at follow-up, then the measured change is a 50% decrease in SBR (i.e., 100x(3.0 – 1.5)/3.0). The 95% confidence interval for the true change in SBR is is$\left(1.5-3.0\right)\pm 1.96\sqrt{(1.5×0.077)^{2}+(3.0×0.077)^{2}}$, or [-2.01, -0.99], which represents a 33% to 67% decrease in SBR.

Clinical interpretation with respect to progression or response:
A decrease in SBR that exceeds the lower bound of the confidence interval indicates there is a 95% probability of disease progression. An increase in SBR that exceeds the upper bound has a 95% chance of representing a true biological change in the concentration of DaT. The medical meanings of changes that are greater than the bounds of the confidence interval are beyond the scope of this profile.

While cross sectional accuracy described by Claim 1 has been informed by an extensive review of the literature and expert consensus, it has not yet been fully substantiated by studies that strictly conform to the specifications given here. The expectation is that during field testing, data on the actual field performance will be collected, and any appropriate changes that are indicated will be made to the claim or the details of the Profile. At that point, this caveat may be removed, refined, or re-stated.

# 3. Profile Activities

The Profile is documented in terms of “Actors” performing “Activities”. Equipment, software, staff or sites may claim conformance to this Profile as one or more of the “Actors” in the following table.

Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced Section.

Table 1: Actors and Required Activities

|  |  |  |
| --- | --- | --- |
| **Actor** | **Activity** | **Section** |
| Acquisition Device | Pre-delivery | 3.1. |
| Acceptance tests | 3.2 |
| Periodic QA/QC | 3.3 |
| Clinician | Subject Selection | 3.4 |
| Technologist | Subject Handling | 3.5. |
| Image Data Acquisition | 3.6. |
| Image Data Reconstruction | 3.7. |
| Image QA | 3.8. |
| Image Distribution | 3.9. |
| Reconstruction Software | Image Data Reconstruction | 3.7. |
| Image Analysis Tool | Image Analysis | 3.10. |

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a “shall” declaration in this Profile could be a protocol deviation. Although deviations could invalidate the Profile Claim, such deviations may be reasonable and unavoidable, and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

The sequencing of the Activities specified in this Profile are shown in Figure 1:

<activity sequence diagram>

Figure 1: < SPECT dopamine transporters > - Activity Sequence



## 3.1. Pre-delivery

This activity describes calibrations, phantom imaging, performance assessments or validations prior to delivery of SPECT imaging equipment to a site (e.g. performed at the factory) that are necessary to reliably meet the Profile Claim.

### 3.1.1 Discussion

Gamma cameras, radionuclide calibrators and computer workstations must have passed manufacturer release testing and need to be under a schedule of periodic QA and maintenance as described in section 3.3. In order to be compliant with this Profile, the gamma camera should be held to the same standard whether it is a mobile unit or a fixed installation; a mobile gamma camera may require additional calibration to achieve proper performance. The selection and consistent use of appropriate collimators as well as an off-the-bed head holder is necessary to achieve the spatial resolution of the striata necessary to minimize variability in measurements.

The DICOM format used by the gamma camera and/or processing workstation should meet the Conformance Statement written by manufacturer of each system. SPECT raw and reconstructed data shall be encoded in the DICOM Nuclear Medicine Image Storage SOP Class with additional parameters in public DICOM fields. Any CT data (used for image correction) should be encoded in CT or Enhanced CT Image Storage SOP Class. DICOM data shall be transferred using the DICOM Part 8 network protocol or as offline DICOM Part 10 files for media storage including CDs and DVDs. They shall be transferred without any form of lossy compression.

Gamma cameras with cadmium-zinc-telluride (CZT) detectors are not currently recommended for quantitative measurements of I-123 ioflupane.

### 3.1.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Release Testing | Manufacturer | The gamma camera (and any replacements parts) must pass all manufacturing in-process and release testing criteria |
| Non-OEM parts supplier | All parts and accessories must meet or exceed OEM specifications and pass all release testing criteria |
| DICOM format | Manufacturer | Shall meet the Conformance Statement written by manufacturer of each system |
| Computer workstations | Vendor | All workstations used to process images must be validated, able to support the image file type generated by the gamma camera and able to perform the image processing and quantification requirements detailed in Sections X.X |
| Collimators | Owned by imaging center; placed by technologist | **Collimator:** A collimator that has sufficient spatial resolution that would allow the concentration of activity in the Caudate and Putamen to be estimated in the reconstructed image corresponding to the phantom study specified in Section 4 shall be used. Collimators should be high-resolution (low-energy, medium-energy or specialty) with a voxel size of not more than 3.5mm-4.5mm with a matrix of 128x128. General-purpose collimators should not be used |
| Head holder | Owned by imaging center; placed by technologist | An off-the-bed head holder (with appropriate cushioning) to achieve an acquisition radius of 12-15cm must be used |

### 3.2 Acceptance tests

## 3.2.1 Discussion

Acceptance tests must be performed on systems when they are installed in order to 1) ensure that they meet the performance criteria set forth in the purchasing process, and 2) establish a baseline for evaluation of performance over time. Thereafter, the performance tests described in Section 3.3 should be performed at the interval prescribed, or after any major repair.

A number of documents (ACR, IAEA,) give specific guidance as to how to conduct these tests.

A qualified medical physicist should perform the tests. Alternatively, the tests may be performed by properly trained individuals approved by the medical physicist. The test results must be reviewed by the qualified medical physicist and properly documented.

### 3.2.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Acceptance tests | Physicist or other trained, qualified personnel | Perform recommended tests at prescribed intervals. |
| Scanner | Must pass initial acceptance tests and perform within prescribed parameters for duration of study. |

## 3.3. Periodic QA

This activity describes calibrations, phantom imaging, performance assessments or validations performed periodically at the site, but not directly associated with a specific subject, that are necessary to reliably meet the Profile Claim.

### 3.3.1 Discussion

A number of documents from several authoritative bodies (e.g., ACR, IAEA, AAPM, NEMA, IPEM, IEC) have been produced that give specific guidance as to how to conduct the tests described below. The list represents a minimum of set of performance measures that should be monitored on a regular basis. Manufacturers’ recommendations and institutional policy may require additional tests or that they be performed at shorter intervals.

A qualified medical physicist should perform these tests. Alternatively, the tests may be performed by properly trained individuals, such as a nuclear medicine technologist, who has been authorized by a supervising medical physicist. The test results must be reviewed by the qualified medical physicist and properly documented.

