QIBA Profile:
Dynamic Susceptibility Contrast MRI (DSC-MRI)

Stage 2: Consensus Profile (maintenance version)

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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
2023.07.17	Change Log	Deleted entries prior to published consensus profile
2023.07.17	3.11	Added reference to QIBA Profile: CT Tumor Volume Change for Advanced Disease to justify volume ranges
2023.07.17	4.7	Changed minimum size for region-of-interest for measuring values in normal appearing white matter to be consistent with the data analysis that was used for determining claims.
2023.07.17	3.9	Added specifications for contrast injection rate that had inadvertently been excluded during edits prior to Public Comment
2023.07.17	Technologist Checklist	Added specifications for contrast injection rate that had inadvertently been excluded during edits prior to Public Comment.

1. Executive Summary

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker.

Profile development is an evolutionary, phased process; this Profile is in the Public Comment Resolution Draft stage. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document's context: http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages.

The **Claim** (Section 2) describes the biomarker performance.
The **Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim.
Assessment Procedures (Section 4) for evaluating specific requirements are defined as needed.
Conformance (Section 5) regroups Section 3 requirements by Actor to conveniently check Conformance.

This QIBA Profile, Dynamic-Susceptibility-Contrast Magnetic Resonance Imaging (DSC-MRI), addresses the measurement of an imaging biomarker for relative Cerebral Blood Volume (rCBV) for the evaluation of brain tumor progression or response to therapy. We note here, that this profile does not claim to be measuring quantitative rCBV due to lack of existing supporting literature; it does provide claims for a biomarker that is proportional to rCBV, which is the tissue-normalized first-pass area under the contrast-agent concentration curve (AUC-TN). The AUC-TN therefore has merit as a potential biomarker for diseases or treatments that impact rCBV. This profile places requirements on Sites, Acquisition Devices, Contrast Injectors, Contrast Media, Radiologists, Physicists, Technologists, Reconstruction Software, Image Analysis Tools and Image Analysts involved in Site Conformance, Staff Qualification, Product Validation, Pre-delivery, Periodic QA, Protocol Design, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, Image Distribution, Image Analysis and Image Interpretation.

The requirements are focused on achieving known (ideally negligible) bias and avoiding unnecessary variability of the of the AUC-TN measurements.

The clinical performance is characterized by a 95% confidence interval for the AUC-TN true change (Y_2-Y_1) in enhancing tumor tissue $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times 0.31)^2 + (Y_2 \times 0.31)^2}$ and in normal tissue $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times 0.40)^2 + (Y_2 \times 0.40)^2}$, where Y_1 is the baseline measurement and Y_2 is the follow-up measurement. These estimates are based on current literature values but may be updated based on future studies (see Section 2.2 for details).

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

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

QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET, and Ultrasound can be

found at qibawiki.rsna.org.

2. Clinical Context and Claims

Clinical Context

DSC-MRI is frequently used in clinical practice for measuring rCBV to evaluate brain tumor progression or response to therapy. rCBV may be used to assess true tumor viability after therapy, allowing differentiation of pseudoprogression (PsP) (apparent progression when tumor is actually responding to therapy) and pseudoresponse (apparent response to therapy when tumor is actually not responding) [1-3]. Pseudoresponse could be a factor in the discordance seen between high response rates and prolonged progression free survival without increased overall survival in GBM [4]. Some work has shown that DSC-MRI might predict outcome following anti-angiogenic therapy where temporal changes in rCBV might predict overall survival [5, 6]. DSC-MRI may also be useful for classifying tumor grade [7]. Patel, et al. [8] found that thresholds separating viable tumor from treatment changes demonstrate relatively good accuracy in individual studies. Finally, rCBV may also be of value in stratifying patients for different types of therapy, as it may identify patients most likely to benefit from certain classes of therapeutic agents [9].

While rCBV is the *clinical* marker, this profile focuses on measuring its imaging biomarker, which is the Area Under the Curve-Tissue Normalized (AUC-TN), typically normalized to normal-appearing white matter (NAWM) in the opposite hemisphere. This involves characterizing the performance of DSC-MRI sequences to measure the change in signal intensity with injection of a paramagnetic gadolinium-based contrast agent (GBCA). This profile also does not specify the exact methods by which a software extracts key points in the signal-intensity curve to compute the rCBV from the AUC-TN. This is an area of active research, and studies have shown good agreement among software even among those that are proprietary [10].

An additional application of DSC-MRI is to estimate the 'leakiness' of vessels within a tumor, using the 'K2' coefficient, for which K2 is assumed to be proportional to the leakage rate [11]. Normal brain has an intact blood brain barrier (BBB), and do not demonstrate signal intensity changes due to extravasation of GBCA. In areas of BBB disruption, DSC-MRI will typically demonstrate slow drift in signal intensity due to GBCA extravasation. Characterizing this leakage rate is usually a critical step in calculating the AUC described above, and thus, the claims are closely linked. However, the literature supporting repeatability/reproducibility of K2 measurements is limited. Furthermore, there are numerous techniques to correct for 'leakiness' [12, 13]. Therefore, K2 claims are not presented in the current profile.

Conformance to this Profile <u>by all relevant staff and equipment</u> supports the following claim(s):

Claim 1: For a measured change in Area Under the Curve-Tissue Normalized (AUC-TN) in enhancing tumor tissue of $(Y_2 - Y_1)$, the 95% confidence interval for the true change is $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times 0.31)^2 + (Y_2 \times 0.31)^2}$ [14, 15], where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

Claim 2: For a measured change in Area Under the Curve-Tissue Normalized

(AUC-TN) in normal brain tissue of $(Y_2 - Y_1)$, the 95% confidence interval for the true change is $(\boldsymbol{Y_2 - Y_1}) \pm \mathbf{1.96} \times \sqrt{(\boldsymbol{Y_1} \times \mathbf{0.40})^2 + (\boldsymbol{Y_2} \times \mathbf{0.40})^2}$, where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

2.1 Clinical Interpretation

QIBA Claims describe the technical performance of quantitative measurements. The clinical significance and interpretation of those measurements is left to the clinician. Some considerations are presented in the following text.

The 95% confidence interval can be thought of as "error bars" or "noise" around the measurement of AUC-TN **change** in the *enhancing tumor* or in *normal tissue* [15]. Note that this does not address the biological significance of the change, just the likelihood that the measured change is real. We reiterate here that the boundaries represent the 95% CI on the measured change, assuming the images are obtained at 3 Tesla (3T), on the same scanner, using same software, same analyst and with careful attention to repeating similar image planes and technique. We focus on 3T since the claims were based on studies performed on a 3T system.

Clinical interpretation with respect to the magnitude of true change in enhancing tumor: The magnitude of the true change is defined by the measured change and the error bars. If you measure the AUC-TN to be 1.0 at baseline (Y_1) and 3.45 at follow-up (Y_2), then the measured change is a 245% increase in AUC-TN (i.e., 100x(3.45-1.00)/1.00). The 95% confidence interval for the true change is $100 \times (3.45 - 1.00) \pm 1.96 \times \sqrt{(1.00 \times 0.31)^2 + (3.45 \times 0.31)^2}$ = 27% to 463% increase in AUC-TN. This also assumes that the relationship is linear and that the slope of the regression line of the measured values vs. true values is one.

Clinical interpretation with respect to the magnitude of true change in normal tissue: The magnitude of the true change in normal tissue is defined by the measured change and the error bars. If you measure the AUC-TN to be 1.0 at baseline and 3.45 at follow-up, then the measured change is a 245% increase in AUC-TN (i.e., 100x(3.45-1.00)/1.00). The 95% confidence interval for the true change is $100 \times (3.45 - 1.00) \pm 1.96 \times \sqrt{(1.00 \times 0.40)^2 + (3.45 \times 0.40)^2}$ = –37% to 527% increase in AUC-TN again noting the assumption of a linear relationship and slope of 1.0.

2.2. Discussion

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

The claims are based on estimates of perfusion AUC-TN coefficient of variation (wCV) for regions of interests (ROIs) of specified range located in enhancing tumor or normal tissue. For estimating the critical % change, the % Reproducibility Coefficient (%RDC) is used: $2.77 \times wCV \times 100$ for which wCV=0.31 in enhancing tumor and wCV=0.40 in normal tissue [15]. We use the more

conservative wCV based on manual NAWM ROIs, rather than the higher precision values (wCV approximately 0.1 to 0.2 for enhancing tumor and 0.1 to 0.25 for normal brain [15, 16] based on automated standardization and normalization methods [17, 18] since these automated methods may not be readily available. Selection of "normal" brain may also be affected by how the contralateral ROI is drawn. In papers of normal volunteers scanned 1-week apart, wCV was less than 0.1 using automated methods and less than 0.2 for manual methods [19]. Differences in performance compared to the above patient studies [15, 16] are likely due to lower flip angle (30 degrees) used for the healthy subjects compared to the patient cohorts (90 degrees). Thus, using automated approaches for AUC-TN calculations and test-retest, we can expect the RDC for change in AUC-TN to be reduced (e.g. 0.1 and 0.2). It should be noted that some of the errors might be due to differences in subject placement and physiology. In a study of healthy volunteers who were scanned multiple times in a single session[20], wCV was 0.18, but results might have been confounded by multiple injections [21] and AUC values were not normalized and ROIs were manually drawn.

A limitation of our claims is that it is based on a handful of studies due to the limited number of published test-retest studies of DSC-MRI due to the risk of nephrogenic systemic fibrosis. In fact, the Jafari-Khouzani [16] and Prah [15] papers are derived from overlapping patient cohorts, but because of differences in processing have different wCV. Furthermore, because DSC-MRI requires the injection of a GBCA, true repeat studies cannot be performed since the 2nd contrast agent will inherently be performed under altered imaging conditions. In addition, the test-retest studies were performed early on before consensus clinical recommendations were reached with acquisition protocols different than what is used routinely in clinical practice. We tried to adjust for this in the profile, under the assumption that the standard clinical practice protocols will lead to higher precision than is stated in our claims.

It is critical to measure the lesion in a consistent fashion, and to have enough pixels to accurately represent the lesion. While it is recognized that there may be non-enhancing tumor, by convention, AUC-TN is measured in contrast-enhancing tumor. That means it is necessary to review the pre-contrast T1-weighted images to assure that all increased signal on post-contrast imaging is due to contrast enhancement. Once that has been determined, an ROI should be drawn to include at least a $1cm^2$ area.

Some patients will have multiple lesions. This can present several problems. The first is that it may make it difficult to find a large region of normal appearing white matter, and that should be considered when measurements are reported. Second, the way to report multiple lesions will be context-dependent. In some cases, the maximum value may be the most relevant, likely representing the most aggressive lesion. In some cases, mean or minimum values may be more relevant. While multiple lesions are rather uncommon, planning for handling these cases is important.

