QIBA Profile: Quantifying Dopamine Transporters with ^{123}Iodine Labeled Ioflupane in Neurodegenerative Diseases

(Short Title: SPECT dopamine transporters)

Stage 2: Consensus, Version 2.0. Awaiting technical conformance testing

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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)
2016.03.22	References	John Seibyl adds first draft
2016.04.14	3 & 4	F2F meeting moves much of Section 3 to 4
2016.04.14	3.1	Accept Patrick Cella revisions of acceptance testing, etc.
2016.04.15	3.1	Revisions by Johannes of Siemens with copies to Cella of GE
2016.04.15	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
2016.05.17	3, 4	B. Zimmerman incorporated changes discussed during 2016.5.17 conference call
2016.05.20	3.10, 4	J. Dickson suggested a new value (±10%) for variability across qualified imaging systems (3.10) and revised the section on phantom filling
2016.05.20	Whole Document	Mozley did some trivial line editing
2016.06.07		Eric Frey. Some minor fixes. Made some comments about Open Issues. Added a discussion of calibration and sensitivity in QA section. Moved requirement for attenuation coefficient scaling to QA section. Blended in postfiltering with reconstruction since it depends on the analysis method.
2016.06.07	All	Accepted some minor edits made by others
2016.06.07	Section 4	Added a couple of paragraphs on Assessment Procedure. Also

		some cleaning up of Section 4 and refining based on Tuesday June 7 call.
2016.07.05	3.10	Robert Miyaoka added some text referring to the digital reference objects and how they can also be input data for image analysis
2016.07.10	All	Mozley started deleting instructions from the margins and accepting trivial line edits in preparation for last push to public comment phase
2016.07.12	3.10	Robert Miyaoka made changes in text as discussed in meeting. Added some details about DRO phantom; mentioned the physical phantom; and made slight change to language about number of slices to sum for VOI data analysis.
2016.07.15	All	Big Biomarker Committee reviewed work product and set deadline for final comments prior to public release
2016.07.19	Sections 3, 4	Significant editing done by BZ and JD with regards to performance testing and phantom preparation. Many changes accepted during Phantom and DRO Subcommittee call.
2016.07.29	4	Editing of section 4 and some parts of section 3.6 and 3.7 by Yuni during Aug 2 Tuesday call.
2016.08.12	3.8, 4	Significant edits and reorganization of Section 4 by JD, BZ. To be presented at WebEx on Aug16
2016.08.17	3.8, 3.11, 4	Revisions following 16-Aug WebEx. Moved table in 3.8 image motion, conspicuous margins etc. into section 3.11 Image interpretation as a prerequisite check prior to image quantification. Change from background region to reference region. Voxel noise CoV value of 15% goes into open issues because size of reference region influences CoV. Other minor text revisions.
2016.08.22	Reference	References added by Seibyl, other minor edits
2016.09.14	3.10	Accepted changes and made small modification to text for consistency with section 4.2.4. rsm
2016.09.16	Whole document	Moz Line editing: ran spell checker, changed fonts, accepted trivial edits, accepted major edits that had been vetted (e.g., references) etc.
2016.09.26	Whole document	Moz: Line editing for consistency. Stylistic word smithing that didn't change content or address controversy. Made changes to 3.2.2 where comments provoked consensus.
2016.10.01	Sec. 2	Revision of claim statements by Dr. Obuchowski & Dr. Jha.
2016.10.01	Whole document	Moz: General line editing
2016.10.20	Open issues, claims	Moz: Revisions in response to suggestions from Steering Committee

2016.11.01	Whole document	Broadcast to public with request for peer review & feedback
2017.03.31	Whole document	Public comment period closed; begin addressing stakeholder feedback
2017.05.18	Whole document	YD, JD, RM: Revisions in response to public comments.
2017.06.06	Whole document	Point-by-point response to all comments complete; draft of Version 1.1 sent back to stakeholders for re-review
2017.06.16	Whole document	SPECT Biomarker Committee votes to approve Version 1.1 at BIG meeting
2017.06.30	Whole document	QIBA Coordinating Committee approves Profile Version 1.1
2017.07.01	Whole document	Performance Testing begins
2017.10.07	Claims and Section 4.5	YD: Revisions to incorporate new claims based on groundworks and NO analysis
2017.11.06	Claims and Section 4.5	JCD: Changed striatal phantom filling concentrations to use 3 x more activity which will facilitate faster scanning of 20 replications.
2017.11.13	Open issues	JCD: Discussion of linearity issues and the loss of Claim 2b on longitudinal change of SBR.
2018.5.15	Formatting for consistency across profiles	JPS: Format c/w profile template 2.0
2018.8.01	Whole document	JCD: Formatting checks. Movement of Periodic QC described in section 3.8 to the more appropriate section 3.3. Section 3.8 rewritten to capture Image QC element such as visual assessment, trapping motion, ensuring good registration between CT AC and emission data, and ensuring appropriate count levels have been acquired.

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. Uncertainty in some scalar values has been highlighted in yellow throughout the text for the purpose of drawing the field's attention.

Q. Uncertainty and concern pervades using this profile to distinguish, or "discriminate", between patients with neurodegenerative diseases and other causes of parkinsonism, such as essential tremor. Would a discrimination claim be acceptable to the community? A. The SPECT Biomarker Committee suggests discriminatory claims have value, and can be adequately trustworthy when used with caution in the context described. However, some residual stakeholder concerns led to discrimination being described as a "use case" in this version of the profile, which appears in the section on cross sectional claims, but is not labeled as a claim per se.
Q. The community cannot agree on a method for distinguishing the anterior from the posterior putamen, but the committee notes that there are several software systems that do this. Their groundwork data and analyses are not available for vetting at this time. A. Enterprises claiming conformance based on distinctions between anterior and posterior putamen will need to describe their own methods and present their own evidence of qualification.
Q. Challenges with the linearity of bias. A. Although groundworks have allowed an estimate of bias, we are not currently in a position to assess the linearity of bias. This means that we have had to lose claim 2b which addresses longitudinal change of SBR.

Addressed 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. standards: solid (e.g., Cobalt 57, Tellurium-123) or fillable (e.g., solutions of residual ^{123}I ioflupane). A. Decision has been made to go with fillable striatal phantom for this version. There are plans to develop solid phantoms in the future.
Q. Measurand: specific binding ratio or percent injected dose per gram? A1. start with striatal binding ratio; launch absolute quant during the next iteration. A2. Decision to delete absolute quant from version 1 implemented on 17 May 2016
Q. Are the minimal number of counts known? **A.** Groundwork sponsored during Round 6 of NBIB funding successfully characterized some of the relationships between counts and quality. See Section 4.2.1
Q. Scalar values surrounding bias are currently uncertain. We note that there are a range of claims in the literature. We expect the reproducibility of estimates of bias to continue varying as new hardware (e.g., CZT detectors, novel pinhole collimator geometry, innovations in in-line CT, etc.), and signal processing algorithms rapidly evolve. A. The issue of bias was mooted for the time being by eliminating any claims that were dependent on knowing the scalar magnitude of bias.

1. Executive Summary

Parkinsonism is a major health problem. Distinguishing neurodegenerative causes of parkinsonism from non-degenerative movement disorders that can mimic Parkinson's disease (PD) has important implications for prognosis and clinical management. The goal of this QIBA Profile is to optimize the performance of Iodine-123 (^{123}I) ioflupane single photon emission computed tomography (SPECT) for quantifying the concentration of regional cerebral dopamine transporters (DaT) in patients with movement disorders.

The **Claim** (Section 2): This profile claims that conformance with its specifications will provide test-retest technical variance of less than 15% COV. In clinical use this might permit the ability to distinguish true biological change from measurement noise in clinical trials of participants who will be studied cross—sectionally, to aid accurate cohort recruitment and longitudinally with ^{123}I-ioflupane. The claim is founded on observations that neurodegenerative disorders, such as idiopathic PD and Diffuse Lewy Body Dementia (DLBD), are associated with dopaminergic neuronal degeneration, which can be particularly pronounced in the substantia nigra. The degeneration of the axonal projections from the substania nigra to the basal ganglia is manifested as a loss of DaT activity. In most clinical imaging contexts where the question is about a neurodegenerative disorder, 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 can distinguish normal and abnormal states.