### 3.3.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| SPECT Calibration Factor  | Physicist | Shall assess the current SPECT Calibration Factor at least quarterly. See 4.3 Assessment Procedure: SPECT Calibration Factor.Shall record the date/time of the calibration for auditing. |
| Acquisition Device | Shall be capable of performing the SPECT Calibration Factor assessment.Shall record the most recent SPECT Calibration Factor for use in subsequent activities. |
| Qualification | Physicist | Shall be a Qualified Medical Physicist (QMP) as defined by AAPM. |
| Time sync | Physicist | Shall confirm on a weekly basis that all device clocks are synchronized to within +- 1 minute. |
|  |  |  |
|  |  |  |

|  |  |  |
| --- | --- | --- |
| Planar Uniformity | Imaging Site | Uniformity of response to a uniform flux of radiation from a I-123 point source should be measured intrinsically every quarter. On a daily basis planar uniformity with collimators used for I-123 imaging should be performed using a Tc-99m or Co-57 source |

|  |  |  |
| --- | --- | --- |
| System Uniformity | Physicist | Performed to check all commonly used collimators for defects that might produce artifacts in planar and tomographic studies. Test should be conducted semiannually. |
| System Spatial Resolution | Physicist | Tests the resolution of the system in terms of the FWHM of its point spread function. Test should be conducted semiannually with the collimators routinely used with 123I ioflupane studies. |
| System Sensitivity | Physicist | Tests the response of the system in terms of counting rate per known unit of activity. Should be performed semiannually, with the results deviating no more than 5 % from reference value established during initial testing. |
| Count Rate Parameters | Physicist | Tests spatial resolution, uniformity, and linearity of the count rate response in clinical images acquired at high count rates |
| Center-of-Rotation (COR) | Physicist | Tests the COR offset, alignment of camera Y-axis, and head tilt with respect to the scanner center of rotation. Mean value of the COR offset should not exceed 2 mm when measured at the center and edges of the FOV. Position of Y=0 axis and the Y gain should be the same for all heads in a multihead system. |

**3.3.3 Ancillary Equipment**

3.3.3.1 Radionuclide Calibrator

The following guidelines are collected from ANSI standard N42.13, 2004 and IAEA Technical Report Series TRS-454. All requirements assume measurements on unit doses of I-123 ioflupane and that calibration sources are in the 'syringe' geometry (i.e., no bulk doses).

The Constancy test ensures reproducibility of an activity measurement over a long period of time by 698 measuring a long-lived source of known activity.

The Accuracy test ensures that the activity values determined by the radionuclide calibrator are correct and traceable to national or international standards within reported uncertainties.

The Linearity test confirms that, for an individual radionuclide, the same calibration setting can be applied to obtain the correct activity readout over the range of use for that radionuclide calibrator.

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| Constancy | Technologist | Shall be evaluated daily (or after any radionuclide calibrator event) using a NIST-traceable (or equivalent) I-123, Cs-137, or Co-57 radionuclide calibrator standard and confirmed that net measured activity differs by no greater than ±2.5 % from the expected value. |  |
| Accuracy | Technologist | Shall be evaluated monthly (or after any radionuclide calibrator event) with a NIST-traceable (or equivalent) I-123 standard or simulated I-123 radionuclide calibrator standard (if available). Shall confirm that net measured activities differ no greater than ±2.5% from expected value. The scanner calibration shall be tested using a NIST-traceable (or equivalent) simulated I-123 source object, e.g. a uniform cylinder, large enough to avoid partial volume effects or other resolution losses. |  |
| Linearity | Technologist or Radiation safety officer or Qualified Medical Physicist | Shall be evaluated annually (or after any radionuclide calibrator event) using an appropriate radionuclide (for example, F-18 or Tc-99m) and should be within ±2.5 % of the true value over an operating range of 37-1110 MBq (1 to 30 mCi) and the true value is determined by a linear fit (to the log data) over the same operating range.  |  |
| Radiation Dose | Dose Calibrator | Shall record the radiation dose from the administered activity and accompanying information in a DICOM Radiopharmaceutical Administration Radiation Dose Structured Report. |  |

3.3.3.2 Clocks and timing devices

The SPECT scanner computer and all clocks in an imaging facility used to record activity/injection measurements should be synchronized to standard time reference within +/-1 minute. These include any clocks or timekeeping systems that are connected with a subject’s I-123 ioflupane study, in particular those associated with the radionuclide calibrator, the injection room, the scanner, and the acquisition computer(s). The synchronization of all clocks (to date, time of day and to time zone) should be monitored periodically as part of ongoing QA program. In particular, clocks should be inspected immediately after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur). Correct synchronization could be achieved using the Consistent Time Integration Profile as defined in the IHE IT Infrastructure Technical Framework. A Consistent Time Profile can be achieved with the use of the Network Time Protocol (NTP) ([www.NTP.org](http://www.NTP.org)).

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| Scanner and site clocks  | Approved personnel  | SPECT scanner computer and all clocks in an Imaging facility used to record activity/injection measurements shall be synchronized to standard time reference within +/-1 minute. Synchronization of all clocks used in the conduct of the I-123 ioflupane study shall be checked weekly and after power outages or civil changes for Daylight Savings (NA) or Summer Time (Eur)  |  |
| Scanner and site clocks  | Specific Device  | Provide time synchronization as per the IHE Consistent Time Integration Profile.  |  |
| Dose calibrator clock  | Dose Calibrator  | Electronic record of output from a dose calibrator shall be synchronized with other time keeping devices.  |  |

## 3.4. Subject Selection

This activity describes criteria and procedures related to the selection of appropriate imaging subjects that are necessary to reliably meet the Profile Claim.

### 3.4.1 Discussion

The study is contraindicated in patients with allergies or hypersensitivity reactions to ioflupane, the excipients in the formulation, or iodine, as about 120 mg of Iodine in the form of potassium iodide should be administered by mouth 0.5-to-2 hours prior to the intravenous administration of the 123I ioflupane formulation to minimize thyroid exposure to any free I-123.

A urine or serum pregnancy test should be performed prior to the procedure in women of childbearing potential. Radiation exposure makes the procedures relatively contraindicated in subjects who are pregnant. Subjects who are breast-feeding at the time of the examination are advised to stop and discard all breast milk for about one week, after which they may resume.

The study is not approved by health authorities for use in children who might have juvenile forms of Parkinson’s disease. While it is known that the product, or similar products, have been approved for research studies in children, this profile is limited to adults with typical basal ganglia size and morphology.