The performance values in the claims reflect the likely impact of variations permitted by this Profile. The Profile does not permit different compliant actors (acquisition device, radiologist, image analysis tool, etc.) at the two timepoints (i.e., it is required that the same scanner or image analysis tool be used for both exams of a patient). If one or more of the actors are not the same, it is expected that the measurement performance will be worsened. The wCV used for the claims

will need to be updated. Under the assumption that the various sources of variability are additive (an assumption that has not been validated), the wCV can be estimated as follows:

$$wCV = \sqrt{DSC_{variance} + Software_{variance} + Normalization_{Variance} + ROI_{variance}}$$

DSC-MRI method variance is defined as inherent to the technique of measuring AUC of the DSC-MRI GBCA bolus measured using test/retest studies holding all other parameters constant. Software variance includes variation in integration of AUC while Normalization Variance is variance related to how the AUC values are normalized; these two can be linked if software includes automated standardization. For example, some software use histogram equalization [17] while others use automated NAWM selection [18] for standardization - both approaches decrease wCV [15, 16]. Expected variance in measurements of NAWM ROI (using 1.8 mm radius) was found to be approximately 20% [22]. Software variance could be measured using digital reference objects (DROs). ROI variance is variance related to interrater placement of ROIs in enhancing tumor or normal brain. ROI variance could be assessed by evaluating inter-rater variance on the same patients. Inter-rater variation due to ROI placement has been estimated to be approximately 30% for maximum AUC-TN (maximum AUC-TN in 4 or 6 ROIs of 1.8 mm radius), 43% for mean AUC-TN in one ROI and 35% in average of 3 ROIs [22]. Interobserver variance when using manual NAWM and tumor ROI was reported to be approximately 30% for maximum AUC-TN method [23]. Scanner variance is variability of results across scanners and may be affected by differences in hardware and acquisition protocol; this variance could be measured using a physical phantom.

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 Table 1.

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
Site	Site Conformance	3.0
Acquisition Device	Product Validation	3.2.
	Pre-delivery	3.3.
	Periodic QA	3.5.
Contrast Injector	Product Validation	3.2
	Pre-delivery	3.3
	Periodic QA	3.5
Contrast Medium	Product Validation	3.2
Radiologist	Staff Qualification	3.1
	Protocol Design	3.6
	Image Interpretation	3.14
Physicist	Staff Qualification	3.1
	Pre-delivery	3.3
	Periodic QA	3.5
	Protocol Design	3.6
Technologist	Staff Qualification	3.1.
	Subject Handling	3.8.

	Image Data Acquisition	3.9.
Image Analyst	Staff Qualification	3.1
	Periodic QA	3.5
	Image Data Reconstruction	3.10
	Image QA	3.11
	Image Distribution	3.12
	Image Analysis	3.13
Reconstruction Software	Product Validation	3.2
	Image Data Reconstruction	3.10
Image Analysis Tool	Product Validation	3.2
	Image Analysis	3.13

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" in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable, and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

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

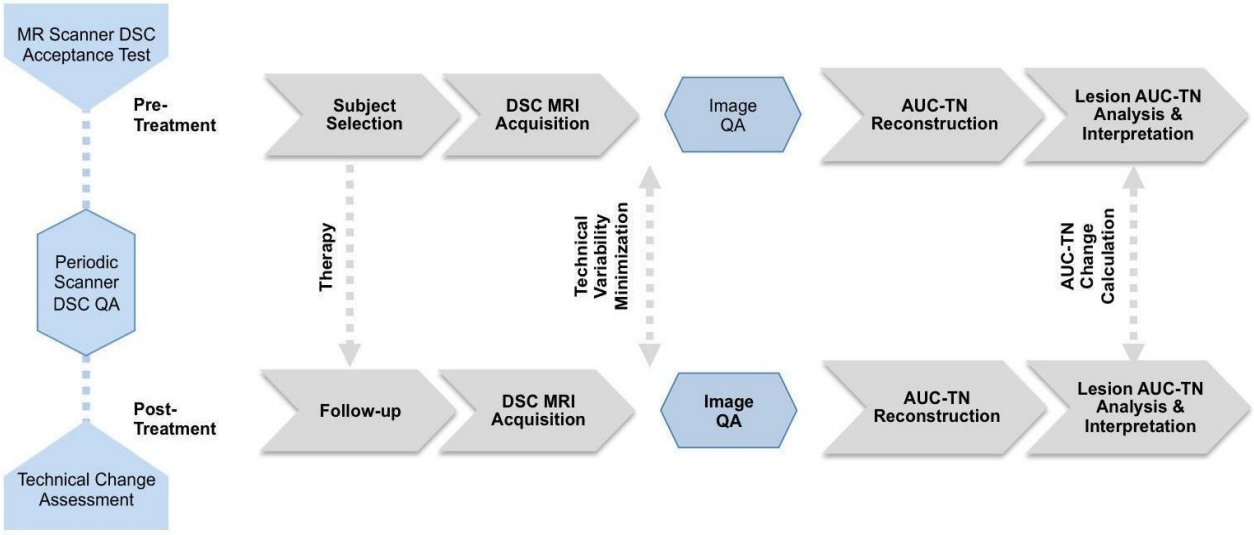

Figure 1: Dynamic Susceptibility Contrast MRI (DSC-MRI)- Activity Sequence

3.0. Site Conformance

This activity involves establishing the overall conformance of an imaging site to this Profile. It includes criteria to confirm the conformance of each of the participating Actors at the site.

3.0.1 Discussion

A site conforms to the Profile if each relevant actor conforms to each requirement assigned in the Activities of the Profile. Activities represent steps in the chain of preparing for and generating biomarker values (e.g. product validation, system calibration, patient preparation, image acquisition, image analysis, etc.).

Since a site may assess conformance actor by actor, a checklist document is available in Appendix E which extracts, for convenient reference, all the requirements in this Profile and regroups the requirements by Actor.

Sites may be able to obtain a QIBA Conformance Statement for some actors (e.g. Acquisition Devices) attesting to their conformance to this Profile, rather than the site having to confirm conformance themselves.

3.0.2 Specification

Parameter	Actor	Specification
Acquisition Devices	Site	Shall confirm all participating acquisition devices conform to this Profile.
Contrast Injector	Site	Shall confirm all participating contrast injectors conform to this Profile.
Contrast medium	Site	Shall confirm all participating contrast media conform to this Profile.
Radiologists	Site	Shall confirm all participating radiologists conform to this Profile.
Physicists	Site	Shall confirm all participating physicists conform to this Profile.
Technologists	Site	Shall confirm all participating technologists conform to this Profile.
Image Analyst	Site	Shall confirm all participating image analysts conform to this Profile.
Reconstruction. Software	Site	Shall confirm all participating reconstruction software conform to this Profile.
Image Analysis Tools	Site	Shall confirm all participating image analysis tools conform to this Profile.

3.1. Staff Qualification

This activity involves evaluating the human Actors (Radiologist, Physicist, and Technologist) prior to their participation in the Profile. It includes training, qualification or performance assessments that are necessary to reliably meet the Profile Claim.

3.1.1 Discussion

These requirements, as with any QIBA Profile requirements, are focused on achieving the Profile Claim. Evaluating the medical or professional qualifications of participating actors is beyond the scope of this profile. MR technologists or other imaging expert(s) performing DSC-MRI procedures should be MR-certified according to local regulations or institutional requirements. These individuals should have prior experience in conducting DSC-MRI. The personnel should also be experienced in clinical study related imaging and should be familiar with good clinical practices (GCP). Competence in the performance of DSC-MRI should never be limited to a single individual at the imaging center, as scheduled and unplanned personnel absences are to be expected in the course of a DSC-MRI trial. In most clinical practice situations, and in the clinical research setting, the image analyst may be a non-radiologist professional such as a medical physicist, biomedical engineer, MRI scientist or image analyst. The Technologist is always assumed to be the operator for subject scanning, while phantom scanning can be performed by a technologist, or physicist or scientist. At some facilities, there may not be a Physicist, and in these circumstances the task assigned to the Physicist may be subsumed by an individual with the qualifications described below. NB: The same individual may assume multiple roles if qualifications are met.

3.1.2 Specification

Parameter	Actor	Specification
Qualification	Radiologist	Shall be a qualified individual with experience in clinical DSC acquisition and interpretation
Qualification	Physicist	Shall be a qualified individual with experience in establishing protocols on the MRI system and performing quality assurance checks on the MRI equipment.
Qualification	Technologist	Shall be a qualified individual with experience in clinical DSC acquisition, including use of power injector and administration of contrast material and familiar with good clinical practice
Qualification	Image Analyst	Shall be an individual trained in (1) understanding of key DSC acquisition principles of perfusion-weighted imaging and test procedures to confirm that related DICOM metadata content is maintained along the network chain from Scanner to PACS and analysis workstation, (2) assessing quality of acquired images, (3) placement of regions of interest in appropriate anatomical locations and (4) use of Reconstruction Software and Image Analysis Tools.

3.2. Product Validation

This activity involves evaluating the product Actors (Acquisition Device, and Image Analysis Tool) prior to their use in the Profile (e.g. at the factory). It includes validations and performance assessments that are necessary to reliably meet the Profile Claim.

3.2.1 DISCUSSION

Performance measurements of specific protocols are not addressed here. Those are included in section 3.6.2.

Segmentation may be performed automatically by a software algorithm, manually by a human observer, or semi-automatically by an algorithm with human guidance/intervention, for example to identify a starting seed point, stroke, or region, or to edit boundaries.

3.2.2 SPECIFICATION

Parameter	Actor	Requirement
Field Strength	Acquisition Device	Shall confirm field strength is 3 Tesla (3T)
Pulse sequence	Acquisition Device	Shall be capable of acquiring gradient echo data with echo planar imaging
MRI Equipment Specifications	Acquisition Device	See Section 4.1. Assessment Procedure: MRI Equipment Specifications and Performance
Acquisition Protocol	Acquisition Device	Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.
		Shall prepare a protocol conformant with section 3.6.2 "Protocol Design Specification"
Image Header	Acquisition Device	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column in sections 3.6.2 "Protocol Design Specification".
		Shall record actual timing and triggers in the image header by including the Contrast/Bolus Agent Sequence (0018,0012).
		Shall support recording in the image header (Image Comments (0020,4000) or Patient Comments (0010,4000)) information entered by the Technologist about the acquisition.
Image Data Acquisition	Contrast Injector	Shall be capable of performing power injection with all the parameters set as specified in section 3.9 “Image Data Acquisition”
	Contrast Media	Shall confirm gadolinium-based contrast agent (GBCA) used for study conforms with local and FDA safety guidelines.
Reading Paradigm	Reconstruction Software	Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint.
		Shall re-process the first time point if it was processed by a different Reconstruction Software or Analyst.
Digital Reference	Reconstruction Software	Shall demonstrate linear performance and has expected wCV on digital reference objects. See Section 4.2. Assessment Procedure:

Object		Digital Reference Object.
AUC-TN and K2 maps	Reconstruction Software	Shall record the image analysis tool version.
		Shall record AUC-TN and K2 images
		Shall record ROIs used for normalization.
		Shall record parameters used for calculation of AUC-TN
Multiple Tumors	Image Analysis Tool	Shall allow multiple tumors to be measured.
		Shall either correlate each measured tumor across time points or support the analyst to unambiguously correlate them.
ROI Result Recording	Image Analysis Tool	Shall record the image analysis tool version.
		Shall record percentage AUC-TN change relative to baseline for each tumor
		Shall record ROIs used
		Shall record the volume of each ROI.
		Shall record the confidence interval of result for each AUC-TN change measurement

3.3. Pre-delivery

Standard scanner and contrast injector calibrations, phantom imaging, performance assessments or validations prior to delivery of equipment to a site (e.g., performed at the factory) for routine clinical service are beyond the scope of this profile but are assumed to be satisfied.