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** who 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 ^{123}Iodine 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 technical variability of the DaT measurements to distinguish neurodegenerative causes of parkinsonism from non-degenerative causes.

The clinical performance target is to achieve a 95% confidence interval for the striatal binding ratio with both a reproducibility and a repeatability of +/- 15%.

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.

This QIBA Profile, and others like it addressing CT, MRI, PET and ultrasound can be found at www.qibawiki.rsna.org .

2. Clinical Context and Claims

Clinical Context

Parkinson's disease (PD) and Diffuse Lewy Body Dementia (DLBD) are major health problems. The prevalences are 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, or "discriminate", between neurodegenerative causes, such as idiopathic PD, and movement disorders like essential tremor that mimic it. In addition, clinical research therapeutic trials employ quantitative DaT SPECT in effort to improve diagnostic reliability for trial eligibility and longitudinal monitoring of putative neuroprotective agents. . Ensuring appropriate diagnosis for clinical trial eligibility has become important need given the trials are occurring earlier and earlier in the course of the disease process when diagnosis is most troublesome. This profile focuses on a marketed radiopharmaceutical for this use, Iodine-123 (^{123}I) 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 <u>by all relevant staff and equipment</u> supports the following claim:

Claim 1: Technical performance claims

Claim 1a. Measurement of the specific binding ratios (SBR) of striata have a within subject Coefficient of Variation (wCV) of 15%.

*****The wCV was estimated from a phantom experiment where 5 repeat measurements were performed of a striatal phantom on two systems. SBR was determined for L Caudate, L Putamen, R Caudate and R Putamen. The 95% CIs for the wCV varied around [6%, 11%], depending on the degree of corrections performed. The 15% value chosen for the claim reflects recognition of the additional variability in human subjects.

Claim 1b: Measurement of the caudate:putamen activity concentration ratio has a within subject Coefficient of Variation (wCV) of 8%.

***** The wCV was estimated from a phantom experiment where 5 repeat measurements were performed of a striatal phantom on two systems. The estimated wCV from that experiment was 5.6% with 95% CI of [3.8%, 10.7%].

Caveats of Context. These claims hold when:

- Clinical evaluation finds no other cause of parkinsonism, such as recent exposure to known toxins that can present with movement disorders, such as MPTP
- 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, such as dopamine transporter antagonists
- The patient does not have a deformity or condition that prevents proper positioning in the scanner, such as a severe kyphosis;

- 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;
- And other such conditions, which, in the opinion of the professional staff, confound the examination.
- Note that a change of 42% is required when considering an individual patient in isolation. Well-powered clinical trials will be able to detect mean changes much smaller than 42%.

Discussion

The primary measurand, or outcome measure, is the specific binding ratio (SBR) obtained in the striatum. The measurand is 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, hippocampus, and cortical gray matter, these regions are beyond the scope of this profile.

The SBR is defined as the count density in a striatal volume of interest (VOI) minus the count density in in a reference region divided by the count density in the reference region, which is often expressed in an equivalent form as the count density in a striatal VOI divided by a count density in a reference region VOI 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. And, it might be an ideal outcome measure in some settings. However, this profile does not mandate absolute quantification.

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 $Y \pm 1.96 \times Y \times wCV$. 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 after all corrections is < 15%). For estimating the critical % change, the % Repeatability Coefficient (%RC) is used: $2.77 \times wCV \times 100$.

The +/- 15% 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

$(1.5 - 3.0) \pm 1.96\sqrt{(1.5 \times 0.077)^2 + (3.0 \times 0.077)^2}$, or [-2.01, -0.99], which represents a 33% to 67% decrease in SBR.

Statement of Use: Cross Sectional Discrimination. Note: This statement of use is proffered with caution on an experimental basis. QIBA encourages all stakeholders to comment. Data supporting or refuting this use are particularly welcome.

The ability of measurements made in conformance with this profile to discriminate between relevant groups holds when assessing patients during their initial presentations of parkinsonian symptoms, if, but only if, the requirements for quantitative DAT scanning defined in this Profile are met, and the constraints around the clinical context described in this section are valid. If the measurements conform to the requirements of this profile, then measurements of SBR in the posterior putamen that are either (a) 50% or less than the value in aged-matched controls, or (b) 80% or less than the value in the whole striatum are diagnostic for a neurodegenerative cause of the symptoms with a sensitivity of at least 85% and specificity of at least 80%,* provided none of the contextual caveats described below are violated.

Longitudinal Change. 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 implications of changes that are greater than the bounds of the confidence interval are beyond the scope of this profile. While the cross sectional power of discrimination between patients with dopaminergic neurodegenerative diseases and patients without neurodegenerative diseases 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 actual 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.

*These sensitivity and specificity values represent lower 95% confidence bounds.

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.
Physicist	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 Analyst	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.

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

The Acquisition Device 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.

3.1.2 SPECIFICATION

Parameter	Actor	Requirement
Release Testing	Acquisition Device	Shall pass all manufacturing in-process and release testing criteria
File Format	Acquisition Device	Shall encode SPECT raw data in the DICOM Nuclear Medicine Image Storage SOP Class.
		Any CT data (used for image correction) should be encoded in CT or Enhanced CT Image Storage SOP Class.
	Reconstruction Software	Shall encode SPECT reconstructed data in the DICOM Nuclear Medicine Image Storage SOP Class.
	Image Analysis Tool	Shall support the DICOM NM Image SOP Class.

3.2 Acceptance Tests

3.2.1 DISCUSSION

Acceptance tests are 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. At the very least, acceptance tests should include the intrinsic uniformity, system uniformity, planar spatial resolution, and center of rotation tests described in Section 3.3, although they will typically be more substantive than this.

A number of documents (for example, see those produced by the ACR and the IAEA listed in the Reference section) give specific guidance as to how to conduct acceptance testing.

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 should be reviewed by the qualified medical physicist and properly documented.

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.

Note that some specifications that follow come from IAEA Human Health Series 6.

3.3.2 SPECIFICATION

Parameter	Actor	Requirement
Phantom tests: Frequency	Physicist	Shall perform and document results of all tests at the required frequency, no less than quarterly, and always after scanner upgrades, and repairs or recalibration of the gamma camera motions and/or detectors
Intrinsic Uniformity	Physicist	Shall confirm quarterly that the intrinsic uniformity from a I-123 point source is comparable with that measured at acceptance testing and within 4% in the UFOV. See 4.1 Assessment Procedure: Intrinsic Uniformity
System Uniformity	Physicist	Shall confirm daily that the system uniformity from a Tc-99m or Co-57 source is comparable with that measured at acceptance testing and within 4% in the UFOV. See 4.2 Assessment Procedure: System Uniformity
Planar Spatial Resolution	Physicist	Shall confirm semiannually that the planar FWHM spatial resolution from the collimators used for Ioflupane imaging is less than 8mm. Fanbeam collimators shall be capable of achieving an equivalent spatial resolution. See 4.3 Assessment Procedure: Planar Spatial Resolution.