The study is indicated in patients who present with signs and symptoms that are consistent with, but not definitively diagnostic of, Parkinson’s disease (PD), and sometimes for confirming a presynaptic dopamine deficit in patients who are entering a clinical trial. Its U.S. regulatory approval is limited to use as a “visual adjunct imaging agent to aid in the differentiation between essential tremor and parkinsonian syndromes.” Parkinsonian syndromes include Idiopathic Parkinson’s disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and other conditions. Ioflupane is not qualified by national regulatory authorities to distinguish among these conditions.

### 3.4.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Subject Selection | Referring health care provider | For the cross sectional claim, shall establish a differential diagnosis that includes parkinsonism versus essential tremor. |
| For the longitudinal claim, shall refer eligible subjects |
| Health care provider (nurse, physician, or technologist) | Shall take a history of allergies to iodine;Shall perform a pregnancy test in women of childbearing potential |

## 3.5. Subject Handling

This activity describes details of handling imaging subjects that are necessary to reliably meet the Profile Claim, specifically with regard to preparation, injection, SPECT scan acquisition, follow up instructions, and other logistics occurring on the scanning day.

### 3.5.1 Discussion

All procedures should conform to good clinical practices regarding the provision of information to the patient about the risks, benefits, logistics, and reasonable expectations concerning the imaging activities.

No special preparation is required of the patient regarding diet or fasting prior to the procedure. On the scan day the patient should be questioned regarding iodine allergies prior to the administration of nonradioactive potassium iodide. Additional queries should be made about any thyroid disease or surgeries. If the patient has had a thyroid ablative procedure, complete thyroidectomy or otherwise receives exogenous thyroid hormone replacement, it may not be necessary to perform thyroid blockade. Nonradioactive potassium iodide (100-120 mg) is provided by mouth 30-60 min before anticipated injection of ioflupane. Uptake of the potassium iodide is rapid with some absorption through the gastric mucosa. It is common for patients to describe metallic taste following administration of the thyroid blockade. For patients with iodine allergies potassium perchlorate (400-1000 mg) p.o. has been used, or alternatively, no blockade is performed. Note the low mass dose of iodine contained in radioactive ioflupane does not trigger hypersensitivity reactions in patients with iodine allergies.

Preparation for ioflupane injection involves establishing an intravenous line, usually with the small gauge needle or catheter and confirming patency. Injection of 3-5 mCi of I-123 ioflupane is performed as a bonus over 5 to 20 seconds followed by saline flush of at least 20 mL. There are no specific product guidelines for altering the dose in the context of renal or hepatic impairment. It is not necessary to maintain the patient in a special environment to minimize sensory stimulation during the brain uptake phase. Imaging commences 4 h ± 15 min post injection when a secular equilibrium of washout from the basal ganglia and reference region has occurred. Imaging earlier than four hours underestimates specific binding ratios in some individuals.

 After 3.5 hours following the ioflupane injection the patient is invited to empty their bladder then positioned in the camera. For most SPECT systems a head holder is required to allow the imaging heads to come within a maximum 15 cm radius. It is important that the patient be comfortable from the outset as they will be in the camera for 30 to 45 minutes. Stress on the lumbar spine may be reduced by providing support under the patient’s knees. The head may be gently restrained within the head holder to minimize movement. In addition, instructions highlighting the importance of remaining still should be given several times. During the scan acquisition there should be a low level of stimulation in the room (lights dim, no conversational banter, etc.) to minimize motion.

### 3.5.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Pre-injection | Nuclear pharmacy | Shall provide a system that is capable of receiving, dispensing and administering non-radioactive potassium iodide and 123I ioflupane. |
| Health care provider (nurse, physician, or technologist) | Shall perform a formal “time out” identification procedure; |
| Shall administer about 120 mg of Iodine in the form of Lugol’s solution or supersaturated potassium iodide (SSKI) at least 60 minutes prior to administration of ioflupane, and monitor subjects for adverse events and allergic reactions , such as nausea, vomiting, stomach ache, diarrhea, metallic taste in the mouth, fever, headache, runny nose, or sneezing. |
| Shall establish an intravenous line and prove its patency by showing the rate of a saline drip can be easily altered with an inclined roller. |
| Post-injection | Technologist | Shall ensure the subject voids prior to placement on the table |
| Shall place the subject on the table in such a way that maximizes comfort, minimizes the risk of motion, and positions the basal ganglia as close to the center of the field of view as feasible. |
| Shall select the proper acquisition protocol of 123I ioflupane |
| Shall do whatever else we want to specify |
| Shall begin image acquisition at 4 hours +/- 15 minutes post intravenous administration of ioflupane |

## 3.6. Image Data Acquisition

This activity describes details of the data acquisition process that are necessary to reliably meet the Profile Claim.

### 3.6.1 Scanner acquisition mode parameters

We define acquisition mode parameters as those that are specified by the Technologist at the start of the actual SPECT/CT scan. These parameters do not include aspects of the acquisition that occur earlier (e.g., injected activity) or later (e.g., reconstruction parameters) in the overall scan process.

***SPECT Acquisition***

The SPECT acquisition is performed on a properly calibrated SPECT/CT or stand-alone SPECT system with at least two imaging heads fitted with collimators as described in the specifications below. Single headed SPECT systems are not recommended**.** Low Energy High Resolution (LEHR), Low Energy Ultra-High Resolution (LEUHR) and fan beam collimators with manufacturer specified (or measured according to NEMA standards) planar system resolution of < 8 mm FWHM (in ‘air’ at 10 cm distance) typically meets the resolution requirement in the table below. Some LEAP collimators allow too much septal penetration of the high-energy emissions I– 123, resulting in ring artifacts which may affect quantitation. ME collimators, which reduce septal penetration may be insufficient in terms of the resolution requirement. If available, collimators designed specifically for 123I brain SPECT can be used. These include Low to Medium Energy General Purpose (LMEGP, Nuclear Fields), Extended Low Energy General Purpose (ELEGP, GE), LELGP, and multi Pinhole BIOSPECT collimators.

Once the patient is placed on the imaging table it is important to have the radius of the rotation as small as possible. This may be particularly challenging in patients with degenerative spine disease or other orthopedic problems affecting posture. The acquisition is ideally performed in step and shoot mode with angular sampling every 3 degrees collecting photopeak counts (159 keV +/- 10%) into a 128 x 128 matrix. Acquisitions are obtained over 25 to 45 min or a minimum of 1.5 million counts. There are no data that support a rationale for variable SPECT acquisition mode parameters, specifically the acquisition time depending on subject weight and or amount of injected I-123.