3.3.1 Discussion

3.3.2 Specification

Parameter	Actor	Requirement
Scanner performance benchmark	Acquisition Device	Scanner shall meet vendor-established performance benchmark ranges for the given model
	Physicist	Shall qualify that device meets vendor-established performance benchmark ranges for the given model
Pulse sequence	Acquisition Device	Shall be qualified by a physicist as capable of acquiring gradient echo data with single shot echo planar imaging (EPI) readout within vendor-established performance benchmark ranges
	Physicist	Shall qualify device as capable of acquiring gradient echo data with single shot echo planar imaging (EPI) readout within vendor-established performance benchmark ranges
Injector performance benchmark	Contrast Injector	Injector shall meet vendor-established performance benchmark ranges for the given model and capable of injection rates as specified in section 3.9 “Image Data Acquisition”

3.4. Installation

Standard scanner and contrast injector calibrations, phantom imaging, performance assessments or validations following installation of equipment at the site for routine clinical service are beyond the scope of this profile but are assumed to be satisfied. Periodic Q&A (section 3.5) is expected to be followed.

3.5. 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.

3.5.1 Discussion

The MRI scanner and receiver coils must undergo routine quality assurance and quality control processes (including preventive maintenance schedules) appropriate for clinical MRI applications.

The QIBA NIST DSC-MRI phantom, or a similar multi-compartment phantom with range of susceptibility (T2*) values appropriate for the DSC-MRI study to be performed, should be used if the Profile Claim given above is to be assured. Appendix F tabulates a standardized protocol in vendor-specific terms that can be used for scanning the DSC-MRI phantom. A recipe for creating such a phantom is provided in Appendix G.

The phantom scans should be repeated on a regular interval (e.g., 3 months) during the course of the study. Ongoing image quality inspection on a per-scan basis is essential. Any changes to scanner equipment, including major hardware changes or any software version change, need to be documented and will result in the need for imaging qualification renewal.

The power injector needs to be properly serviced and calibrated at regular intervals, as recommended by the particular vendor.

All scanner software version updates and hardware changes must be documented since changes in scanner sequences can affect data acquisition and reproducibility of longitudinal studies [24].

3.5.2 Specification

Parameter	Actor	Requirement
Scanner performance benchmark	Physicist	Shall assess scanner performance metrics are within vendor-established performance benchmark ranges for the given model.
		Shall document all hardware/software upgrades.
		Shall record the date/time of calibrations as recommended by the vendor.
	Acquisition Device	Shall meet vendor-established performance benchmark ranges for the given model.

Contrast Injector Performance Benchmark	Technologist	Shall assess injector performance are within vendor-established performance benchmark ranges for the given model.
		Shall document all hardware/software upgrades.
		Shall record the date/time of calibrations as recommended by the vendor.
	Contrast Injector	Shall meet vendor-established performance benchmark ranges for the given model.
Scanner Stability	Physicist	Shall perform periodic system QA using QIBA-NIST DSC phantom (see Appendix F). See Section 4.3. Assessment Procedure: Scanner Stability.
		Shall confirm correlation coefficient measurements between ΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging vs multi-echo gradient echo acquisition is within 98.4 to 99.3% for both inner and outer vials (See Appendix F.2)
		Shall confirm correlation coefficient measurements between ΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging across multiple time points is at least 95% for both inner and outer vials. (see Appendix F.2)
Reconstruction Software Upgrades	Image Analyst	Shall document all software upgrades and shall confirm performance within benchmark on digital reference objects
Image Analysis Tool Upgrades	Image Analyst	Shall document all software upgrades

3.6. Protocol Design

This activity involves designing acquisition and reconstruction protocols for use in the Profile. It includes constraints on protocol acquisition and reconstruction parameters that are necessary to reliably meet the Profile Claim.

3.6.1 Discussion

The Profile considers Protocol Design to take place at the imaging site, however, sites may choose to make use of protocols developed elsewhere.

The approach of the specifications here is to focus as much as possible on the characteristics of the resulting dataset, rather than one particular technique for achieving those characteristics. This is intended to allow as much flexibility as possible for product innovation and reasonable adjustments for patient size (such as increasing FOV for larger patients), while reaching the performance targets. Again, the technique parameter sets in the Conformance Statements for Acquisition Devices and Reconstruction Software may be helpful for those looking for more guidance.

- The claims of the profile is based on gradient-echo acquisitions with echo-planar imaging (EPI) readout. Spin echo EPI is an acceptable acquisition protocol but there is little existing literature on repeatability and reproducibility and therefore GRE sequences are preferred. An active area of research is the development of new MRI acquisition techniques other than single-shot EPI that can reduce spatial distortion or can improve spatial or temporal resolution [25], but there are little existing studies of their repeatability and reproducibility. These sequences are also not yet widely available clinically and thus not discussed in the current profile.

- Studies employing digital reference objects highlight significant interaction between repetition time, flip angle and contrast agent dosing scheme and have been leveraged to identify optimal acquisition protocols [26].

- Clinical recommendations [27] for DSC-MRI do not recommend 90 degree FA, that was used to achieve our Profile claims [15], due to high T1 sensitivity that can contaminate the signal in conditions of disrupted BBB. Instead, FA of 60 to 70 degrees are recommended, as a tradeoff between SNR and T1-effects. Lower flip angles (around 35 degrees) reduce T1-effects, but result in lower SNR, which in turn can lead to reduced precision in AUC estimates in white matter. Based on simulation results, the expected variation in results compared to "ground truth" are [26]:

FA	TE (ms)	TR (s)	Preload Dose (fraction of standard dose)	Bolus Dose (fraction of standard dose)	Simulated Coefficient of Variation from Ground Truth
90	30	1.5	1	1	8.8%*
60	30	1.5	1	1	6.6%
30	30	1.5	1	1	6.8%
30	30	1.5	0	1	8.2%

*Unpublished 90 degree FA results using simulation approach as described by Semmineh et al [26]. Assumes leakage correction applied to the disrupted BBB.

Note that the coefficient of variation results in the table are based on simulations of leakage corrected AUC-TN values with respect to "ground truth", i.e., AUC-TN values not confounded by disrupted BBB. The values are not reflective of expected test-retest CV values as those used in establishing the profile claims. However, it should be noted that the 90 degree FA with full pre-dose load has a greater degree of variation than acquisitions obtained with 60 degree FA, which not surprisingly has the lowest degree of expected variation. Therefore, we recommend 60 degree FA, to meet the Profile claims. If patients are unable to tolerate 2 full doses, then using a low FA, will likely have similar variability as that of the claims. Prospective test-retest studies at low FA will be needed to properly assess the RDC.

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Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Radiologist	Shall approve protocol developed by the Physicist to meet the requirements of this profile	N/A
		Shall ensure technologists have been trained on the requirements of this profile.	
	Physicist	Shall build a protocol that has been previously prepared in consultation with the Radiologist and validated for this purpose.	N/A
		Shall confirm protocol is capable of covering area of interest, since most sequences cannot cover the entire brain and achieve sufficient temporal resolution to be clinically useful	
		Shall clearly label and store protocol on MRI system for recall in repeat serial scans of patients.	
		Shall track edits to the protocol with version control and archive prior versions	
		Shall report if any parameters are modified beyond the specifications below.	
Imaging sequence	Physicist	Shall confirm imaging sequence is a Gradient Echo acquisition with Echo Planar Imaging Readout	N/A
Total Acquisition Time	Physicist	Shall confirm series acquisition duration is at least 120s.	N/A
Bolus Quality	Physicist	Shall confirm that the protocol achieves a bolus signal drop at least 10% from baseline when using specified contrast agent and dosage. (See Section 4.4)	N/A
Pixel Spacing	Physicist	Shall confirm that in-plane resolution is between 1.72 and 1.9 mm^2	0028,0030
Repetition Time (TR)	Physicist	Shall confirm Maximum TR = 1500ms	0018,0080
Acquisition Matrix	Physicist	Shall confirm Acquisition Matrix achieves required pixel spacing	0018,1310
Flip Angle	Physicist	Shall confirm Flip Angle (60)*	0018,1314
Field Strength	Physicist	Shall confirm Field Strength is 3T	0018,0087
Slice Thickness	Physicist	Shall confirm Slice Thickness (<= 5mm)	0018,0050
Echo time (TE)	Physicist	Shall confirm Echo Time (TE)=25-35 ms	0018,0081
Number of	Physicist	Shall confirm Number of excitations: 1	0018,0083

excitations			
Interslice Gap	Physicist	Shall confirm Interslice gap (max 1mm) (slice thickness – position of adjacent slice)	0018,0088
Field-of-view (FOV)	Physicist	Shall select Reconstruction Diameter to cover brain	0018, 1100
Acquisition Plane	Physicist	Shall confirm Axial or oblique plane of acquisition	0020,0037

*Flip Angle may differ depending on dose. See Discussion Section 3.6.1. Sources: [26, 28]

3.7. Subject Selection

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

3.7.1 Discussion

- All subjects considered safe for clinical contrast-enhanced MRI may be considered for a DSC-MRI study. If a patient needs adjustment in GBCA dose beyond the recommended doses listed in this profile due to impaired kidney function, the claims of the profile may not apply.

- The QIBA DSC-MRI committee acknowledges that there are potential risks associated with the use of GBCAs. The default recommendations for intravenous GBCA administration that follow assume there are no known contraindications in a particular patient other than the possibility of an allergic reaction to the GBCA. The committee assumes that local standards for good clinical practices (GCP) will be substituted for the default in cases where there are known risks.

- Recent FDA safety communications http://www.fda.gov/drugs/drugsafety/ucm455386.htm highlight recent concerns regarding the accumulation of gadolinium in the brain. The DSC-MRI committee advises reference to these documents when considering the DSC-MRI clinical trial protocol.