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Center of Rotation (COR)	Physicist	Shall confirm the mean value of the COR offset does not exceed 1/2 pixel (typically 2 mm) when measured at the center and edges of the FOV. Shall confirm the position of Y=0 axis and the Y gain are the same for all heads in a multi-head system. See 4.4 Assessment Procedure: Center of Rotation
Tomographic Uniformity	Physicist	Shall confirm the use of appropriate attenuation correction by visually confirming a flat profile through the center of the phantom on several transaxial slices. See 4.5 Assessment Procedure: Tomographic Uniformity
Suitability for basal ganglia imaging	Physicist	Shall confirm that the caudate and putamen are clearly visualized and that the image does not contain any artefacts. Shall confirm that the estimated wCV of SBR is below 11% Shall confirm that the wCV of Caudate:Putamen ratio is less than 6% See 4.6 Assessment Procedure: Suitability for Basal Ganglia Imaging
Voxel Noise	Physicist	Should confirm quarterly that the voxel noise in the reference region/background compartment should be below 15%. See 4.7 Assessment Procedure: Voxel Noise in the Reference/Background Compartment
Photon Energy Analyzer	Physicist	Shall confirm (typically daily) that the accuracy of the photon energy analyzer is within manufacturer specifications.
CT Attenuation map registration	Physicist	Shall confirm that the attenuation maps are registered to the SPECT images within the manufacturer specifications.

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.

300 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 ^{123}I 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	Clinician	For the cross sectional claim, shall establish a differential diagnosis that includes Parkinson's disease versus other causes of parkinsonism, such as essential tremor.
		For the longitudinal claim, shall refer eligible subjects
	Clinician	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 $\pm$ 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, technologist	Shall provide a system that is capable of receiving, dispensing and administering non-radioactive potassium iodide and ^{123}I 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.

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Parameter	Actor	Requirement
		Shall select the proper acquisition protocol of 123I ioflupane
		Shall begin image acquisition at 4 hours +/- 15 minutes post intravenous administration of ioflupane
Head Holder	Technologist	Shall use an off-the-bed head holder (with appropriate cushioning) to achieve an acquisition radius of 12-15cm.

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 DISCUSSION

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**.** Parallel-beam 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. These are typically referred to as Low Energy High Resolution (LEHR), Low Energy Ultra-High Resolution (LEUHR) collimators. Some (typical low-energy) collimators allow too much septal penetration of the high-energy emissions of I– 123, resulting in ring artifacts that may affect quantitation. ME collimators, which reduce septal penetration, may be insufficient in terms of the resolution requirement. If available, collimators designed specifically for ^{123}I brain SPECT should be used.

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 adequately 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 for a minimum of 1.5 million counts. Total time to collect at least 1.5 million counts can be calculated by viewing the count rate in the anterior view. Time per view is total time divided by number of projections.

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. The acquisition can also be performed as a dynamic SPECT (for example, six 5 minute frames) to better assess motion. Only those frames where significant motion is not evident are summed for the reconstruction.

3.6.2 SPECIFICATION

Parameter	Actor	Requirement	DICOM Tag
Imaging device	Technologist	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.	
	Technologist	Shall be certified by local authorities to operate the instrument in compliance with this profile.	
Collimator	Technologist	Shall use a collimator that provides planar system resolution of < 8 mm FWHM (in 'air' at 10 cm distance) for Tc-99m (or equivalent for fanbeam collimators).	

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Parameter	Actor	Requirement	DICOM Tag
SPECT Acquisition mode	Technologist	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. An off the table head rest is usually needed to achieve this. **Matrix and pixel size**: A matrix size and zoom factor that gives a pixel size of one-third to one-half the expected spatial resolution shall be used. Typically, a 128 x 128 matrix and pixel 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) or as recommended by the system manufacturer. If triple energy-window (TEW) based scatter correction is to be used, two additional narrow	

SPECT dopamine transporters (continued)

Parameter	Actor	Requirement	DICOM Tag
		windows (typically 7%) adjacent to the photopeak or as recommended by the system manufacturer 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). The CT acquisition parameters should be selected based on Image Wisely guidelines (see http://www.imagewisely.org/imaging-modalities/nuclear-medicine/articles/ct-protocol-selection) and availability on the scanner.

Parameter	Actor	Requirement	DICOM Tag
CT Acquisition mode	Technologist	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.	

SPECT dopamine transporters (continued)

Parameter	Actor	Requirement	DICOM Tag
		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.	

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 (see Section 3.8). 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., OSEM or conjugate gradient) 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 must 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 translated so that 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 preferred, and should take into account down scatter from high energy photopeaks. Scatter correction can be implemented using energy-window-based scatter estimates (e.g., the TEW method) or scatter modeling methods (e.g., ESSE [Frey, 1996] or Monte Carlo-based [Dewaraja 2006, Beekman 2002]). 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 > 100 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 thus is 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 and avoid truncation of voxel values. Storing scale factors needed to convert the images to activity concentration units is encouraged.

A core lab and/or common reconstruction methods will provide lower variability and may offer benefits in certain scenarios[Buchert, et al, 2016].

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Parameter	Actor	Requirement
SPECT Image Reconstruction	Technologist	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).
Estimated Attenuation Map (if used)	Technologist	Shall be defined so that it conforms to the outline of the head as closely as possible.
Correction: Scatter	Technologist	Scatter correction shall be used when possible. TEW or equivalent is recommended.
Reconstructed image	Technologist	Shall be reconstructed in such a way as to compensate for attenuation and scatter. Optimal reconstruction depends on the image analysis method used (see Section 3.10). **Whole striatum VOI method**: the reconstruction shall be implemented to reduce partial volume effects, e.g., using CDR and partial volume compensation. Controlling voxel-level noise is less important, so post-reconstruction filtering is not recommended, though may be used for visual interpretation. **Small VOI method:** the reconstruction shall be implemented to

SPECT dopamine transporters (continued)

Parameter	Actor	Requirement
		control the effects of voxel-level artifacts such as noise spikes and ringing, including the use of 3-dimensional low-pass post-reconstruction filtering (with 8 – 10 mm FWHM). The reconstructed image shall have sufficient spatial resolution to allow reliable independent estimates of the SBR in the Caudate and Putamen.
Stored Reconstructed Image	Camera Manufacturer	Reconstructed images shall be stored in such a way as to preserve the image dynamic range.

3.8. Image QA/QC

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

3.8.1 DISCUSSION

Visual image assessment is performed to assess the adequacy of the acquisition for a quantitative endpoint and to ensure that there are no acquisition artefacts. 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. Furthermore an assessment of motion and image noise is essential to ensure that the images can meet the profile claim.

To assess motion, after acquisition and before reconstruction a review of sinograms and projection data in cine mode shall be used for an initial determination of scan quality, patient motion, and artifacts. A sinogram review will reveal transverse patient motion as discontinuities in the sinusoidal form of shapes included within the image, while a review of cine projection data can help show head a raising/lowering of the chin, or indeed the complete head following each projection. Cine review of planar images will show up patient motion along the axis of rotation. Motion can also be assessed following reconstruction. 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.

Where CT attenuation correction is to be performed, it is essential that there has been no movement between the emission and CT acquisitions. If motion has occurred between these two acquisitions, the attenuation correction will be compromised. Some software allows retrospective alignment of the CT and emission data, and this should be used if available. If such software is not available, attenuation correction should not be applied, or a repeat acquisition should be considered.

Where Chang attenuation correction is performed, it is important that the boundaries defining the object are accurately defined to ensure appropriate correction.

If 1.5 million counts are acquired in the SPECT acquisition, noise levels in the data will be acceptable. If there is extravasation of the Ioflupane, an excessive time per projection will be selected during the acquisition setup (see Section 3.6). Other issues which may lead to noisy data include the incorrect

measurement of injected activity, poor or variable peaking during the acquisition, or the incorrect selection of an energy window. Once more many of these issues should be picked up during the acquisition setup where an excessive time per projection would be calculated, although energy peaking that varies during the data acquisition process would not be picked up until after data acquisition. If noisy data is suspected, reconstructed slices should be summed and the total number of reconstructed counts calculated to ensure that the 1.5 million count target has been met.

3.8.2A SPECIFICATION QC

Parameter	Actor	Specification
Artifact assessment	Technologist	Shall ensure that the data is not confounded by ring artifacts, artifacts related to too large a radius for COR (i.e., should be <15 cm, or edge artifacts
Patient Motion	Technologist	Shall assess projection and reconstructed emission data for patient motion.
Mis-registration of SPECT and CT for attenuation correction	Technologist	Shall ensure that the attenuation map is visually registered to the CT map within one reconstructed voxel dimension.
Definition of Chang AC boundaries	Technologist	Shall ensure that boundaries used in the Chang attenuation correction process are accurately defined.
Image Noise	Technologist	Shall ensure that 1.5 million counts have been acquired to achieve an acceptable level of image noise.