###

### 3.6.2 Specification

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| Imaging device | Study sponsor | The acquisition device shall be selected to produce comparable results regardless of the scanner make and model. **Camera:** Multi detector SPECT or SPECT/CT cameras shall be used.**Collimator:** A collimator that has sufficient spatial resolution to allow independent estimates of the concentration of activity in the Caudate and Putamen in the reconstructed image shall be used.  |  |
| Technologist | Shall be certified by local authorities to operate the instrument in compliance with this profile. |  |

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| SPECT Acquisition mode | Study sponsor | The key SPECT acquisition mode parameters shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model. The key parameters are:**Rotational radius**: shall be fixed at 11 – 15 cm (circular orbit) or smallest possible.**Matrix and voxel size**: A matrix size and zoom factor that gives a voxel size of one-third to one-half the expected spatial resolution shall be used. Typically, a 128 x 128 matrix and voxel size of no larger than 4 mm.**Angular sampling:** 360 degree coverage of the head with angular sampling of not less than 120 views shall be used (<= 3 degree increments). Step-and-shoot is typically used, but continuous mode can be used to provide shorter total scan time.**Total counts:** The scan time shall be adjusted to obtain > 1.5 million total counts detected in the photopeak window. Typically, this requires a 25 – 45 min scan.**Energy windows:** The photopeak window shall be set at 159 keV +- 10% (143 – 175 keV). If triple energy-window based scatter correction is to be used, two additional narrow windows (7%, 15% ?) adjacent to the photopeak shall be used.  |  |
| Technologist | The technologist shall set up the acquisition, acquire the data, and store the data. |  |

***CT Acquisition***

## For the CT component of the SPECT/CT scan, this Profile only addresses the aspects related to the quantitative accuracy of the SPECT image. The focus is on attenuation correction and anatomical localization only. This profile does not describe a diagnostic CT scan. When CT is used for attenuation correction only, the CT can be performed with 5 – 10 mAs. When used for anatomic localization, the CT can be performed with 30 – 60 mAs (with 110-130 kVp, pitch 0.8-1.5). This is based on Image Wisely guidelines.

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| CT Acquisition mode | Study sponsor | The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model, and with the lowest radiation doses consistent for the role of the CT scan: correction for attenuation and for localization. The CT acquisition mode shall utilize the protocol that delivers the lowest possible amount of radiation dose to the subject (e.g. a relatively low dose protocol) that retains the quantitative accuracy of corrections for attenuation.  |  |
| Technologist | The key CT acquisition mode parameters (kVp, mAs, pitch, and collimation) shall be set as specified by study protocol and used consistently for all subject scans.  |  |

| **Parameter** | **Actor** | **Requirement** | **DICOM Tag** |
| --- | --- | --- | --- |
| CT Technique: Protocol Design  | Technologist / Physician / Medical Physicist  |  A team comprising a Technologist / Physician / Medical Physicist shall ensure that CT techniques protocols are designed such that dose exposure is the lowest radiation dose necessary to achieve the objective. Protocols defined by Image Gently and Image Wisely should be used where feasible. The protocol shall be recorded and documented.  |  |
| Technologist | The technologist shall ensure that the CT dose conforms to the dose prescribed by the supervising physician or protocol.  |  |

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## 3.7. Image Data Reconstruction

This activity describes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim.

### 3.7.1 Discussion

Reconstruction is performed on the projection data following a quality control check of the sinogram to assess for any motion and potential artifacts. Goal of the reconstruction is to provide a well-delineated basal ganglia which allows regional sampling of the caudate and putamen. Alterations in dopamine transporter density are asymmetric with regard to the caudate and putamen as well as the left and the right side of the brain. The optimal reconstruction, correction, and filtration method depends on the image analysis method used (see Section 3.10).

Images can be reconstructed using either iterative (e.g., iterative) or analytic reconstruction methods provided appropriate compensations are included, as described below. Iterative methods are typically preferred as they allow for more accurate and complete compensation.

Reconstructed images are required to be corrected for attenuation. The attenuation map used in the correction can either be measured with a transmission scan, e.g., x-ray CT (preferred), or estimated from boundaries of the head, (e.g. using ellipses). The attenuation correction can be implemented either using iterative (e.g., OSEM), analytical (e.g., Tretiak-Metz), or approximate (e.g., Chang 0) algorithms. Approximate and analytic attenuation correction methods typically use an estimated map and assume uniform attenuation. The use of measured attenuation maps and iterative reconstruction is preferred. Measured attenuation maps obtained from CT images should have the attenuation values appropriately translated so they are appropriate for 159 keV and be registered to the emission images with an accuracy of better than 2 mm.

Correction for scatter is prefered, and should take into account downscatter from high energy photopeaks. Scatter correction can be implemented using energy-window-based scatter estimates (e.g., the TEW method) or scatter modeling methods. For filtered backprojection-based reconstruction the scatter estimate is typically subtracted from the projection data. For iterative reconstruction the scatter compensation should be incorporated into the reconstruction algorithm in order to obtain the best noise properties.

For the whole striatum VOI image analysis method (see Section 3.10), collimator-detector-response (CDR) compensation, a large number of iterations (typically > 300 image updates for OSEM), and little or no post-reconstruction filtering is recommended in order to reduce partial volume effects. Explicit partial volume compensation may be useful for this the whole striatum VOI method. For the small VOI method, CDR compensation may lead to ringing artifacts that complicate quantification and his thus not recommended. A smaller number of iterations and some post-reconstruction low-pass filtering can be useful to help control noise and its effects on the regional activity estimates.

If pre-or post-reconstruction low-pass filtering is applied to the images it is important that the filter be linear across the count ranges. It is desirable that reconstructed images be saved in such a way as to preserve as much dynamic range (numeric precision) as possible.