- All subjects considered safe for clinical MRI may be considered for a DSC study. Bioimplants and devices categorized with status “Unsafe” for MRI are considered an absolute contraindication [29-31]. Bioimplants and devices having status “Safe” or “Conditional” for MRI should be evaluated per local MRI safety review procedures to assess relative risk status. Despite having an acceptable risk status, metal-containing bioimplants and devices near the tissue/organ/lesion of interest may introduce artifact and may not be suitable for quantitative DSC. Contraindications unrelated to bioimplants should be considered as well. These include but are not limited to: 1st trimester pregnancy, claustrophobia, age and subject cooperability [32-34].

- Beyond implanted devices, the presence of metal, air or large hemorrhage may result in significant susceptibility artifact that can influence the quantitative value of DSC measurements such that the claims made in this profile may not be achieved in some

patients and clinical situations. For this reason, it is recommended that quantitative DSC-MRI examinations should not be performed shortly after surgical procedures or biopsies of lesions of interest.

- Although the vascular half-life of the GBCAs addressed by the Profile is approximately 90 min, it is strongly recommended that patients should not have received ANY gadolinium-based contrast agent within 24 hours before a DSC-MRI procedure as some residual contrast agent may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation in enhancing tumors is unknown.
- For a specific study/trial, subject scheduling should be appropriately synchronized with the assayed subject condition (e.g., clinical state or therapeutic phase) per study design.

3.8. Subject Handling

This activity describes details of handling imaging subjects that are necessary to reliably meet the Profile Claim.

3.8.1 Discussion

- This technique requires rapid injection of intravenous contrast material, and as such, requires correct placement of a large bore IV catheter, or some other access for rapid injection (central IV line) ideally placed in the right antecubital fossa. An 18 gauge catheter (at least 0.8 mm inner diameter) or larger is recommended. The claims of the profile may not be met if smaller bore catheters are used.
- Injection through a port-a-catheter or permanent indwelling catheter is not recommended. What is critical is that the same injection site and catheter size be used for repeat studies, if at all possible.
- There is significant variability in contrast usage in tumors. The below specifications are based on expert consensus. In general, it is important to use the same contrast administration technique for a given subject through time.
- The injection rate for the **preload** is not considered important for meeting claims of this profile, and thus may be delivered either by hand injection such as by a nurse, or by power injector. The preload should be administered at least 5 minutes before the DSC-MRI scan.

3.8.2 Specification

Parameter	Actor	Requirement
Subject Positioning	Technologist	Shall position the subject consistent with baseline. If baseline positioning is unknown, position the subject Supine if possible, with devices such as positioning wedges placed.
	Technologist	Shall use the prescribed intravenous contrast medium parameters.

Use of intravenous contrast		Shall use the same injection site and catheter size used for baseline study (if applicable)
		Shall use the same total volume of contrast medium administered, the concentration, the injection rate, and volume of saline flush used for baseline study (if applicable)
		Shall document the total volume of contrast medium administered, the concentration, the injection rate, and volume of saline flush used.
Artifact Sources	Technologist	Shall remove or position potential sources of artifacts (including EEG leads and other metal equipment) such that they will not degrade the MRI.

3.9. Image Data Acquisition

This activity describes details of the data acquisition process that are necessary to reliably meet the Profile Claim. It may also include calibrations, performance assessments or validations during acquisition (such as laying the subject on a calibrator or placing a pocket phantom next to the subject) that are necessary to reliably meet the Profile Claim.

3.9.1 Discussion

A power injector is required for DSC-MRI studies. Typical injection rates are 4-5 cc/sec into an antecubital vein but there may be some variation due to clinical circumstances. The injection of contrast media should be immediately followed with a 20 cc ‘saline chaser’ to push the contrast agent into the heart, rather than staying in peripheral veins.

Appendix D tabulates a standardized DSC protocol for phantom evaluation in vendor-specific terms that might also be useful to harmonize patient DSC protocol across platforms.

3.9.2 Specification

Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose (See section 3.6.2 "Protocol Design Specification").	
		For longitudinal studies, shall confirm patient is scanned on the same scanner as previous studies using the same parameter settings	
		Shall collect suitable localizer (scout) images at the start of exam to confirm proper coil placement and selection of appropriate region to image	

		Shall report if any parameters are modified beyond the specifications in section 3.6.	
		Shall confirm for the specified TR, that the acquisition protocol covers as much of the tumor as possible. It is critical to not increase the TR to include more slices.	
Image Header	Technologist	Shall enter on the console any factors that adversely influenced subject positioning or limited their ability to cooperate (e.g., remaining motionless, agitation in subjects with decreased levels of consciousness, subjects with chronic pain syndromes, etc.).	Image Comments (0020,4000) or Patient Comments (0010,4000)
Scan Plane (Image Orientation)	Technologist	Shall set consistent with baseline (if applicable).	Image Orientation Patient (0020,0037)
Acquisition Field of View (FOV)	Technologist	Shall set consistent with baseline (if applicable).	Reconstruction Diameter (0018, 1100)
Number of slices	Technologist	Shall set consistent with baseline (if applicable). Otherwise, shall confirm number of slice locations provides coverage of tumor.	
Use of intravenous contrast injection delay	Technologist	Shall wait pre-specified number of phases (at least 60s) before bolus injection	
Contrast injection rate	Technologist	Shall set contrast injection rate on power injector to be 4 to 5 cc/sec unless clinical circumstances require a different rate.	
Use of intravenous contrast flush	Technologist	Shall inject at least 20cc of saline immediately after the contrast medium bolus through the same line and venous access point	
Image data reconstruction	Technologist	Shall post-process images either in-line if the acquisition device has available image analysis or transfer images to an off-line analysis workstation.	

3.10. 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.

3.10.1 Discussion

Once the images are acquired, the MRI scanner produces a 4D series of images reflecting the intensity profile before, during and after the bolus injection. These images must be processed to compute the 'AUC-TN' and 'K2' [11] images from the 4D series of images.

The basic steps required include determination of the baseline signal intensity (intensity prior to contrast agent appearance), conversion from acquired T2* data to the R2* signal, correctly determining the intensity/shape of intensity curve as the bolus passes through the tissue, and determination of intensity changes after bolus. The latter may not be at the same intensity as the pre-contrast baseline and may also not be a constant intensity due to continued leakage of contrast agent out of the intravascular space and into the tissue. Correctly characterizing this leakage rate is critical to characterizing the correct shape of the curve and because the leakage rate may be biologically useful as a biomarker.

This profile does not specify the exact methods by which software implements the above steps. This is an area of active research, and studies have shown good agreement among software even among those that are proprietary [10]. In general, it is expected that most software will follow the steps described in Section 3.10.2 to calculate AUC and K2. In areas of intact BBB, K2 is approximately 0, but with increasing leakage, K2 may increase or decrease depending on the relative T1 and T2 effects [12] and can also vary depending on the tumor. There are alternative methods to correct for leakage [13] but the claims in the current profile do not cover them. Some software utilizes an arterial input function (AIF) to measure AUC. The effects of AIF selection on AUC remain unclear and is beyond the scope of the profile.

The software used to produce parametric images from the DSC-MRI acquisition is a critical element of the analysis leading to optimal clinical interpretation. The software used is typically proprietary and also is updated on a regular basis. Therefore, it is not possible for this profile to specify the software analysis method, as one cannot know the implementation. We recommend downloading digital reference objects (DROs) from http://qibadscdro.rsna.org/home that have known values, and then applying your preferred software to that data in order to assure valid results. The variation of results based on the DRO for the noise of your equipment should be added to the expected variance of the tissue of interest and RDC for measured change calculated as described in 2.2.

The tissue normalization step for calculating AUC-TN involves selecting an ROI from contralateral NAWM and normalizing the calculated AUC with mean AUC values in the ROI. While various factors such as pulse sequence parameters, leakage correction methods and different post-processing kinetic modeling approaches can result in variability of AUC-TN measurements, the method of semi-quantification using AUC normalization is perhaps the most important [35]. Different methods have been proposed regarding the tumoral and contralateral ROI selection that is subject to wide variation [8, 22, 23, 36, 37]. Despite the fact these methods are user-friendly and feasible in daily practice, a well-known limitation is suboptimal repeatability and reproducibility [23]. An evolving alternative method that could eliminate the need for user-defined normalization is a technique where AUC maps are transformed to a standardized

intensity scale [15, 17, 35]. A main drawback is that this algorithm is currently not widely available across software packages.

Automated approaches have also been used to select ROIs for tissue normalization [38, 39] which can potentially improve reproducibility. In a study by Bell et al [38], the NAWM coefficient of variation across subjects for the radiologist-drawn ROIs was 0.30, whereas it decreased to 0.18 when automated approaches were used [22, 23, 38, 40].

Since many centers may not have access to specialized software that automates the image reconstruction, specifications for manual input to satisfy the claims in this profile are provided in 3.10.2.

3.10.2 SPECIFICATION

Parameter	Actor	Requirement
Pre-Bolus Baseline	Image Analyst	Shall visually identify and document pre-bolus baseline. See Section 4.4. Assessment Procedure: Pre-bolus baseline
Post-Bolus Time-point	Image Analyst	Shall visually identify and document post-bolus baseline. See Section 4.5. Assessment Procedure: Post-bolus Time-point
AUC and K2 maps calculation	Image Analyst	Shall use the same procedural steps for image reconstruction of AUC-TN and K2 map generation for all subjects and time points. See Section 4.6. Assessment Procedure: AUC-TN and K2 maps calculation.
Normalization	Image Analyst	Shall visually select an ROI to be used to normalize AUC values to create AUC-TN maps. Created AUC-TN and ROI shall be saved. See Section 4.7. Assessment Procedure: Normalization.
AUC-TN and K2 maps	Reconstruction Software	Shall be able to calculate and save AUC-TN and K2 maps with either manual input data from the Image Analyst or automated calculation of above parameters. See Section 3.2.
AUC-TN and K2 maps	Image Analyst	Shall use the same software to calculate AUC-TN and K2 maps

3.11. Image QA

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

3.11.1 DISCUSSION

Tumor Size can affect the bias and precision of measurements [41]. Both theoretical considerations and the groundwork projects done by QIBA indicate that for tumors that are small, errors in measurement represent a greater percentage of the measured size. For tumors that are

smaller than the limits defined in this profile, there may not be enough pixels to accurately represent the lesion. For tumors that are extremely large, the limitations on measurement are based less on imaging physics and more on anatomy. Such tumors are likely to cross anatomical boundaries and abut structures that make consistent segmentation difficult.

Tumor Margin Sharpness refers to the clarity with which the boundary of the tumor can be discerned from the surroundings. Conspicuity can directly impact the ability to place ROIs. Conspicuity problems can derive from poor contrast enhancement, from the inherent texture, homogeneity, or structure of the tumor, or from attachment of the tumor to other structures.

Imaging Artifacts: Poor quality data may be grounds to reject individual datasets since artifacts can alter apparent size/shape/volume of tissues of interest thereby confound ROI definition, as well as adversely affect AUC-TN values.