3.8.2B SPECIFICATION QA

The normative list below is based on the recommendations from several national and international guidance documents.

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: Planar Uniformity	Imaging Site	Shall ensure uniformity of response to a uniform flux of radiation. An I-123 point source shall 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. See also Section 3.3.2
System Spatial Resolution	Physicist	Shall test 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 ^{123}I ioflupane studies. The result of the test should be less than 8 mm at 10 cm. See also Section 3.3.2

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Phantom tests: transaxial uniformity measurement	Imaging Site	Shall use a uniform cylinder filled with I-123, to obtain a within slice variability of less than 5%.
Phantom tests: suitability for basal ganglia imaging	Imaging Site	Shall employ an anthropomorphic phantom with basal ganglia and reference region background compartments filled at a homogeneous striatal ratio of 4.5:1, to distinguish the caudate nuclei and putaminal, and also with a caudate/putamen gradient of 4.5:1 caudate, 2.25:1 putamen to assess systems ability to determine an uptake gradient across the striata. This phantom should also be used to check for adequacy of attenuation correction.
Phantom test:	Imaging Site	Shall assess voxel noise in the reference region/background compartment. The COV of the volume of interest thus determined should be recorded and should be below 15%.
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 above.

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: SPECT scanner console, SPECT 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	Shall ensure the original projections (sinogram) images (scanner raw data), are always 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 SPECT 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™, GE Healthcare, Arlington Heights, IL) 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 healthy participants. The profile describes the data analysis methodology.

Quantitative Specific Binding Ratio (SBR) of Ioflupane 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., ±15% of reference value) for quantitative imaging of I-123 Ioflupane for the basal ganglia phantom (described in this profile). Further, the coefficient of repeatability (RC) should be <15% for repeat studies of VOIs that are the size of the whole striatum. The profile seeks to provide the methodology for data analysis and also for qualification of systems and processing for I-123 Ioflupane 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. In addition to output images from Image Reconstruction, physical phantom and digital reference object images may also be used as input for Image Analysis to validate the Image Analysis and workstation tools. Two types of digital reference objects will be considered. The first will represent the actual I-123 Ioflupane tracer distribution without any of the effects associated with the data acquisition and image reconstruction process. The second object will be a digital representation of first object including all physical effects and image reconstruction. Both digital reference objects will have

known SBR's that can be used to assess the data analysis tools and workstation. The SBR for one half of the DRO will represent healthy control and the other side a patient with Parkinson's disease. The true caudate to reference region (background) SBR will be the same for both sides and set to 4.5. The Caudate to reference region SBR after image reconstruction is 2.5. The true SBR for the healthy putamen will be 4.5 and 2.25 for the diseased putamen. The physical phantom will be the commercially available striatal Head Phantom. The caudate, putamen and reference/background regions will be filled with activity concentrations that mimic the digital reference object (i.e., actual tracer distribution).

Methods to be Used:

Uptake in the striatum (i.e., caudate, anterior putamen and posterior putamen) and reference 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:

$$\frac{striatum_{VOI} - backgrnd_{VOI}}{backgrnd_{VOI}} \qquad \text{(eq 1)}$$

where the reference/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 plus and minus up to two adjacent 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. 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.

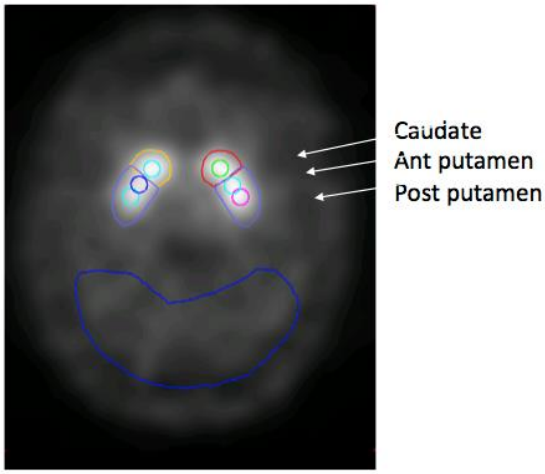

Figure 3.10.1. Illustration of Small VOI placement on summed slice image.

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. Reference/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.

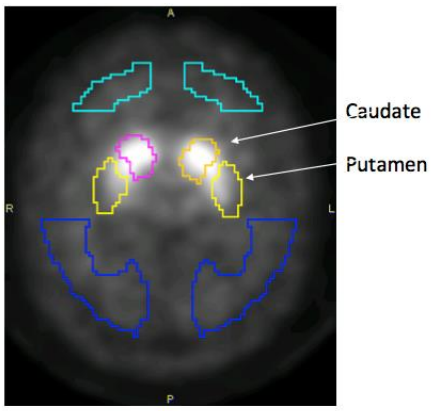

Figure. 3.10.2. Illustration of Large VOI placement on summed image.

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 reference region was used for normalization (e.g., occipital cortex or cerebellum).

The analysis software should generate a report.

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 Japan, the European Union, 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.

3.10.2 SPECIFICATION

Parameter	Actor	Requirement
Specific Binding Ratio	Image Analyst	Analysis Workstation Shall 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 analysis Shall make sure images for data analysis are reconstructed in accordance with parameters as described in Section 3.7. If needed, image shall be spatially normalized. If using the Small VOI approach, the transaxial slice with the highest striatal uptake plus and minus up to two adjacent slices spanning an axial extent of 2 cm or less shall be averaged to generate a single slice image.
		VOI software analysis tools Shall use analysis workstation tools to place volumes of interest placed on the left and right caudate, the left and right putamen, and the reference tissue. Count densities for each region shall be extracted to calculate SBRs for each of the striatal regions and for the striatum as a whole. VOIs shall 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.

4. Assessment Procedures

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

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” 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: Intrinsic Uniformity

This procedure can be used by a vendor or an imaging site to assess the uniformity of images from an acquisition device detector. Planar Uniformity is assessed in terms of the integral uniformity and differential uniformity of pixel values when imaging a uniform source. Due to the expense of I-123, this assessment is performed less frequently than the System Uniformity assessment (See 4.1b).

Additional guidelines for this procedure are available from authoritative bodies such as IAEA, AAPM, NEMA, IPEM, IEC.

The assessor shall suspend a small point source of I-123 above the uncollimated gamma camera at a distance of five times the diameter of the crystal. The assessor shall acquire a flood image with count densities of at least 10,000 counts per pixel (about 30 million total counts for a 64x64 matrix). The image should be visually assessed for variations in count density, noting any areas that clearly stand out. The assessor shall measure and record the integral uniformity and differential uniformity as defined in the above-mentioned guidelines.

4.2 Assessment Procedure: System Uniformity

This procedure can be used by a vendor or an imaging site to assess the uniformity of images from the combined system of a detector and a collimator in an acquisition device. System Uniformity is assessed in terms of the integral uniformity and differential uniformity of pixel values when imaging a uniform source.

Additional guidelines for this procedure are available from the manufacturer and authoritative bodies such as IAEA, AAPM, NEMA, IPEM, IEC.

The assessor shall prepare a flood source using either Tc-99m or Co-57 following the guidelines recommended by system manufacturers. The assessor shall place the flood source in contact with the face of the collimator that will be used for I-123 imaging and acquire 10 - 30 million total counts. The image should be visually assessed for variations in count density. The assessor shall measure and record the coefficient of variation, integral uniformity and differential uniformity as defined in the above-mentioned guidelines.

4.3 Assessment Procedure: Planar Spatial Resolution

This procedure can be used by a vendor or an imaging site to assess the planar spatial resolution of the acquisition device. Planar Spatial Resolution is assessed in terms of the Full-Width Half-Max (FWHM) of a line spread function.