### 3.7.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| SPECT Image Reconstruction | Study Sponsor ?Medical Physicist? | The key SPECT reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be specified in a manner that is expected to produce comparable results regardless of the scanner make and model. The key SPECT image reconstruction parameters shall be specified according to pre-determined harmonization parameters.  |
| Technologist | The key SPECT reconstruction parameters (algorithm, iterations, smoothing, field of view, voxel size) shall be followed and set as specified in order to produce comparable results regardless of the scanner make and model.  |
| SPECT Matrix/Voxel size | Technologist | The Technologist shall perform the image reconstruction such that the matrix, slice thickness, and reconstruction zoom shall yield a voxel size of < 4 mm (same as projection bin size) in all three dimensions, although not necessarily isotropic. The final size shall not be achieved by re-binning, etc., of the reconstructed images.  |
| Correction: Attenuation | Technologist | Uniform or non-uniform attenuation correction shall be included in the reconstruction. For uniform correction a narrow beam attenuation coefficient of 0.148 cm-1 shall be used when scatter correction is included while a broad beam attenuation coefficient of 0.11 cm-1 shall be used when scatter correction is not included.For non-uniform attenuation correction the attenuation map shall be obtained by a transmission measurement or x-ray CT (preferred). |
| CT Attenuation map | Medical physicist | Shall confirm that attenuation be scaled appropriately to those for the 159 keV I-123 photopeak.  |
| Estimated Attenuation Map (if used) | Technologist | Shall be defined so that it conforms to the outline of the head as closely as possible. |
| Reconstructed image | Technologist | Shall be reconstructed in such a way as to compensate for attenuation and scatter. If the whole striatum VOI image analysis method is used (see Section 3.10), the reconstruction should be implemented to reduce partial volume effects, e.g., using CDR and partial volume compensation. Controlling voxel-level noise is less important for the whole striatum VOI method. For the small VOI method, the reconstruction should be implemented to control the effects of voxel-level artifacts such as noise spikes and ringing. |
| Post-filtering | Technologist | For data reconstructed without CDR, 3-dimensional post-filtering shall be used. A low pass (e.g. Butterworth) filter is recommended. |
| Stored Reconstructed Image | Camera Manufacturer | Reconstructed images should be stored in such a way as to preserve the image dynamic range. |

## 3.8. Image QA

This activity describes criteria and evaluations of the images that are necessary to reliably meet the Profile Claim.

### 3.8.1 Discussion

**Many factors can adversely influence image quality, and degrade quantification. Some of these problems can be inferred from a qualitative assessment of the images by an experienced operator, such as a nuclear radiologist.**  For example, while advanced Parkinson’s disease can produce globally decreased ioflupane uptake in all structures of the basal ganglia, these findings are more likely to represent an infiltrated dose in patients who are making their initial presentations.

### 3.8.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| count sufficiency | nuclear medicine specialist or nuclear radiologist | Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm3 and 524 cm3.) |
| clear, conspicuous margins | Shall confirm the tumor margins are sufficiently conspicuous and unattached to other structures of equal density to distinguish the volume of the tumor. |
| Excessive motion |  |
| Proper positioning in FOV |  |
| artifacts | Shall ensure assessment is not confounded by ring artifacts, artifacts related to too large a radius for COR (i.e., should be <15 cm, or edge artifacts |
| Mis-registration of SPECT/CT or discordance of Chang’s |  |
|  |  |
|  |  |

## 3.9. Image Distribution

This activity describes criteria and procedures related to distributing images that are necessary to reliably meet the Profile Claim.

### 3.9.1 Discussion

Discussions of archiving and distributing SPECT data often mention 'raw data'. This is an ambiguous term as it can refer to: scanner raw data (i.e., sinograms) or image raw data. To avoid confusion, the term raw data should not be used without making it clear which form is under discussion.

***Scanner raw data*** include the sinograms as acquired from the SPECT scanner, i.e., a list of planar projection images, one image for each acquired angle and energy window. This is always a single DICOM file containing projections images grouped by acquisition energy window. These projections can be analyzed by the Image Data Reconstruction Software.

***Image raw data*** is the image data exactly as produced by the reconstruction process by the Image Data Reconstruction Software, i.e., a stack of DICOM slices/files constituting a SPECT image volume with no processing other than that occurring during image reconstruction. This is always a stack of DICOM slices/files constituting a SPECT image volume that can be analyzed on one or more of the following: SPECT scanner console, SPECT image display workstation, PACS system, etc.

***Post-processed image data*** are images that have been transformed after reconstruction in some manner, including but not limited to: smoothing, image zoom, rotation/translation, resampling, spatial normalization, interpolation, slice averaging, MIP, etc. This is typically a stack of DICOM slices/files constituting a SPECT image volume that can still be analyzed on one or more of the following: PET scanner console, PET image display workstation, PACS system, etc.

For distributing and archiving at the local site or imaging core lab (if relevant), the most important data are the reconstructed images, i.e., the image raw data, and post processed image data including averaged images if any. In the unlikely event that the scanner raw data (which should be archived by the local site) is required for later reprocessing; this should be made clear in the protocol. Should scanner raw data be archived, all information needed for proper reconstruction and attenuation correction should be kept in DICOM files.

### 3.9.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Image Distribution | Technologist | The original projections (sinogram) images (scanner raw data), shall always be archived at the local site.The reconstructed SPECT images (image raw data), along with all required corrections, and CT images shall always be archived at the local site.If processed PET images are required, they shall be archived as separate secondary datasets. If scanner raw data need to be archived for future reprocessing, this should be defined prospectively in the Protocol. |

## 3.10. Image Analysis

This activity describes criteria and procedures related to producing quantitative measurements from the images that are necessary to reliably meet the Profile Claim.

### 3.10.1 Discussion

The Image Analyst using computer workstation analysis tools shall perform the specified measurements. The main quantitative data analysis task is to determine the Specific Binding Ratios (SBR) of Ioflupane DaTscan for the right and left caudate and putamen. The derived results are then compared to an age-normalized database to provide a reference for the SBR versus age-matched normals. The profile describes the data analysis methodology.

Quantitative Specific Binding Ratio (SBR) of Ioflupane DaTscan will be based upon patient SBR and compared to an age normalized database (or striatal phantom or digital reference object as the case may be). Qualified systems will be able to achieve a SBR within a certain range (i.e., ±5% of reference value) for quantitative imaging of I-123 Ioflupane for the DaTscan phantom (described in this profile). Further the coefficient of repeatability should be <20% for repeat studies. The profile does not seek to make disease determination but to provide the methodology for data analysis and also for qualification of systems and processing for I-123 Ioflupane DaTscan data analysis.

Input Data:

The output images from Image Reconstruction are considered the input for Image Analysis. Once stored on the analysis workstation the image data will be processed for region of interest image analysis as described below. The original input data will be maintained as a separate file and will be stored along with the processed data for image analysis.

Methods to be Used:

Uptake in the striatum (i.e., caudate, anterior putamen and posterior putamen) and background region (e.g., cerebellum or occipital region) is characterized by defining a volume-of-interest (VOI). The measurand is the specific binding ratio and is determined from the following equation:

   (eq 1)

where the background (*backgrnd)VOI* counts are normalized to the same VOI volume as the striatal VOI (i.e., caudate or anterior putamen or posterior putamen).