3.11.2 SPECIFICATION

Parameter	Actor	Requirement
Tumor Size	Image Analyst	Shall confirm that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm^3 and 524 cm^3.)
Tumor Margin Conspicuity	Image Analyst	Shall confirm the tumor margins are sufficiently conspicuous to place ROIs.
Patient Motion Artifacts	Image Analyst	Shall confirm the images containing the tumor are free from artifact due to patient motion that are not correctable with motion correcting algorithms. See Section 4.8. Assessment Procedure: Patient Motion
Bolus Profile	Image Analyst	Shall confirm that the bolus profile can be detected in individual voxels compared to signal fluctuation. See Section 4.9. Assessment Procedure: Bolus Profile
Susceptibility Artifacts	Image Analyst	Shall confirm the images containing the tumor are free from artifact due to paramagnetic objects, materials or anatomic positioning. See Section 4.10. Assessment Procedure: Susceptibility Artifacts.
Ghost/parallel imaging artifacts	Image Analyst	Shall confirm tissue of interest is not obscured by discrete ghosts from extraneous signal sources along phase-encode direction
Severe spatial distortion	Image Analyst	Shall confirm tissue of interest are free from severe spatial distortion due to poor magnet homogeneity [42, 43]
AUC-TN Measurability	Image Analyst	Shall disqualify any tumor that might reasonably degrade the consistency and accuracy of AUC-TN measurement. Conversely, if artifacts are present but the analyst is confident and prepared to edit the ROIs to eliminate the impact, then the tumor might be judged conformant to the Profile.
Consistency	Image	Shall confirm that the image processing is similar to baseline in terms

with Baseline	Analyst	of processing parameters
		Shall reprocess the images if baseline image was processed by a different Image Analysis Tool or Analyst.

3.12. Image Distribution

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

3.12.1 Discussion

Archiving and data distribution procedures are recommended so that all analysis results can be recomputed for verification and validation purposes. In addition to saving of all original images in DICOM formats, the following information must be archived along with the image data:

- Image Reconstruction: All information used for Image Reconstruction (see Section 3.10), including any user specified parameters, software version, and ROIs. In addition, all computed maps (AUC-TN, K2), should be saved in DICOM format.
- Registration: Recorded parameters and user inputs required for registration, if used. Time-series image registration may be used to align data spatially over time. Any parameters which control the performance of the registration algorithm (metric used, optimization parameters, user click-points/sub regions used for alignment, etc) must be stored in suitable format. It is preferable to save the registration transform parameters so that identical registration can be reproduced in a multi-center environment.
- Interpretation results: All ROIs where analysis is performed, and statistics are computed should be saved. All interpretation of results should be saved for purposes of verification and audit.
- Secondary DICOM images: If Image Reconstruction relies on other DICOM images, these DICOM images need to also be archived.

3.12.2 Specification

Parameter	Actor	Requirement
DICOM data	Image Analyst	Shall archive raw source DSC-MRI data and any secondary DICOM series used for analysis to be available for verification and validation
AUC-TN and K2	Image Analyst	Shall archive all calculated AUC-TN (and K2) maps as well as all parameters used for the computation (e.g. number of baseline points, integration duration, etc)
Regions of Interest (ROI)	Image Analyst	Shall save all ROIs used for analysis or statistics. See Section 3.10.1 for a discussion of how to place and impact on performance
Registration	Image Analyst	Shall save all parameters used for time-series image registration and registration to anatomical images (if applicable)
Interpretation Results	Image Analyst	Shall save all interpretation of results made by Radiologist for purposes of verification and audit

3.13. 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.

3.13.1 Discussion

Image analysis software typically processes the 4D DSC-MRI data set to produce the AUC-TN and K2 images (see section 3.10). Once these are calculated, it is important to measure tumors in the correct fashion. One of the first steps is that the images must be co-registered to the Post-Contrast T1-weighted image [44]. Commonly, the multiple 3D images in the 4D DSC-MRI dataset are summed together, and that is used to create the transformation matrix that is used to co-register the DSC-MRI to the T1-weighted image.

Once that is done, the contrast-enhancing component is then used for measurement. Depending on the software used for segmentation, in some cases, the user selects a threshold or draws an ROI on the post-contrast T1-weighted image that encompasses the contrast-enhancing portion. Interrater variability can lead to loss of repeatability and reproducibility [22, 23], which might be mitigated by having a single reader. However, for large scale clinical trials this will likely not be feasible. Using software that automatically produce a contrast-enhancing lesion segmentation will compensate for this source of variance. Otherwise one can calculate the interobserver variance and update expected wCV as described in Section 2.2.

Some patients will have multiple lesions. This can present several problems. The first is that it may make it difficult to find a large region of normal appearing white matter, and that should be considered when measurements are reported. Second, the way to report multiple lesions will be context dependent. In some cases, the maximum value may be the most relevant, likely representing the most aggressive lesion. In some cases, mean or minimum values may be more relevant. While multiple lesions are rather uncommon, planning for handling these cases is important.

Once the contrast-enhancing lesion is segmented, the pixels corresponding to that are selected from the AUC-TN images. There are at least 5 accepted methods for reporting values measured within the contrast-enhancing lesion ROI: the mean value, the 95%-ile, the fractional tumor burden, the % of pixels above white matter, and maximum mean value of 4 to 6 ROIs (radius of 1 pixel) [22]. Each of these methods have challenges. Since both tumor and pseudoprogression can show enhancement, one should expect to have pixels of both types in the ROI. In that case, computing the mean value will be the average of the mix of both tissue types and unless one is dominant, the result may be misleading. Mean values may have less clinical value because they may combine areas of therapy effects as well as tumor that both enhance. The same is true for percent above white matter. The 95%-ile method attempts to address this by reporting how much above white matter, the brightest parts are. The challenge with this method is that it is very susceptible to noise—with a low-resolution matrix, an ROI may be only 100 pixels. In that case, the 95%-ile value would depend on just 1 pixel, and thus suffers from high variability. The

maximum mean value of 4 to 6 ROIs method have been shown to have better wCV (0.30) than mean value of a single ROI (wCV=0.43).

3.13.2 Specification

Parameter	Actor	Requirement
ROI Determination	Image Analyst	Shall segment the region of interest (ROI) measured in enhancing brain tumor tissue as identified on the pre-contrast versus post-contrast T1-weighted images and placed by the same analyst as the baseline scan (if applicable)
		Shall segment an ROI volume that is at least a $1cm^2$ area
		Shall use the same software to place ROIs and measure ROI values
Image Registration	Image Analyst	Shall align the AUC-TN image to the T1 post-contrast image and save transformation parameters.
Mean value	Image Analyst	Shall measure the mean of AUC-TN values in the ROI in the tissue of interest
Results Recording	Image Analysis Tool	Shall measure ROI metrics based on manually or automatically delineated ROIs and record results as specified in Section 3.2

3.14. Image Interpretation

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

3.14.1 Discussion

In general, increased values of AUC-TN suggest tumor presence, and increasing values are linked with tumor progression. Conversely, areas of low AUC-TN are associated with dead or dying tissue. In areas of low blood flow or volume, AUC-TN value may not be reliable. The use of specific thresholds for AUC-TN will depend on the metric applied to the ROI.

3.14.2 Specification

Parameter	Actor	Requirement
AUC-TN Change	Radiologist	Shall confirm all steps were performed to interpret if there is a valid change consistent with a reproducibility coefficient within the enhancing tumor or normal brain tissue

4. Assessment Procedures

Most of the requirements described in Section 3 can be assessed for conformance by direct observation, however some of the performance-oriented requirements are assessed using a procedure. When a specific assessment procedure is required or to provide clarity, those procedures are defined in subsections here in Section 4 and the subsection is referenced from the corresponding requirement in Section 3.

4.1. Assessment Procedure: MRI Equipment Specifications and Performance

Conformance with this Profile requires adherence of MRI equipment to U.S. federal regulations or analogous regulations outside of the U.S., MRI equipment performance standards outlined in American Association of Physicists in Medicine and/or by the American College of Radiology* as well as quality control benchmarks established by the scanner manufacturer for the specific model. These assessment procedures include a technical performance evaluation of the MRI scanner by a qualified medical physicist or MRI scientist at least annually. Evaluated parameters include: magnetic field uniformity, patient-handling equipment, gradient and RF subsystems safety, calibration and performance checks. Periodic MR quality control must monitor image uniformity, contrast, spatial resolution, signal-to-noise and artifacts using specific test objects and procedures (e.g., ACR phantom and QA procedure). In addition, preventive maintenance at appropriate regular intervals must be conducted and documented by a qualified service engineer.

Gradient subsystems are *explicitly* calibrated to properly encode 3D space. Performance procedures indicated above assess spatial encoding quality, although DSC-MRI performance requires additional tests detailed in Appendix F. Key quantitative DSC-MRI performance metrics include: susceptibility bias at magnet isocenter, random error within ROI (precision), SNR as a function of contrast agent *concentration*, ΔR2* dependence on *concentration* and spatial position from isocenter. To conform to this Profile, system performance benchmarks for these metrics are provided in Appendix F to ensure negligible contribution of technical errors to the above defined confidence intervals measured for tissue. These benchmarks reflect the baseline MRI equipment performance in clinical and clinical trial settings which produced the data used to support the Claims of this Profile. To establish tighter confidence bounds for AUC-TN metrics, additional technical assessment procedures may be introduced according to specific clinical trial protocol.

*http://www.acr.org/~/media/ACR No Index/Documents/QC Manual/2015_MR_QCManual_Book.pdf.

4.2. Assessment Procedure: Digital Reference Object

The assessor shall verify that the reconstruction software performs within expected limits on the digital reference object. One example Digital Reference Object is available at: http://qibadscdro.rsna.org/home. The assessor shall measure the variance of their software on a DRO, for the signal to noise level measured on their acquisition and use that measure as the $Software_{Variance}$ to update expected RDC (see Section 2.2). It is expected that the software should

produce a linear predicted value given specified values into the DRO. It is recommended that at least 5 values be used to assess for linearity, in the range of expected clinical values such as from 0.5 up to 2.5.

4.2.1. Assessment Procedure: Linearity

The assessor should test for linearity in software performance and that the slope is 1. Linearity is the "ability to provide measured quantity values that are directly proportional to the value of the measurand in the experimental unit" [45]. To assess linearity, the measurements (Y values) are regressed on the true values (X values). If the relationship between Y and X is well explained by a line, then the assumption of linearity is met.