Additional guidelines for this procedure are available in NEMA NU 1-2012 for measuring system spatial resolution without scatter.

The assessor shall fill a capillary tube with an inside diameter < 1 mm with Tc-99m to an active filled length of at least 120mm. The assessor shall position the tube 100mm from the face of the collimator in air and along the axis of measurement. The assessor shall acquire an image, with the collimators routinely used for 123I ioflupane studies, and measure the FWHM of the line spread function as outlined in NEMA NU 1-2012.

4.4 Assessment Procedure: Center of Rotation

Center of rotation performance can be assessed by following the NEMA guidelines for measuring system alignment of gamma camera tomographic systems. The mean value of the COR offset should not exceed 1/2 pixel (typically 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 multi-head system.

4.5 Assessment Procedure: Tomographic Uniformity

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. This can be achieved by acquiring a high count (~15 million counts) SPECT acquisition of a cylindrical phantom filled with Iodine-123 solution. Following reconstruction with corrections applied for attenuation and possibly scatter, a profile about 3 cm wide should be placed through the center of rotation of the phantom, and the resulting count distribution visually assessed for the appropriateness of CT or calculated attenuation correction. A correctly applied attenuation correction should yield a flat profile other than image noise.

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.

4.6 Assessment Procedure: Suitability for Basal Ganglia Imaging

To qualify the SPECT scanner for clinical practice or for a clinical trial, a phantom imaging procedure is required. For the specific application described in this document, the commercially-available striatal Head Phantom with removal brain shell is to be used for the tests described below. Typically, the phantom filled with an activity concentration in the uniform area of the brain shell of approximately 5 kBq/ml (0.135 uCi/ml), is 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 of up to 185 MBq (5 mCi). However, to speed up the phantom scanning process, increasing the activity concentration in the uniform area of the brain shell to 15 kBq/ml (0.405 uCi/ml) is possible, without producing any unwanted deadtime effects.

To characterize system performance, two different scenarios should be created within the striatal phantom: one side will represent a healthy subject, while the other will demonstrate dopaminergic degeneration typical of Parkinson's disease.

Both striatal compartments on the right side of the phantom should be filled with the same concentration representing a true uptake ratio of 4.5:1. Given that the reference/background compartment has a value of 15 kBq/ml and on the basis that SBR = (compartment – background) / background, the activity concentration of these striatal compartments will be 82.5 kBq/ml (2.23 uCi/ml). The left striatal compartment will also have a caudate SBR of 4.5:1 and a putamen SBR of 2.25:1. This putaminal ratio of 2.25:1 will require a solution with an activity concentration of 48.75 kBq/ml (1.32

uCi/ml). Assuming a reference/background compartment volume of 1500 ml, the required concentration can be reached by adding 22.5 MBq (0.61 mCi) of I-123 to this volume. The volume of the right striatum and left caudate is 17.4 ml. Creating 20ml of solution to fill these compartments would require 1.65 MBq (44.60 uCi). The left putamen volume is 6 ml. Producing 10ml of filling solution for this compartment would require 0.49 MBq (13.18 uCi). Multiple dilutions will often be necessary to reach accurate values for the striatal dilutions given the issues of radionuclide calibrators in this range. All activities should be measured on a dose calibrator undergoing Quality Control as recommended by, e.g., AAPM, IAEA and with accuracy traceability to NIST or equivalent metrology labs.

Once the phantom is prepared with the above filling ratios, 20 SPECT scans using the imaging/acquisition parameters specified in Section 3.6 should be performed with re-positioning after each scan. Each scan should be set up to achieve ~ 3 million counts total per scan, which typically takes 20 – 30 min per scan. Image reconstruction should be performed as specified in Section 3.7.

All images should be visually assessed to ensure that the caudate and putamen compartments of the phantom are visible, and that there are no artefacts present.

The striatal compartments (L and R caudate, L and R putamen) can be segmented on the CT of the SPECT/CT when available or can be defined as specified in Section 3.10. The background should be defined as specified in Section 3.10. Then, for each of the repeat scans the SBR for the striatal compartments should be determined. For conformance testing the within-subject Coefficient of Variation (wCV) of the SBR values should be calculated for each of the striatal regions. The wCV of the SBR is the relative standard deviation (standard deviation of the replicate measurements divided by their mean) estimated from the multiple scans:

$\%wCV = (\widehat{SD}/\bar{x}) \times 100$. Estimate the % Repeatability Coefficient as $\widehat{\%RC} = 2.77 \times \%wCV$

To be 95% confidence that the claims are met (i.e. that the wCV of the SBR is $\leq$15%), the estimated wCV of the SBR must be < 11%. Similarly, the caudate:putamen uptake ratio should be determined for each scan and the wCV should be estimated. The wCV of the caudate:putamen ratio must be < 6% (to be 95% confident that the wCV of caudate:putamen uptake ratio is $\leq$8%).

Following reconstruction with corrections applied for attenuation and possibly scatter, a profile about 3 cm wide should be placed through the identified uniform region of the brain background. The count distribution should be visually assessed for the appropriateness of the attenuation correction. A correctly applied attenuation correction should yield a flat proflie other than image noise.

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. Moreover, image reconstruction methods and settings used for the phantom study should be equal to those specified in the trial protocol or equal to those routinely applied in the local clinical setting.

4.7 Assessment Procedure: Voxel Noise in the Reference/Background Compartment

Specific Binding Ratio (SBR) calculations involve the regions of interest in the striata and also a region such as the cerebellum or occipital lobe, which acts as a measure of non-specific tracer binding. Noise levels in the non-specific binding region will therefore have an impact on the uncertainty in SBR.

Image noise levels in this region should be measured using the anthropomorphic striatal phantom of (Section 4.6) with a uniform area to assess image 'noise' by means of the coefficient of variation (COV). The COV is 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 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 (the brain compartment), with its size and position chosen to match that used to quantify SBR. The COV of the volume of interest 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

References

INSTALLATION, Acceptance tests, AND Periodic QA

American Association of Physicists in Medicine. Rotating Scintillation Camera SPECT Acceptance Testing and Quality Control, Rep. 22, AAPM, New York (1987).

American College of Radiology. Nuclear medicine accreditation program requirements [Internet]. Reston, VA: American College of Radiology; 2012. Available from:

http://www.acr.org/~/media/ACR/Documents/Accreditation/Nuclear%20Medicine%20PET/Requirements.pdf

Graham, LS. The AAPM/RSNA Physics Tutorial for Residents: Quality Control for SPECT Systems. Radiographics. 1995 15:1471-1481.

Hines H, Kayayan R, Colsher J, et al. National Electrical Manufacturers Association recommendations for implementing SPECT instrumentation quality control. J Nucl Med 2000;41:383-389.

Institute of Physics and Engineering in Medicine. Quality Assurance in Gamma Camera Systems, Rep. 86, IPEM, New York (2003).

International Electrotechnical Commission. Radionuclide imaging devices - Characteristics and test conditions - Part 2: Single photon emission computed tomographs, 60789-2, IEC, Geneva (1998).

International Electrotechnical Commission. Radionuclide imaging devices - Characteristics and test conditions - Part 2: Single photon emission computed tomographs, Amendment 1, 60789-2-am 1, IEC, Geneva (2004).

International Electrotechnical Commission. Characteristics and test conditions - Part 3: Gamma camera based wholebody imaging systems, 61675-3, IEC, Geneva (1998).

National Electrical Manufacturers Association., Performance Measurements of Scintillation Cameras, National Electrical Manufacturers Association, NU 1-2001, NEMA, Rosslyn, Virginia, USA (2001).

Tossici-Bolt L, Dickson JC, Sera T, de Nijs R, Bagnara MC, Jonsson C, et al. Calibration of gamma camera systems for a multicentre European 123I-FP-CIT SPECT normal database. Eur J Nucl Med Mol Imaging 2011;38(8):1529-40.