Volumes of interests will be drawn on preprocessed images as described below.

Two volume of interest analysis strategies are described. The first method is referred to as the Small VOI approach. The second method is referred to as the whole striatum VOI approach.

The small VOI approach is described as follows. On spatial normalized SPECT image volumes the transaxial slice with the highest striatal uptake is identified and the adjacent hottest slices spanning an axial extent of 2 cm or less are averaged to generate a single slice image. VOIs are then placed on the left and right caudate, the left and right putamen, and the occipital cortex (reference tissue), as shown in Figure 3.10.1. It should be clear which values belong to which striatal structures. This can be done by capturing DICOM coordinates along with VOI values or secondary screen capture of the VOI for identification. MRI anatomical images can be used for VOI drawing if they exist. VOIs maybe placed according to VOI template or using semi-automated or automated placement tools. Count densities for each region are extracted and used to calculate specific binding ratios (SBRs) for each of the striatal regions. SBR is calculated as ((target region – reference region)/reference region), as described above in eq 1.

Figure 3.10.1. Illustration of Small VOI placement on summed slice image.

The whole striatum VOI approach is similar to the Small VOI approach but uses larger volumes of interest (VOIs) and does not separate the putamen into two regions. The whole striatum VOI approach is implemented in many commercial software packages. The reconstructed image is spatially normalized to a SPECT template. Volumes of interest sampling most of the right and left caudate and putamen are drawn on the image as illustrated in Figure. 3.10.2. Background VOIs are drawn on the occipital cortex, as shown. VOIs can be systematically placed or semi-automatically or automatically defined over the caudate nucleus and putamen to assess specific tracer binding and over the occipital cortex to assess non-specific binding. The striatal specific binding ratios are calculated using equation 1.

 Figure. 3.10.2. Illustration of Large VOI placement on summed image.

Required characteristics of resulting data:

The specific trial protocol shall prospectively define the SBR parameter that is required for the striatum and the caudate and putamen, specifically. Some studies may also compare different metrics (e.g., right to left asymmetry or caudate to putamen ratio) and will require recording multiple parameters. SBR measures (and the analysis tools used to obtain them, including software version) shall be used consistently across all subjects and across all sequential SBR measurements.

SBR’s are intended as a measure of relative uptake and in that sense, can be regarded as dimensionless (unitless)

It should be clear which values belong to which structures (e.g., the whole striatum, left – right caudate, left – right putamen). This can be done by capturing DICOM coordinates along with the SBR or secondary screen captures of the VOI for identification. It should be reported what background region was used for normalization (e.g., occipital cortex or cerebellum).

The analysis software should generate a report

### 3.10.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Specific Binding Ratio | Image Analyst | Analysis WorkstationShall have a suitable monitor of appropriate size and pixel density for diagnostic viewing of medical images. Shall be placed in a room with in room lighting appropriate for image data analysis and interpretation (i.e., a radiology reading room). Shall have appropriate computation power and memory to carryout VOI data analysis. |
| Post processed image for data analysisImage for data analysis shall be reconstructed in accordance with parameters as described in Section 3.7. If needed image is spatially normalized. If using the Small VOI approach, the transaxial slice with the highest striatal uptake is identified and the adjacent hottest slices spanning an axial extent of 2 cm or less are averaged to generate a single slice image |
| VOI software analysis toolsUsing analysis workstation tools, volumes of interest are placed on the left and right caudate, the left and right putamen, and the occipital cortex (reference tissue). Count densities for each region are extracted to calculate SBRs for each of the striatal regions and for the striatum as a whole. VOIs may be systematically placed by the image analyst or by the image analysis software.  |
| Certify VOI | Qualified professional | Shall either (1) agree with region boundaries, (2) reject boundaries and return for reprocessing, or (3) make revisions “on the fly” as indicated. |

## 3.11. Image Interpretation

This activity describes criteria and procedures related to clinically interpreting the measurements and images that are necessary to reliably meet the Profile Claim.

### 3.11.1 Discussion

**In the USA**, under the Centers for Medicare & Medicaid Services’ Medicare Improvements for Patients and Providers Act of 2008 (MIPPA), the American College of Radiology (ACR) is required to validate compliance with accreditation requirements on advanced diagnostic imaging service facilities. Facilities should refer to the tool kit available on the ACR website at the bottom of the Breast MRI, CT, MRI, Nuclear Medicine and PET Accreditation Program pages located at <http://www.acraccreditation.org/modalities/mri> . These documents will help facilities gather and organize information for periodic the site surveys.

Some of the most common items that are not found during a survey are the following:

• Policies for primary source verification, verifying that personnel are not included on the Office of Inspector General’s exclusion list and a consumer complaint notice that gives the patients contact information for the ACR (one can be found on our website at <http://www.acr.org/~/media/ACR/Documents/Accreditation/PatientNotice.pdf> .

• Documentation of initial qualifications, continued education and continued experience for the interpreting physician and medical physicist. Self-documentation is not acceptable.

**In the European Union (EU)**, the qualifications for interpreting physicians and medical physicists may be found at (add on-line citation here) . . .

**In Japan**, and other regions, professional health care providers should meet, and maintain, standards set by their local regulatory authorities for the practice of medicine with unsealed radioactive material.

 Visual image assessment is performed to assess he adequacy of the acquisition for a quantitative endpoint. Checks for the integrity of the reconstruction include well-defined basal ganglia, nonspecific cortical uptake with sharp boundaries of the cortical edge, and well-defined scalp uptake. Signs of motion include blurring of the boundaries between high uptake areas in the basal ganglia and adjacent regions, e.g. the heads of the caudate may appear too close.

 Assessment of the quality of the subsequent quantitative analysis is critical, with particular focus on the accurate anatomic placing of the regions of interest.

### 3.11.2 Specification

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Place VOI | Technologist or image analysis specialist | For SBR, shall cause to have placed volumes of interest (VOI) on structures of interest and appropriate background tissue. VOIs include caudate, anterior putamen, and posterior putamen on each side of brain. |
| For absolute quantification of percent injected dose per unit volume in the VOI, shall also place VOI around external reference source in field of view. |
| Calculate measurand | Technologist or image analysis specialist | Shall calculate time-point measurand (SBR or %dose/mL) |
| Certify VOI | Qualified physician | Shall either (1) agree with region boundaries, (2) reject boundaries and return for reprocessing, or (3) make revisions “on the fly” as indicated. |
| Certify measurand | Qualified physician |  |

# 4. Assessment Procedures

To conform to this Profile, participating staff and equipment (“Actors”) shall support each activity assigned to them in Table 1.