Ideally, to establish linearity with slope equal to 1, five truth values (0.5, 1, 1.5, 2,3) shall be assessed, each with five repetitions. The slope may then be assessed by the following procedure:

For each case, calculate the "measured value" (denoted Y_i), where *i* denotes the *i*-th case. Let X_i denote the true value for the i-th case. Fit an ordinary least squares (OLS) regression of the Y_i's on X_i 's. A quadratic term is first included in the model to rule out non-linear relationships: $Y=\beta_0+\beta_1 X+\beta_2 X^2$. If $|\beta_2|<0.5$, then a linear model should be fit: $Y=\beta o+\beta_1 X$, and R^2 estimated. Let $\widehat{\beta_1}$ denote the estimated slope. Calculate its variance as $\widehat{Var_{\beta_1}} = \left\{\sum_{i=1}^{N}\left(Y_i-\widehat{Y_l}\right)^2/(N-2)\right\}/\sum_{i=1}^{N}(X_i-\bar{X})^2$, where $\widehat{Y_l}$ is the fitted value of Y_i from the regression line and $\bar{X}$ is the mean of the true values. The 95% CI for the slope is $\widehat{\beta_1} \pm t_{\alpha=0.025,(N-2)df}\sqrt{\widehat{Var_{\beta_1}}}$.

The absolute value of the estimate of β_2 should be <0.50 and R-squared (R2) should be >0.90. The 95% CI for the slope should be completely contained in the interval 0.95 to 1.05.

4.2.2. Assessment Procedure: Within Subject Coefficient of Variance (wCV)

The assessor shall calculate the wCV of AUC_TN measured with the software on a DRO using at least 30 simulated tissue specimens ("cases") of AUC_TN simulated within enhancing tumor and in normal tissue, each measured twice. AUC_TN for enhancing tumor is approximately 1.65±0.83 and for healthy cortical tissue 1.51±0.32 [16]. wCV can then be measured as follows:

1. Make measurements on N cases. For each case, measure the AUC_TN at timepoint 1 (Y_{i1}) and at time point 2 (Y_{i2}) where *i* denotes the *i*-th case (*i*=1,2, …N).
2. For each case, calculate the mean and wSD^2:

$$\overline{Y_i} = (Y_{i1}+Y_{i2})/2\,;\, wSD_i^2 = (Y_{i1}-Y_{i2})^2/2$$

3. Estimate wCV:

$$wCV = \sqrt{\sum_{i=1}^{N}\left(wSD_i^2/\overline{Y_i}^2\right)/N}$$

4. Estimate %RDC:

$$\widehat{\%RDC} = 2.77 \times wCV$$

5. Calculate test statistic and assess compliance. The null hypothesis is that the RDC does not satisfy the requirement in the Profile (i.e. the RDC is too large); the alternate hypothesis is that the RDC does satisfy the requirement. The test statistic T is:

$$T = {N \times \left(\widehat{\%RDC^2}\right)} \Big/ {\delta^2}$$

where δ is either 0.31 or 0.40 (depending on whether simulation of AUC_TN as enhancing or normal tissue respectively). Compliance with the claim is shown if $T < \chi^2_{\alpha,N}$, where $\chi^2_{\alpha,N}$ is the α-th percentile of a chi-square distribution with N dfs (for a one-sided test with α type I error rate).

4.3. Assessment Procedure: Scanner Stability

For a given MRI system, stability shall be assessed near isocenter using a quantitative DSC-MRI phantom. This phantom should contain media with known susceptibility properties. A recipe for making such a phantom is provided in Appendix G. Instructions for performing phantom experiments and data analysis can be found:

http://qibawiki.rsna.org/index.php/Perfusion,_Diffusion_and_Flow-MRI_Biomarker_Ctte

Experiments should be performed using both EPI and multi-echo gradient echo sequences. Example protocols in vendor-specific terms that can be used can be found in Appendix F. Intraclass correlation coefficients (ICC) between ΔR2* values measured with echo-planar imaging vs multi-echo gradient echo acquisition in inner vials and outer vials shall be calculated and recorded.

Experiments should be repeated at least 24 hours later in a separate scan session. ICC between ΔR2* values measured with EPI-sequences at this second session compared to prior session shall be calculated and recorded for both inner vials and outer vials.

4.4. Assessment Procedure: Pre-bolus Baseline

The assessor shall identify the last point prior to a definite change in signal intensity due to bolus passage marked by a decrease if viewing raw T2* signal intensity or increase if viewing an R2* image. An example is shown in Figure 4-1. This entails the following steps: 1) drawing a large ROI to cover most of an imaging slice (typically chosen from the middle slice); 2) visualize the mean signal intensity of the curve; 3) if dummy or discarded acquisitions were not used, there shall be a need to specify the number of timepoints to skip before the acquisition reached equilibrium; 4) identify point of maximum drop after the baseline; 5) work backwards from point of minimum signal intensity or maximum drop to determine when the start of the bolus arrived prior to definite change in signal; 6) calculate mean and standard deviation of values between skip and pre-bolus baseline; 7) work backwards from point of maximum drop to where the signal is within 1 standard deviation of the measured mean baseline value; 8) Repeat steps 6 and 7 until the calculated Pre-bolus Baseline stops changing.

4.5. Assessment Procedure: Post-bolus Time-point

The assessor shall visually identify the first time point after the Maximum Drop in signal when

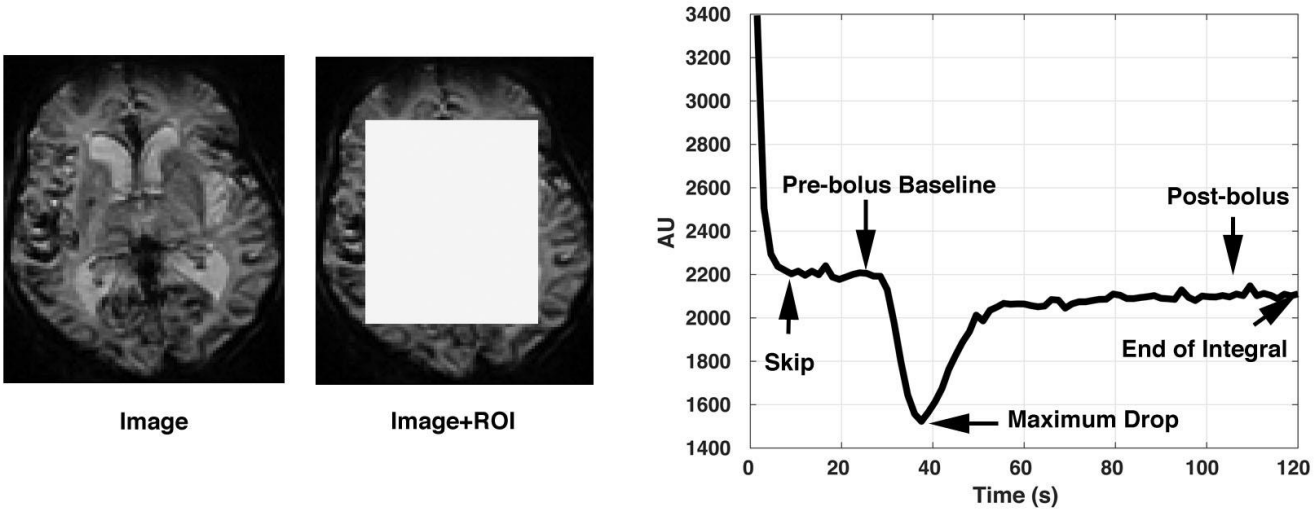

Figure 4-1 Example of time points determination after placement of ROI (large white box) on slice of interest.

the signal intensity plateaus as the Post-Bolus time-point (see Figure 4-1), where the slope of the curve is approximately 0. The signal intensity may also show a continued gradual signal enhancement if there is contrast leakage, or small oscillatory peaks due to recirculation after this timepoint (see Figure 4-2). For either case, the assessor shall select the Post-Bolus time-point to be the first timepoint the signal intensity reaches within 1 standard deviation, σ_b, of the mean Pre-bolus baseline signal, S_b. Others have used a set number of timepoints (e.g. 10) from the last acquired time point [11]. The assessor shall calculate S_b as the mean value of the Pre-bolus baseline timepoints after discarding the skipped timepoints, N_b:

$$S_b = \frac{1}{N_b} \sum_{skip+1}^{Pre-bolus} S(t)$$

and the standard deviation as:

$$\sigma_b = \sqrt{\frac{\sum (S(t) - S_b)^2}{N_b}}$$

to determine which voxels are enhancing.

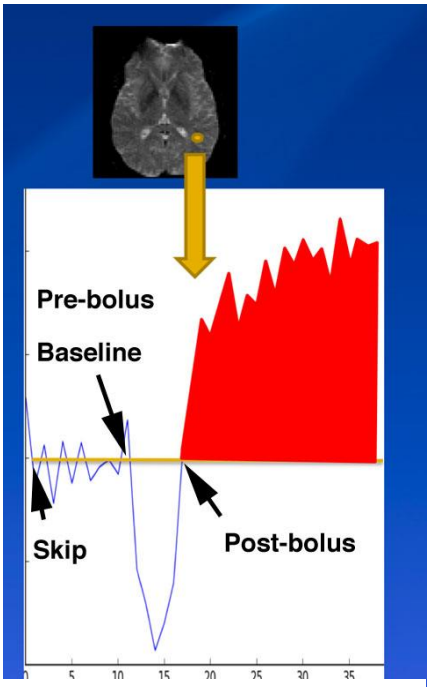

Figure 4-2 Example of post-bolus signal enhancement

It is important to note that the Post-bolus time-point does not determine the end of integration. The assessor shall typically set End-of-integral time point to the last time point of S(t).

4.6. Assessment Procedure: AUC-TN and K2 maps calculation

The assessor shall use the mean Pre-bolus baseline determined in Section 4.4 to convert T_2* signal intensity values, S(t) to an R_2* curve using the following formula: $R_2^*(t) = -1/TE \ln S(t)/S_b$. The assessor shall calculate the uncorrected AUC (uAUC) of the R2*(t) curve by integrating from the end of the Pre-bolus timepoint to End-of-Integral time point. This integration shall be

790 performed using the trapezoidal rule [11, 15].
791
792 The assessor shall calculate the AUC after leakage-correction [11, 13] using the following formula:

793 $$AUC = uAUC + K_2 \int_0^T dt'' \int_0^{t''} \overline{R_2^\star}(t')dt'$$

794 where T is the End-of-Integration time point and K_2 is calculated based on the following formula:

795 $$\widetilde{R_2^\star}(t) = K_1\overline{R_2^\star}(t) - K_2 \int_0^t \overline{R_2^\star}(t')dt'$$

796 where $\overline{R_2^\star}(t)$ is the average of R_2*(t) voxels without enhancement more than 2 standard
797 deviations compared to voxel's baseline intensity, S_b. Voxels with signal intensity enhancement
798 shall be determined using the average of time points between the Post-bolus Time-point to End-
799 of-Integration time-point. K_1 and K_2 shall be calculated using a linear least squares fit of the above
800 equation.