Subject Selection and Subject Handling

Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Kapucu OL, Någren K, Nobili F, Walker Z, Van Laere K. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging. 2010 Feb;37(2):443-50.

Djang DS, Janssen MJ, Bohnen N, Booij J, Henderson TA, Herholz K, Minoshima S, Rowe CC, Sabri O, Seibyl J, Van Berckel BN, Wanner M. SNM practice guideline for dopamine transporter imaging with 123I-ioflupane SPECT 1.0. J Nucl Med. 2012 Jan;53(1):154-63.

Datscan Prescribing Information: http://www3.gehealthcare.com/en/products/categories/nuclear_imaging_agents/datscan

Walker, Z., E. Moreno, A. Thomas, F. Inglis, N. Tabet, M. Rainer, G. Pizzolato, A. Padovani and T. D. L. B. P. S. G. Da (2015). "Clinical usefulness of dopamine transporter SPECT imaging with 123I-FP-CIT in

patients with possible dementia with Lewy bodies: randomised study." Br J Psychiatry **206**(2): 145-152.

Vlaar, A. M., T. de Nijs, A. G. Kessels, F. W. Vreeling, A. Winogrodzka, W. H. Mess, S. C. Tromp, M. J. van Kroonenburgh and W. E. Weber (2008). "Diagnostic value of 123I-ioflupane and 123I-iodobenzamide SPECT scans in 248 patients with parkinsonian syndromes." Eur Neurol **59**(5): 258-266.

Tolosa, E., T. V. Borght, E. Moreno and T. C. U. P. S. S. G. Da (2007). "Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study." Mov Disord **22**(16): 2346-2351.

Seifert, K. D. and J. I. Wiener (2013). "The impact of DaTscan on the diagnosis and management of movement disorders: A retrospective study." Am J Neurodegener Dis **2**(1): 29-34.

O'Brien, J. T., W. H. Oertel, I. G. McKeith, D. G. Grosset, Z. Walker, K. Tatsch, E. Tolosa, P. F. Sherwin and I. D. Grachev (2014). "Is ioflupane I123 injection diagnostically effective in patients with movement disorders and dementia? Pooled analysis of four clinical trials." BMJ Open **4**(7): e005122.

Menendez-Gonzalez, M., F. Tavares, N. Zeidan, J. M. Salas-Pacheco and O. Arias-Carrion (2014). "Diagnoses behind patients with hard-to-classify tremor and normal DaT-SPECT: a clinical follow up study." Front Aging Neurosci **6**: 56.

Martinez-Valle Torres, M. D., S. J. Ortega Lozano, M. J. Gomez Heredia, T. Amrani Raissouni, E. Ramos Moreno, P. Moya Espinosa and J. M. Jimenez-Hoyuela (2014). "Longitudinal evaluation using FP-CIT in patients with parkinsonism." Neurologia **29**(6): 327-333.

Kupsch, A. R., N. Bajaj, F. Weiland, A. Tartaglione, S. Klutmann, M. Buitendyk, P. Sherwin, A. Tate and I. D. Grachev (2012). "Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study." J Neurol Neurosurg Psychiatry **83**(6): 620-628.

Kupsch, A., N. Bajaj, F. Weiland, A. Tartaglione, S. Klutmann, R. Copp, P. Sherwin, A. Tate and I. D. Grachev (2013). "Changes in clinical management and diagnosis following DaTscan SPECT imaging in patients with clinically uncertain parkinsonian syndromes: a 12-week follow-up study." Neurodegener Dis **11**(1): 22-32.

Hauser, R. A. and D. G. Grosset (2012). "[123I]FP-CIT (DaTscan) SPECT brain imaging in patients with suspected parkinsonian syndromes." J Neuroimaging **22**(3): 225-230.

Gomez-Rio, M., M. M. Caballero, J. M. Saez and A. M. Castellanos (2015). "Diagnosis of Neurodegenerative Diseases: the Clinical Approach." Curr Alzheimer Res.

Gayed, I., U. Joseph, M. Fanous, D. Wan, M. Schiess, W. Ondo and K. S. Won (2015). "The impact of DaTscan in the diagnosis of Parkinson disease." Clin Nucl Med **40**(5): 390-393.

Cummings, J. L., C. Henchcliffe, S. Schaier, T. Simuni, A. Waxman and P. Kemp (2011). "The role of dopaminergic imaging in patients with symptCristian Salinas-Valenzuela <cristian.salinasvalenzuela@biogen.com>oms of dopaminergic system neurodegeneration." Brain **134**(Pt 11): 3146-3166.

Cummings, J. L., M. J. Fine, I. D. Grachev, C. R. Jarecke, M. K. Johnson, P. H. Kuo, K. L. Schaecher, J. A. Oberdorf, M. Rezak, D. E. Riley and D. Truong (2014). "Effective and efficient diagnosis of

parkinsonism: the role of dopamine transporter SPECT imaging with ioflupane I-123 injection (DaTscan)." Am J Manag Care **20**(5 Suppl): S97-109.

Catafau, A. M., E. Tolosa and T. C. U. P. S. S. G. Da (2004). "Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes." Mov Disord **19**(10): 1175-1182.

Tossici-Bolt L, Hoffmann SM, Kemp PM, Mehta RL, Fleming JS. Quantification of [123I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. Eur J Nucl Med Mol Imaging 2006;33(12):1491-1419.

Koch W, Unterrainer M, Xiong G, Bartenstein P, Diemling M, Varrone A, et al. Extrastriatal binding of [(1)(2)(3)I]FP-CIT in the thalamus and pons: gender and age dependencies assessed in a European multicentre database of healthy controls. Eur J Nucl Med Mol Imaging 2014;41(10):1938-1946.

Image Data Acquisition and Reconstruction

Zaknun, J. J., H. Schucktanz and F. Aichner (2007). "Impact of instrumentation on DaTSCAN imaging: how feasible is the concept of cross-systems correction factor?" Q J Nucl Med Mol Imaging **51**(2): 194-203.

Varrone et al. Comparison between a dual-head and a brain-dedicated SPECT system in the measurement of the loss of dopamine transporters with [123I]FP-CIT. Eur J Nucl Med Mol Imaging. 2008 Jul;35(7):1343-9.

Varrone A, Dickson JC, Tossici-Bolt L et al. European multicentre database of healthy controls for [123I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. Eur J Nucl Med Mol Imaging. 2013 Jan;40(2):213-27.

Skanjeti, A., G. Castellano, B. O. Elia, M. Zotta, F. Dazzara, M. Manfredi, A. Galati, S. Grimaldi, M. Balma, R. E. Pellerito and V. Podio (2015). "Multicenter Semiquantitative Evaluation of (123)I-FP-CIT Brain SPECT." J Neuroimaging **25**(6): 1023-1029.

Rault E et al. Comparison of image quality of different iodine isotopes (I-123, I-124, and I-131). Cancer Biother Radiopharm. 2007 Jun;22(3):423-30.

Tossici-Bolt L, Dickson JC, Sera T et al. Calibration of gamma camera systems for a multicentre European ^{123}I-FP-CIT SPECT normal database. Eur J Nucl Med Mol Imaging. 2011 Aug;38(8):1529-40.

Rajeevan, N., I. G. Zubal, S. Q. Ramsby, S. S. Zoghbi, J. Seibyl and R. B. Innis (1998). "Significance of nonuniform attenuation correction in quantitative brain SPECT imaging." J Nucl Med **39**(10): 1719-1726.

Lange, C., A. Seese, S. Schwarzenbock, K. Steinhoff, B. Umland-Seidler, B. J. Krause, W. Brenner, O. Sabri, J. Kurth, S. Hesse and R. Buchert (2014). "CT-based attenuation correction in I-123-ioflupane SPECT." PLoS One **9**(9): e108328.