To support an activity, the actor shall conform to the requirements (indicated by “shall language”) listed in the specifications table of the activity subsection in Section 3.

Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement will reference an assessment procedure in a subsection here in Section 4.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. Vendors publishing a QIBA Conformance Statement shall provide a set of “Model-specific Parameters” (as shown in Appendix D) describing how their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing.

## 4.1. Assessment Procedure: Voxel Noise

This procedure can be used by a vendor or an imaging site to assess the voxel noise of reconstructed images. Voxel noise is assessed in terms of the standard deviation of voxel values when imaging a material with uniform density.

 The assessor shall first warm up the scanner’s x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations. The assessor shall then scan a phantom of uniform density, such as the ACR CT Accreditation Program (CTAP) Phantom’s module 3, which is a 20 cm diameter cylinder of water equivalent material. The phantom shall be placed at the isocenter of the scanner. The acquisition protocol and reconstruction parameters shall conform to this Profile (See Section 3.6.2 and 3.7.2). The same protocol and parameters shall be used when performing the assessments in 4.1 and 4.2.

When the scan is performed, the assessor shall select a single representative slice from the uniformity portion of the phantom. An approximately circular region of interest (ROI) of at least 400 mm2 shall be placed near the center of the phantom.

The assessor shall record the values reported for the ROI mean and standard deviation.

The procedure described above is provided as a reference method. Sites or vendors may submit to QIBA a proposed alternative method (such as using the water phantom portion of a manufacturer’s QA phantom) and evidence that the results produced by the proposed method are equivalent to this reference method. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.

The test procedure described here is based on the use of conventional filtered backprojection reconstruction methods; extreme care must be taken when iterative reconstruction methods are used as their use may invalidate some of the assumptions inherent in this method.

## 4.2. Assessment Procedure: <Parameter Y>

## 4.3. Assessment Procedure: SPECT Calibration Factor

This procedure can be used by a vendor, physicist or an imaging site to assess the SPECT Calibration Factor of an acquisition device. SPECT Calibration Factor is assessed in terms of compensating value that needs to be applied to get the image voxel values produced by the acquisition device to match the known activity in kBq/mL of scanned phantom. The units of the SPECT Calibration factor are kBq/mL divided by the arbitrary units used by the acquisition device to record image voxel values.

~~The assessor shall scan a phantom of uniform~~ …We’ve got text describing recipes for scanning bottles of various sizes filled with purportedly known concentrations of radioactivity. The questions are:

1. Eliminate this text for outcome measures based on ratios, e.g., the SBR
2. replace with text describing a solid standard.

## 4.4 et cetera Phantom Imaging (moved from Section 3)

To qualify the SPECT scanner for clinical practice or for a clinical trial, a phantom imaging procedure is required. In addition to certain generally available, commonly used phantoms, purpose-specific phantoms may be provided better suited to the task in hand. Options that might be considered on a per-protocol basis include, but are not limited to:

1. each site uses a single phantom for the duration of the trial but not necessarily the same model of phantom used at other sites

2. all sites use phantoms of the same model for the duration of the trial

3. all sites use phantoms built to precise specifications for the duration of the trial

4. all sites share a single phantom for the duration of the trial.

The phantom scans and performance evaluation should be performed prior to the start of a trial and repeated during the course of the trial as specified by the individual protocol. Any changes to scanner equipment, either hardware or software, should be immediately reported to the trial sponsor and/or imaging CRO and may result in the need for re-qualification prior to imaging additional trial subjects. In particular, it is strongly recommended that subjects in a longitudinal study be scanned on the same SPECT system with the same software version whenever possible.

Image noise levels are measured using an anthropomorphic phantom (or similar) with a uniform area to assess image ‘noise’ by means of the coefficient of variation (COV), also known as the relative standard deviation (%RSD), which is expressed as a percentage and is defined as COV = (SD / Mean) x 100, for the voxel values within a specified volume of interest (VOI). The phantom should be filled such that the activity concentration in the uniform area is approximately XXX kBq/ml (XXX uCi/ml), similar to the expected average normal tissue concentration at the time of imaging in an average weight (70-80 kg) subject in combination with the intended I-123 ioflupane dosage. The phantom should be scanned using the minimal time per bed specified in the trial protocol or using the routinely applied time per bed in the local clinical setting. Moreover, image reconstruction methods and settings should equal those specified in the trial protocol or equal those routinely applied in the local clinical setting. A volume of interest (VOI) should be positioned entirely within the phantom’s uniform area and as much as possible centrally located within the phantom. The VOI should be a cubical or rectangular volume, with the length of each side as close as possible to, but no less than, XX cm. A sphere measuring no less than XX cm. in diameter may also be used as the VOI on systems that have the capability to accommodate this strategy. The COV of the voxel values thus determined should be recorded and should be below 15%. If the COV of the voxel values thus determined is above 15%, the acquisition time should be increased accordingly.

The normative list below is based on the recommendations from several national and international guidance document and should be applied as appropriate.

| **Parameter** | **Actor** | **Specification** |
| --- | --- | --- |
| Phantom tests: Frequency | Imaging Site | Shall perform and document results of all tests no less than quarterly, and always after scanner upgrades, and repairs or recalibration of the gamma camera motions and/or detectors |
| Phantom tests: cross calibration with radionuclide calibrator | Imaging Site | Shall perform quarterly and after scanner upgrades, maintenance or repairs, new setups and modifications to the radionuclide calibrator |
| Phantom tests:Planar Uniformity | Imaging Site | Uniformity of response to a uniform flux of radiation from a I-123 point source should be measured intrinsically every quarter. On a daily basis planar uniformity with collimators used for I-123 imaging should be performed using a Tc-99m or Co-57 source |
| Phantom tests: transaxial uniformity measurement | Imaging Site | Using a uniform cylinder, or the uniform section of an anthropomorphic phantom filled with I-123, obtain a within slice variability of less than 5%. |
| Phantom tests: Centre of Rotation | Imaging Site | Using point sources, the maximum corrected offset in x and y directions should be less than ½ voxel (2 mm for the maximum recommended voxel size of 4.5 mm). |
| Phantom tests:suitability for basal ganglia imaging | Imaging Site | Using an anthropomorphic phantom with basal ganglia and background compartments filled at a ratio of 5:1, be able to distinguish the caudate nuclei and putaminal compartments bilaterally.  |
| Phantom test: data acquisition | Imaging Site | Shall acquire according to Section 3.6 |
| Phantom test: data reconstruction | Imaging Site | Shall reconstruct according to Section 3.7 |
| Phantom test: data analysis | Imaging Site  | Shall ensure noise is less than specified b |