801 4.7. Assessment Procedure: Normalization

802 The assessor shall create an ROI that is approximately 1 cm^3 in the NAWM of the brain opposite
803 from the lesion of interest on the same slice or use automated approaches. In the case that the
804 lesion is in both hemispheres, the ROI may be placed more posteriorly, as far from the lesion as
805 possible. The ROI must NOT include gray matter.

806 4.8. Assessment Procedure: Patient Motion

807 The assessor shall view the images over time at each slice location as a cine sequence to
808 identify patient motion.

809 4.9. Assessment Procedure: Bolus Profile

810 The assessor shall measure the mean signal drop in the whole brain (see Figure 4-1). The assessor
811 shall indicate that the bolus is of poor quality it the Maximum Drop is less than 10% of mean Pre-
812 bolus baseline, S_b [46].

813 4.10. Assessment Procedure: Susceptibility Artifacts

814 The assessor shall identify artifacts as regions of signal dropout or signal increases that is not
815 anatomically consistent. The assessor shall confirm the images containing the tumor are free
816 from artifact due to metal or blood near the surgical site (including small metal filings that may
817 be imperceptible) as well as normal structures like bone and air that can compromise values near
818 the periphery of the brain.

819

5. Conformance

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in Table 1 in Section 3.

To support an activity, the actor shall conform to the requirements (indicated by "shall language") listed in the Specifications table of the activity. Each activity has a dedicated subsection in Section 3. For convenience, the Specification table requirements have been duplicated and regrouped by actor in the form of a checklist in Appendix E.

Some requirements reference a specific assessment procedure in section 4 that shall be used to assess conformance to that requirement.

If a QIBA Conformance Statement is already available for an actor (e.g. your analysis software), you may choose to provide a copy of that statement rather than confirming each of the requirements in that Actors checklist yourself.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement.

Vendors publishing a QIBA Conformance Statement shall provide a set of "Model-specific Parameters" (as shown in Appendix D) describing how their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing.

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Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America [47], Dynamic Susceptibility Contrast Biomarker Committee. The Biomarker Committee is composed of scientists, engineers, and clinicians representing academia, the imaging device manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, government research organizations, professional societies, and regulatory agencies, among others. All work is classified as pre-competitive.

The following individuals have made critical contributions in the development of this Profile:

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Appendix B: Background Information

QIBA Wiki:
http://qibawiki.rsna.org/index.php/Main_Page

QIBA Perfusion, Diffusion, and Flow Biomarker Committee Wiki:
http://qibawiki.rsna.org/index.php/Perfusion,_Diffusion_and_Flow-MRI_Biomarker_Ctte

QIBA DSC Digital Reference Object
https://bit.ly/2QXLo3e

QIBA DSC Phantom Preparation and Software Manual
http://qibawiki.rsna.org/index.php/Perfusion,_Diffusion_and_Flow-MRI_Biomarker_Ctte

Appendix C: Conventions and Definitions

DICOM: Digital Imaging and Communications in Medicine standard for distributing and viewing any kind of medical image regardless of the origin.

Repeatability Coefficient (RC): Represents measurement precision where conditions of the measurement procedure (scanner, acquisition parameters, slice locations, image reconstruction, operator, and analysis) are held constant over a "short interval".

Reproducibility Coefficient (RDC): Similar to RC , the reproducibility coefficient (RDC) may be defined as the least significant difference between two repeated measurements taken under different conditions**.** According to Raunig et al. [48], the repeated measurements can be taken at different sites but also could be designed to measure reproducibility across different scanners, readers/reviewers, algorithms, or software. It is similar to repeatability in the sense that repeated measurements are made on the same subject; however the measurement of reproducibility includes the sum of both the within-subject and the between-condition variances [48].

Linearity: A requirement of a linear relationship between the measured value and the true value over a physiologically-relevant range; the slope of this line should be equal to 1. Ideally, to establish linearity with slope equal to 1, five truth values shall be assessed, each with five repetitions.

Within-subject Coefficient of Variance (wCV): Is often reported for repeatability studies to assess repeatability in test–retest designs. Calculated as seen in the table below:

Steps for Calculating the wCV

1. Calculate the variance and mean for each of N subjects from their replicate measurements.
2. Calculate the wCV^2 for each of the N subjects by dividing their variance by their mean squared.
3. Take the mean of the wCV^2 over the N subjects.
4. Take the square root of the value in step 3 to get an estimate of the wCV.

Appendix D: Model-specific Instructions and Parameters

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

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

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

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

Table D.1 Model-specific Parameters for 3T Acquisition Devices

Acquisition Device	Settings Compatible with Conformance	
	Submitted by: Massachusetts General Hospital	
Siemens	TR	1500 ms (maximum)
	TE	30 ms
	FA	60
	Acceleration	iPAT 2 (no PF)
	Timepoints	At least 120
	Head coil	32 channel
	Scan FoV	220-240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm
	Gap	20%
	Submitted by: Mayo Clinic	
General Electric	TR	1500 ms (maximum)
	TE	30 ms
	FA	60
	Averages	1
	Timepoints	At least 115
	Head coil	32 channel
	FOV Phase	100%
	Acquisition Matrix	128x128
	Slice Thickness	5 mm

	Phase Encoding Direction	A->P
	Bandwidth	1220
	FOV Read	220

Submitted by: Barrow Neurological Institute

Philips	Fast Imaging mode	EPI (single-shot)
	Scan mode	MS (technique = FFE)
	Dynamic study	individual (dyn scans = 100)
	TR	1500 ms (maximum)
	TE	30 ms
	FA	60
	Acceleration (SENSE)	Yes, (P reduction (AP) = 2.29)
	Halfscan	Yes (factor = 0.73)
	Timepoints	At least 120
	Head coil	32 channel
	FOV	220-240
	Acquisition Matrix (M x P)	128x128
	Slice Thickness	5 mm

Submitted by: Canon Medical Systems USA

Canon	TR	1500 ms
	TE	30 ms
	FA	60
	Scan FOV	24 x 24
	Acceleration	2 (SPEEDER)
	Timepoints	At least 120
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128 x 128
	Slice Thickness	5mm skip 1 mm (= 5mm with 1 mm gap)
	Number of slices	19
	Part Fourier	No

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Appendix E: Conformance Checklists

QIBA Checklist:

Dynamic Susceptibility Contrast MRI (DSC-MRI)

INSTRUCTIONS

This Checklist is organized by "Actor" for convenience. If a QIBA Conformance Statement is already available for an actor (e.g. your analysis software), you may choose to provide a copy of that statement rather than confirming each of the requirements in that Actors checklist yourself.

Within an Actor Checklist the requirements are grouped by the corresponding Activity in the QIBA Profile document. If you are unsure about the meaning or intent of a requirement, additional details may be available in the Discussion section of the corresponding Activity in the Profile.

Conforms (Y/N) indicates whether you have performed the requirement and confirmed conformance. When responding **N**, please explain why.

Site Opinion is included during the Technical Confirmation process to allow you to indicate how the requirement relates to your current, preferred practice. When responding **Not Feasible** or **Feasible, will not do** (i.e. not worth it to achieve the Profile Claim), please explain why.

Since several of the requirements mandate the use of specific assessment procedures, those are also included at the end to minimize the need of referring to the Profile document.

Feedback on all aspects of the Profile and associated processes is welcomed.

Site checklist **Page 51**
Acquisition Device checklist **Page 52**
Contrast Injector checklist **Page 54**
Contrast Media checklist **Page 55**
Radiologist checklist **Page 56**
Physicist checklist **Page 57**

Technologist checklist **Page 61**
Image Analyst checklist **Page 64**
Reconstruction Software checklist **Page 68**
Image Analysis Tool checklist **Page 69**

1118

1119 **SITE CHECKLIST**

1120 Name of Site Checked:
1121

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Site Conformance (section 3.0)			
Acquisition Devices		Shall confirm all participating acquisition devices conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast Injector		Shall confirm all participating contrast injectors conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast medium		Shall confirm all participating contrast media conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Reconstruction Software		Shall confirm all participating reconstruction software conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Analysis Tools		Shall confirm all participating image analysis tools conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Radiologists		Shall confirm all participating radiologists conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Physicists		Shall confirm all participating physicists conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Technologists		Shall confirm all participating technologists conform to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Analyst		Shall confirm all participating analysts conforms to this Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

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ACQUISITION DEVICE CHECKLIST

Acquisition Device(s) Checked - Make/Model/Version:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Field Strength		Shall confirm field strength is 3T	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pulse sequence		Shall be capable of acquiring gradient echo data with echo planar imaging	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
MRI Equipment Specifications		Shall meet MRI Equipment Specifications and Performance. See Section 4.1	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Protocol		Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall prepare a protocol conformant with section 3.6.2 "Protocol Design Specification".	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Header		Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column in sections 3.6.2 "Protocol Design Specification".	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record actual timing and triggers in the image header by including the Contrast/Bolus Agent Sequence (0018,0012).	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall support recording in the image header (Image Comments (0020,4000) or Patient Comments (0010,4000)) information entered by the Technologist about the acquisition.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pre-delivery (section 3.3)			
Scanner performance benchmark		Scanner shall meet vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pulse sequence		Shall be qualified by a physicist as capable of acquiring gradient echo data with echo planar	□ Routinely do already □ Feasible, will do

		imaging readout within vendor-established performance benchmark ranges	□ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
Scanner performance benchmark		Shall meet vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

CONTRAST INJECTOR CHECKLIST

Contrast Injector(s) Checked - Make/Model/Version:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Image Data Acquisition		Shall be capable of performing power injection with all the parameters set as specified in section 3.9 “Image Data Acquisition”	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pre-delivery (section 3.3)			
Injector performance benchmark		Injector shall meet vendor-established performance benchmark ranges for the given model and capable of injection rates as specified in section 3.9 “Image Data Acquisition”	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
Contrast Injector Performance Benchmark		Shall meet vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

CONTRAST MEDIA CHECKLIST

Contrast Media/Agent Checked – Brand:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Image Data Acquisition		Shall confirm gadolinium based contrast agent (GBCA) used for study conforms with local and FDA safety guidelines.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

RADIOLOGIST CHECKLIST

Note: The Radiologist is responsible for the protocol parameters, although they may choose to use a protocol provided by the vendor of the acquisition device. The Radiologist is also responsible for ensuring that the protocol has been validated, although the Physicist actor is responsible for performing the validation. Protocol design should be done collaboratively between the physicist and the radiologist with the ultimate responsibility to the radiologist. Some parameters are system dependent and may require special attention from a physicist.