Lange, C., J. Kurth, A. Seese, S. Schwarzenbock, K. Steinhoff, B. Umland-Seidler, B. J. Krause, W. Brenner, O. Sabri, S. Hesse and R. Buchert (2015). "Robust, fully automatic delineation of the head contour by stereotactical normalization for attenuation correction according to Chang in dopamine transporter scintigraphy." Eur Radiol **25**(9): 2709-2717.

Bienkiewicz, M., M. Gorska-Chrzastek, J. Siennicki, A. Gajos, A. Bogucki, A. Mochecka-Thoelke, A. Plachcinska and J. Kusmierek (2008). "Impact of CT based attenuation correction on quantitative

assessment of DaTSCAN ((123)I-Ioflupane) imaging in diagnosis of extrapyramidal diseases." Nucl Med Rev Cent East Eur **11**(2): 53-58.

Iida H, Narita Y, Kado H, Kashikura A, Sugawara S, Shoji Y, et al. Effects of scatter and attenuation correction on quantitative assessment of regional cerebral blood flow with SPECT. J Nucl Med 1998;39(1):181-189.

Frey, E.C., Tsui, B.M.W., A new method for modelling the spatially-variant, object dependent scatter response function in SPECT *Record 1996 IEEE Nuclear Science Symp. and Medical Imaging Conf. (Anaheim, CA, 1996)* (Piscataway, NJ:IEEE) pp 1082–6.

Dewaraja, Y.K., Ljungberg, M., Fessler, J.A., 3-D Monte Carlo-based Scatter Compensation in Quantitative I-131 SPECT Reconstruction. IEEE TNS, vol.53(1):181-188, 2006.

Beekman FJ, de Jong WAM, van Geloven S. Efficient fully 3-D iterative SPECT reconstruction with Monte Carlo based scatter compensation. IEEE Trans. Med. Imag. 2002 Aug;21(8):867–877.

Image QA/QC, Image Distribution, AND Analysis

International Atomic Energy Agency (IAEA), IAEA Human Health Series No. 6: Quality Assurance for SPECT Systems, International Atomic Energy Agency, Vienna (2009).

Pierce LA, Elston BF, Clunie DA, Nelson D, and Kinahan PE. A Digital Reference Object to Analyze Calculation Accuracy of PET Standardized Uptake Value. Radiology. 2015:277(2):538-545.

Zubal, I. G., M. Early, O. Yuan, D. Jennings, K. Marek and J. P. Seibyl (2007). "Optimized, automated striatal uptake analysis applied to SPECT brain scans of Parkinson's disease patients." J Nucl Med **48**(6): 857-864.

Oliveira, F. P. and M. Castelo-Branco (2015). "Computer-aided diagnosis of Parkinson's disease based on [(123)I]FP-CIT SPECT binding potential images, using the voxels-as-features approach and support vector machines." J Neural Eng **12**(2): 026008.

Segovia, F., J. M. Gorriz, J. Ramirez, I. Alvarez, J. M. Jimenez-Hoyuela and S. J. Ortega (2012). "Improved parkinsonism diagnosis using a partial least squares based approach." Med Phys **39**(7): 4395-4403.

Palumbo, B., M. L. Fravolini, T. Buresta, F. Pompili, N. Forini, P. Nigro, P. Calabresi and N. Tambasco (2014). "Diagnostic accuracy of Parkinson disease by support vector machine (SVM) analysis of 123I-FP-CIT brain SPECT data: implications of putaminal findings and age." Medicine (Baltimore) **93**(27): e228.

Seibyl, J. P., K. Marek, K. Sheff, S. Zoghbi, R. M. Baldwin, D. S. Charney, C. H. van Dyck and R. B. Innis (1998). "Iodine-123-beta-CIT and iodine-123-FPCIT SPECT measurement of dopamine transporters in healthy subjects and Parkinson's patients." J Nucl Med **39**(9): 1500-1508.

Padilla, P., J. Ramirez, J. M. Gorriz, D. Salas-Gonzalez, I. Alvarez-Illan and I. Parkinson's Progression Markers (2014). "Statistical significance in the selection of the regions of interest for Parkinson brain image processing." Stud Health Technol Inform **207**: 19-26.

Nobili, F., C. Campus, D. Arnaldi, F. De Carli, G. Cabassi, A. Brugnolo, B. Dessi, S. Morbelli, G. Sambuceti, G. Abbruzzese and G. Rodriguez (2010). "Cognitive-nigrostriatal relationships in de novo, drug-naive Parkinson's disease patients: a [I-123]FP-CIT SPECT study." Mov Disord **25**(1): 35-43.

Menendez-Gonzalez, M., F. Tavares, N. Zeidan, J. M. Salas-Pacheco and O. Arias-Carrion (2014). "Diagnoses behind patients with hard-to-classify tremor and normal DaT-SPECT: a clinical follow up study." Front Aging Neurosci **6**: 56.

Martinez-Murcia, F. J., J. M. Gorriz, J. Ramirez, M. Moreno-Caballero and M. Gomez-Rio (2014). "Parametrization of textural patterns in 123I-ioflupane imaging for the automatic detection of Parkinsonism." Med Phys **41**(1): 012502.

Kupitz, D., I. Apostolova, C. Lange, G. Ulrich, H. Amthauer, W. Brenner and R. Buchert (2014). "Global scaling for semi-quantitative analysis in FP-CIT SPECT." Nuklearmedizin **53**(6): 234-241.

Illan, I. A., J. M. Gorrz, J. Ramirez, F. Segovia, J. M. Jimenez-Hoyuela and S. J. Ortega Lozano (2012). "Automatic assistance to Parkinson's disease diagnosis in DaTSCAN SPECT imaging." Med Phys **39**(10): 5971-5980.

Brahim, A., J. Ramirez, J. M. Gorriz, L. Khedher and D. Salas-Gonzalez (2015). "Comparison between Different Intensity Normalization Methods in 123I-Ioflupane Imaging for the Automatic Detection of Parkinsonism." PLoS One **10**(6): e0130274.

Brahim, A., J. Ramirez, J. M. Gorriz, L. Khedher and D. Salas-Gonzalez (2015). "Correction: Comparison between Different Intensity Normalization Methods in 123I-Ioflupane Imaging for the Automatic Detection of Parkinsonism." PLoS One **10**(7): e0135107.

Brahim, A., J. M. Gorriz, J. Ramirez and L. Khedher (2014). "Linear intensity normalization of DaTSCAN images using Mean Square Error and a model-based clustering approach." Stud Health Technol Inform **207**: 251-260.

Kuo, P. H., H. H. Lei, R. Avery, E. A. Krupinski, A. Bauer, S. Sherman, N. McMillan, J. Seibyl and G. I. Zubal (2014). "Evaluation of an Objective Striatal Analysis Program for Determining Laterality in Uptake of 123I-Ioflupane SPECT Images: Comparison to Clinical Symptoms and to Visual Reads." J Nucl Med Technol **42**(2): 105-108.

Kuo, P. H., R. Avery, E. Krupinski, H. Lei, A. Bauer, S. Sherman, N. McMillan, J. Seibyl and G. Zubal (2013). "Receiver-operating-characteristic analysis of an automated program for analyzing striatal uptake of 123I-ioflupane SPECT images: calibration using visual reads." J Nucl Med Technol **41**(1): 26-31.

Buchert R, Kluge A, Tossici-Bolt L, Dickson J, Bronzel M, Lange C, et al. Reduction in camera-specific variability in [(123)I]FP-CIT SPECT outcome measures by image reconstruction optimized for multisite settings: impact on age-dependence of the specific binding ratio in the ENC-DAT database of healthy controls. Eur J Nucl Med Mol Imaging 2016;43(7):1323-1336.

Nobili F, Naseri M, De Carli F, Asenbaum S, Booij J, Darcourt J, et al. Automatic semi-quantification of [123I]FP-CIT SPECT scans in healthy volunteers using BasGan version 2: results from the ENC-DAT database. Eur J Nucl Med Mol Imaging 2013;40(4):565-573.

Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, et al. European multicentre database of healthy controls for [123I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. Eur J Nucl Med Mol Imaging 2013;40(2):213-27.