**Uniformity and Sensitivity Calibration**

In SPECT systems, uniformity of the scanner response can be measured in two ways: as a planar 2D measurement; and also as a tomographic 3D measurement on reconstructed data. As a prerequisite, the ability to have a uniform response to I-123 across the gamma camera detector is essential for imaging with Iodine-123 labeled Ioflupane. Typically, these measurements will be made intrinsically, without the use of collimators. Sources of Iodine-123 are expensive, and Ioflupane imaging is performed with collimators, so it is recommended that on the day of Ioflupane imaging, collimated uniformity should be assessed using standard Tc-99m or Co-57 sources to assess any problems with the detectors before trial patient scanning begins.

As a SPECT technique, Ioflupane imaging requires correction for photon attenuation within the brain to be accurately quantified. Using either Chang 0 or iterative compensation or estimated or measured attenuation maps, it is important to assess that the correction for attenuation is being applied appropriately. It is also important to assess that center of rotation corrections are fit for purpose. With such potential sources of error, it is important for all trials that transaxial plane uniformity is assessed.

The performance of the system with such tests may change following any detector changes or recalibration, and for SPECT after mechanical changes made to the system, and should therefore be checked after such actions have been performed.

For trials that require a quantitative SPECT measurement in terms of activity concentration per unit volume or percentage of injected activity, a calibration of the SPECT system to activity measured in a radionuclide calibrator should be performed and assessed periodically. As with uniformity measures, such calibrations are vulnerable to change following detector changes and/or calibrations and should therefore be repeated if such changes have taken place.

| **Parameter** | **Entity/Actor** | **Requirement** |
| --- | --- | --- |
| Planar Uniformity QC | Technologist | At least quarterly and following detector changes, calibrations and/or software upgrades the uniformity of detector response to a uniform flux of radiation of Iodine-123 should be assessed.Daily, or at least on the day of a trial subject, the collimated uniformity of the detectors using collimators to be used for Iodine-123 imaging should be assessed using a Tc-99m or Co-57 source.For both measurements, uniformity should be measured and assessed in accordance with local regulatory requirements. |
| SPECT uniformity QC | Technologistor Medical Physicist | At least quarterly and following detector changes, calibrations and/or software upgrades, the SPECT uniformity should be measured using acquisition parameters defined in the clinical protocol trial, and using activity levels expected for Iodine-123 Ioflupane imaging. |
| Sensitivity calibration | Medical Physicist | At least quarterly and following detector changes, calibrations and/or software upgrades to the scanner or any changes to the radionuclide calibrator, the SPECT scanner sensitivity should be monitored and recorded. |

**Centre of Rotation**

Verification of scanner center or rotation is an essential requirement for all SPECT scanners used in trials, be it for trials with a quantitative or qualitative endpoint. The assessment of center of rotation will ensure optimal spatial resolution, and help minimize artifact. The test should be performed for the collimators used for Iodine-123 Ioflupane imaging

| **Parameter** | **Actor** | **Requirement** |
| --- | --- | --- |
| Centre of Rotation | Technologist | At least quarterly and following detector changes, calibrations, software upgrades, or mechanical changes to the system, center of rotation should be assessed. |

**Assessment of appearance of basal ganglia**

An optimal system performance measurement may be obtained with an anthropomorphic striatal phantom, which tests all functions. Can you identify discrete left and right basal ganglia, which have the appearance of a comma shaped object? In addition the head of the caudate should be distinguishable from the tail of the putamen. The appearance of the basal ganglia should be a linear structure (hooked curvilinear similar to a comma with a tail) and improper acquisition and reconstruction parameters will result in a bloated ovidal shape

Then check for voxel noise in the background region.

Then ensure that SBR falls within the biologically plausible range.

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**Replace with literature search by Seibyl et al goes here.**

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# Appendices

## Appendix A: Acknowledgements and Attributions

The QIBA SPECT Committee followed the profile document template of 05 November 2016 proffered by the QIBA something committee, Kevin O’Donnel principal editor.

The SPECT Committee is grateful to the pioneering work of the CT Volumetry Committee, and particularly to the FDG PET Committee, from whom large blocks of text were cut and pasted into this profile with only minor modification.

The following people, listed in alphabetical order, contributed to the development and publication of this profile:

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## Appendix B: Background Information

## Appendix C: Conventions and Definitions

## Appendix D: Model-specific Instructions and Parameters

For acquisition modalities, reconstruction software and software analysis tools, profile conformance requires meeting the activity specifications above in Sections 2, 3 and 4.

This Appendix provides, as an informative tool, some specific acquisition parameters, reconstruction parameters and analysis software parameters that are expected to be compatible with meeting the profile requirements. Just using these parameters without meeting the requirements specified in the profile is not sufficient to achieve conformance. Conversely, it is possible to use different compatible parameters and still achieve conformance.

Sites using models listed here are encouraged to consider using these parameters for both simplicity and consistency. Sites using models not listed here may be able to devise their own settings that result in data meeting the requirements.

**IMPORTANT: The presence of a product model/version in these tables does not imply it has demonstrated conformance with the QIBA Profile. Refer to the QIBA Conformance Statement for the product.**

Table D.1 Model-specific Parameters for Acquisition Devices

| Acquisition Device | Settings Compatible with Conformance |
| --- | --- |
| Acme MedicalCT LightsV3.14 | *Submitted by: Gotham University Hospital* |
|

|  |  |
| --- | --- |
| kVp | 120 |
| Number of Data Channels (N) | 64 |
| Width of Each Data Channel (T, in mm) | 0.625 |
| Gantry Rotation Time in seconds | 1.0 |
| mA | 120 |
| Pitch | 0.984 |
| Scan FoV | Large Body (500mm) |

 |

Table D.2 Model-specific Parameters for Reconstruction Software

| Reconstruction Software | Settings Compatible with Conformance |
| --- | --- |
| Acme MedicalCT WSV3.14 |

|  |  |
| --- | --- |
| Reconstructed Slice Width, mm | 1.25 |
| Reconstruction Interval | 1.0mm |
| Display FOV, mm | 350 |
| Recon kernel | STD |

 |