Image Certification and Interpretation

Seibyl, J. P., A. Kupsch, J. Booij, D. G. Grosset, D. C. Costa, R. A. Hauser, J. Darcourt, N. Bajaj, Z. Walker, K. Marek, I. McKeith, J. T. O'Brien, K. Tatsch, E. Tolosa, R. A. Dierckx and I. D. Grachev (2014). "Individual-

Reader Diagnostic Performance and Between-Reader Agreement in Assessment of Subjects with Parkinsonian Syndrome or Dementia Using 123I-Ioflupane Injection (DaTscan) Imaging." J Nucl Med **55**(8): 1288-1296.

Seibyl, J., K. Marek and I. G. Zubal (2010). "The role of the core imaging laboratory in multicenter trials." Semin Nucl Med **40**(5): 338-346.

MISC

Mozley PD, Schneider JS, Acton PD, Barraclough ED, Stern MB, Leopold NA, Plössl K, Siderowf A, Li PY, Gollomp SM, Alavi A, Kung HF. Binding of [Tc-99m]TRODAT-1 to dopamine transporters in patients with Parkinson's disease and healthy volunteers. J Nucl Med 2000; 41:584-589.

Lynch D, Mozley PD, Sokal S, Maas NMC, Balcer LJ, Siderowf AD. Lack of effect of polymorphisms in dopamine metabolism related genes on imaging of TRODAT-1 in striatum of asymptomatic volunteers and patients with Parkinson's disease. Movement Disorders 2003; 18(7):804-812.

Mozley PD, Stubbs JB, Kim H-J, McElgin W, Kung HF: Dosimetry of an iodine-123-labeled tropane to image dopamine transporters. J Nucl Med 1996; 37:151-159.

Mozley PD, Stubbs JB, Plössl K, Dressl SH, Barraclough ED, Alavi A, Araujo LI, Kung HF. The biodistribution and dosimetry of a [Tc-99m] labeled tropane for imaging dopamine transporters. J Nucl Med 1998; 39:1960-1967.

Mozley PD, Acton PD, Barraclough ED, Plössl K, Gur RC, Mathur A, Alavi A, Saffer J, Kung HF. Effects of age on dopamine transporters in healthy humans. J Nucl Med 1999; 40:1812:1817.

Seibyl, J. P., M. Laruelle, C. H. van Dyck, E. Wallace, R. M. Baldwin, S. Zoghbi, Y. Zea-Ponce, J. L. Neumeyer, D. S. Charney, P. B. Hoffer and R. B. Innis (1996). "Reproducibility of iodine-123-beta-CIT SPECT brain measurement of dopamine transporters." J Nucl Med **37**(2): 222-228.

Seibyl, J. P., K. Marek, K. Sheff, R. M. Baldwin, S. Zoghbi, Y. Zea-Ponce, D. S. Charney, C. H. van Dyck, P. B. Hoffer and R. B. Innis (1997). "Test/retest reproducibility of iodine-123-betaCIT SPECT brain measurement of dopamine transporters in Parkinson's patients." J Nucl Med **38**(9): 1453-1459.

Ravina, B., D. Eidelberg, J. E. Ahlskog, R. L. Albin, D. J. Brooks, M. Carbon, V. Dhawan, A. Feigin, S. Fahn, M. Guttman, K. Gwinn-Hardy, H. McFarland, R. Innis, R. G. Katz, K. Kieburtz, S. J. Kish, N. Lange, J. W. Langston, K. Marek, L. Morin, C. Moy, D. Murphy, W. H. Oertel, G. Oliver, Y. Palesch, W. Powers, J. Seibyl, K. D. Sethi, C. W. Shults, P. Sheehy, A. J. Stoessl and R. Holloway (2005). "The role of radiotracer imaging in Parkinson disease." Neurology **64**(2): 208-215.

Parkinson Progression Marker, I. (2011). "The Parkinson Progression Marker Initiative (PPMI)." Prog Neurobiol **95**(4): 629-635.

Marek, K., J. Seibyl, S. Eberly, D. Oakes, I. Shoulson, A. E. Lang, C. Hyson, D. Jennings and P. I. Parkinson Study Group (2014). "Longitudinal follow-up of SWEDD subjects in the PRECEPT Study." Neurology **82**(20): 1791-1797.

Jennings, D., A. Siderowf, M. Stern, J. Seibyl, S. Eberly, D. Oakes, K. Marek and P. Investigators (2014). "Imaging prodromal Parkinson disease: the Parkinson Associated Risk Syndrome Study." Neurology **83**(19): 1739-1746.

Jacobsen, L. K., J. K. Staley, S. S. Zoghbi, J. P. Seibyl, T. R. Kosten, R. B. Innis and J. Gelernter (2000). "Prediction of dopamine transporter binding availability by genotype: a preliminary report." Am J Psychiatry **157**(10): 1700-1703.

Isaias, I. U., M. Canesi, R. Benti, P. Gerundini, R. Cilia, G. Pezzoli and A. Antonini (2008). "Striatal dopamine transporter abnormalities in patients with essential tremor." Nucl Med Commun **29**(4): 349-353.

Isaias, I. U., R. Benti, S. Goldwurm, M. Zini, R. Cilia, P. Gerundini, A. Di Fonzo, V. Bonifati, G. Pezzoli and A. Antonini (2006). "Striatal dopamine transporter binding in Parkinson's disease associated with the LRRK2 Gly2019Ser mutation." Mov Disord **21**(8): 1144-1147.

Innis, R. B., K. L. Marek, K. Sheff, S. Zoghbi, J. Castronuovo, A. Feigin and J. P. Seibyl (1999). "Effect of treatment with L-dopa/carbidopa or L-selegiline on striatal dopamine transporter SPECT imaging with [123I]beta-CIT." Mov Disord **14**(3): 436-442.

Best, S. E., P. M. Sarrel, R. T. Malison, M. Laruelle, S. S. Zoghbi, R. M. Baldwin, J. P. Seibyl, R. B. Innis and C. H. van Dyck (2005). "Striatal dopamine transporter availability with [123I]beta-CIT SPECT is unrelated to gender or menstrual cycle." Psychopharmacology (Berl) **183**(2): 181-189.

Bajaj, N., R. A. Hauser, J. Seibyl, A. Kupsch, M. Plotkin, C. Chen and I. D. Grachev (2014). "Association between Hoehn and Yahr, Mini-Mental State Examination, age, and clinical syndrome predominance and diagnostic effectiveness of ioflupane I 123 injection (DaTSCAN) in subjects with clinically uncertain parkinsonian syndromes." Alzheimers Res Ther **6**(5-8): 67.

Bajaj, N., R. A. Hauser and I. D. Grachev (2013). "Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes." J Neurol Neurosurg Psychiatry **84**(11): 1288-1295.

Antonini, A., R. Benti, R. De Notaris, S. Tesei, A. Zecchinelli, G. Sacilotto, N. Meucci, M. Canesi, C. Mariani, G. Pezzoli and P. Gerundini (2003). "123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy." Neurol Sci **24**(3): 149-150.

Cheng, G. and J. F. Morley (2014). "Complete and readily reversible blocking of striatal DaTscan binding by methylphenidate." Clin Nucl Med **39**(2): 211-213.

Thomsen G, Knudsen GM, Jensen PS, Ziebell M, Holst KK, Asenbaum S, et al. No difference in striatal dopamine transporter availability between active smokers, ex-smokers and non-smokers using [123I]FP-CIT (DaTSCAN) and SPECT. EJNMMI Res 2013;3(1):39.

Iida H, Nakagawara J, Hayashida K, Fukushima K, Watabe H, Koshino K, et al. Multicenter evaluation of a standardized protocol for rest and acetazolamide cerebral blood flow assessment using a quantitative SPECT reconstruction program and split-dose 123I-iodoamphetamine. J Nucl Med 2010;51(10):1624-31.

Appendices

Appendix A: Acknowledgements and Attributions

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