Radiologist(s) Checked:

Parameter	Conforms (Y/N)	Specification	Site Opinion
Staff Qualification (section 3.1)			
Qualification		Shall be a qualified individual with experience in clinical DSC acquisition and interpretation	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Protocol Design (section 3.6)			
Acquisition Protocol		Shall approve protocol developed by the Physicist to meet the requirements of this profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall ensure technologists have been trained on the requirements of this profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Interpretation (section 3.14)			
AUC-TN Change		Shall confirm all steps were performed to interpret if there is a valid change consistent with the reproducibility coefficient within the enhancing tumor or normal brain tissue	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

PHYSICIST CHECKLIST

Note: The role of the Physicist actor may be played by an in-house medical physicist, a physics consultant or other staff (such as vendor service or specialists or technologists) qualified to perform the validations described.

Physicist(s) Checked:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Staff Qualification (section 3.1)			
Qualification		Shall be a qualified individual with experience in establishing protocols on the MRI system and performing quality assurance checks on the MRI equipment.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pre-delivery (section 3.3)			
Scanner performance benchmark		Shall qualify that device meets vendor-established performance benchmark ranges for the given model	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pulse sequence		Shall qualify device as capable of acquiring gradient echo data with single shot echo planar imaging (EPI) readout within vendor-established performance benchmark ranges	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
Scanner performance benchmark		Shall assess scanner performance metrics are within vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall document all hardware/software upgrades.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record the date/time of calibrations as recommended by the vendor.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Scanner Stability		Shall perform periodic system QA using QIBA-NIST DSC phantom (see Appendix F). See Section 4.3. Assessment Procedure: Scanner Stability.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall confirm correlation coefficient measurements between ΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging vs	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

		multi-echo gradient echo acquisition is within 98.4 to 99.3% for both inner and outer vials (See Appendix F.2)	
		Shall confirm correlation coefficient measurements between ΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging across multiple time points is at least 95% for both inner and outer vials. (see Appendix F.2)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Protocol Design (section 3.6)			
Acquisition Protocol		Shall build a protocol that has been previously prepared in consultation with the Radiologist and validated for this purpose.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall confirm protocol is capable of covering area of interest, since most sequences cannot cover the entire brain and achieve sufficient temporal resolution to be clinically useful.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall clearly label and store protocol on MRI system for recall in repeat serial scans of patients.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall track edits to the protocol with version control and archive prior versions	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall report if any parameters are modified beyond the specifications.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Imaging Sequence		Shall confirm imaging sequence is a Gradient Echo acquisition with Echo Planar Imaging Readout	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Total Acquisition Time		Shall confirm series acquisition duration is at least 120s	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Bolus Quality		Shall confirm that the protocol achieves a bolus signal drop at least 10% from baseline when using specified contrast agent and dosage. (See Section 4.4)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pixel Spacing		Shall confirm that the protocol achieves an in-plane resolution between 1.72 and 1.9 mm^2	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

Repetition Time (TR)		Shall confirm Maximum TR = 1500ms	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Matrix		Shall confirm Acquisition Matrix achieves required pixel spacing	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Flip Angle		Shall confirm Flip Angle (60)*	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Field Strength		Shall confirm Field Strength is 3T	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Slice Thickness		Shall confirm Slice Thickness (<= 5mm)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Echo time (TE)		Shall confirm Echo Time (TE)=25-35 ms	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Number of excitations		Shall confirm Number of excitations: 1	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Interslice Gap		Shall confirm Interslice gap (max 1mm) (slice thickness – position of adjacent slice)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Field-of-view (FOV)		Shall select Reconstruction Diameter to cover brain	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Plane		Shall confirm Axial or oblique plane of acquisition	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

*Flip Angle may differ depending on dose. See Discussion Section 3.6.1.

TECHNOLOGIST CHECKLIST

Technologist(s) Checked:

Parameter	Conforms (Y/N)	Specification	Site Opinion
Staff Qualification (section 3.1)			
Qualification		Shall be a qualified individual with experience in clinical DSC acquisition, including use of power injector and administration of contrast material and familiar with good clinical practice	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
Contrast Injector		Shall assess injector performance are within vendor-established performance benchmark ranges for the given model	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall document all hardware/software upgrades.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record the date/time of calibrations for calibrations as recommended by the vendor.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Subject Handling (section 3.8)			
Subject Positioning		Shall position the subject consistent with baseline. If baseline positioning is unknown, position the subject Supine if possible, with devices such as positioning wedges placed.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous contrast		Shall use the prescribed intravenous contrast medium parameters.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall use the same injection site and catheter size used for baseline study (if applicable)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall use the same total volume of contrast medium administered, the concentration, the injection rate, and volume of saline flush used for baseline study (if applicable)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall document the total volume of contrast medium administered, the concentration, the	□ Routinely do already □ Feasible, will do

		injection rate, and volume of saline flush used.		□ Feasible, will not do □ Not feasible
Artifact Sources		Shall remove or position potential sources of artifacts (including EEG leads and other metal equipment) such that they will not degrade the MRI.		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Data Acquisition (section 3.9)				
Acquisition Protocol		Shall select a protocol that has been previously prepared and validated for this purpose (See section 3.6.2 "Protocol Design Specification").		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		For longitudinal studies, shall confirm patient is scanned on the same scanner as previous studies using the same parameter settings.		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall collect suitable localizer (scout) images at the start of exam to confirm proper coil placement and selection of appropriate region to image.		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall report if any parameters are modified beyond the specifications in section 3.6.		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall confirm for the specified TR, that the acquisition protocol covers as much of the tumor as possible. It is critical to not increase the TR to include more slices.		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Header		Shall enter on the console any factors that adversely influenced subject positioning or limited their ability to cooperate (e.g., remaining motionless, agitation in subjects with decreased levels of consciousness, subjects with chronic pain syndromes, etc.).	Image Comments (0020,4000) or Patient Comments (0010,4000	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Scan Plane (Image Orientation)		Shall set consistent with baseline (if applicable).	Image Orientation Patient (0020,0037)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Field of View (FOV)		Shall set consistent with baseline (if applicable).	Reconstruction Diameter (0018, 1100)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Number of		Shall set consistent with baseline (if applicable).		□ Routinely do already

Slices		Otherwise, shall confirm number of slice locations provides coverage of tumor.	□ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous contrast injection delay		Shall wait pre-specified number of phases (at least 60s) before bolus injection	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast injection rate		Shall set contrast injection rate on power injector to be 4 to 5 cc/sec unless clinical circumstances require a different rate.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous contrast flush		Shall inject at least 20cc of saline immediately after the contrast medium bolus through the same line and venous access point	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image data reconstruction		Shall post-process images either in-line if the acquisition device has available image analysis or transfer images to an off-line analysis workstation.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

1174 # IMAGE ANALYST CHECKLIST

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Parameter	Conforms (Y/N)	Specification	Site Opinion
Staff Qualification (section 3.1)			
Qualification		Shall be an individual trained in (1) understanding of key DSC acquisition principles of perfusion-weighted imaging and test procedures to confirm that related DICOM metadata content is maintained along the network chain from Scanner to PACS and analysis workstation, (2) assessing quality of acquired images, (3) placement of regions of interest in appropriate anatomical locations and (4) use of Reconstruction Software and Image Analysis Tools.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
Reconstruction Software Upgrades		Shall document version and time of all software upgrades and shall confirm performance within benchmark on digital reference objects	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Analysis Tool		Shall document all software upgrades	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Data Reconstruction (section 3.10)			
Pre-Bolus Baseline		Shall visually identify and document pre-bolus baseline. See Section 4.4. Assessment Procedure: Pre-bolus baseline	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Post-Bolus Time-point		Shall visually identify and document post-bolus baseline. See Section 4.5. Assessment Procedure: Post-bolus Time-point	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
AUC and K2 maps calculation		Shall use the same procedural steps for image reconstruction of AUC-TN and K2 map generation for all subjects and time points. See Section 4.6. Assessment Procedure: AUC-TN and K2 maps calculation.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Normalization		Shall visually select an ROI to be used to normalize AUC values to create AUC-TN maps. Created AUC-TN and ROI shall be saved. See Section 4.7. Assessment Procedure: Normalization.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

AUC-TN and K2 maps		Shall use the same software to calculate AUC-TN and K2 maps	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image QA (section 3.11			
Tumor Size		Shall confirm that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm^3 and 524 cm^3.)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Tumor Margin Conspicuity		Shall confirm the tumor margins are sufficiently conspicuous to place ROIs.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Patient Motion Artifacts		Shall confirm the images containing the tumor are free from artifact due to patient motion that are not correctable with motion correcting algorithms. See Section 4.8. Assessment Procedure: Patient Motion	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Bolus Profile		Shall confirm that the bolus profile can be detected in individual voxels compared to signal fluctuation. See Section 4.9. Assessment Procedure: Bolus Profile	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Susceptibility Artifacts		Shall confirm the images containing the tumor are free from artifact due to paramagnetic objects, materials or anatomic positioning. See Section 4.10. Assessment Procedure: Susceptibility Artifacts.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Ghost/parallel imaging artifacts		Shall confirm tissue of interest is not obscured by discrete ghosts from extraneous signal sources along phase-encode direction	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Severe spatial distorion		Shall confirm tissue of interest are free from severe spatial distortion due to poor magnet homogeneity	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
AUC-TN Measurability		Shall disqualify any tumor that might reasonably degrade the consistency and accuracy of AUC-TN measurement. Conversely, if artifacts are present but the analyst is confident and prepared to edit the ROIs to eliminate the impact, then the tumor might be judged conformant to the Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Consistency		Shall confirm that the image processing is	□ Routinely do already

with Baseline		similar to baseline in terms of processing parameters.	□ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall reprocess the images if baseline image was processed by a different Image Analysis Tool or Analyst.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Distribution (section 3.12)			
DICOM Data		Shall archive raw source DSC-MRI data and any secondary DICOM series used for analysis to be available for verification and validation	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
AUC-TN and K2		Shall archive all calculated AUC-TN (and K2) maps as well as all parameters used for the computation (e.g. number of baseline points, integration duration, etc)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Regions of Interest (ROI)		Shall save all ROIs used for analysis or statistics. See Section 3.10.1 for a discussion of how to place and impact on performance	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Registration		Shall save all parameters used for time-series image registration and registration to anatomical images (if applicable)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Interpretation Result		Shall save all interpretation of results made by Radiologist for purposes of verification and audit	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Analysis (section 3.13)			
ROI Determination		Shall segment the region of interest (ROI) measured in enhancing brain tumor tissue as identified on the pre-contrast versus post-contrast T1-weighted images and placed by the same analyst as the baseline scan (if applicable)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall segment an ROI volume that is at least a $1cm^2$ area	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall use the same software to place ROIs and measure ROI values	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Registration		Shall align the AUC-TN image to the T1 post-contrast image and save transformation parameters.	□ Routinely do already □ Feasible, will do □ Feasible, will not do

			□ Not feasible
Mean value		Shall measure the mean of AUC-TN values in the ROI in the tissue of interest	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Results Recording		Shall measure ROI metrics based on manually or automatically delineated ROIs and record results as specified in Section 3.2	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

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1178 **RECONSTRUCTION SOFTWARE CHECKLIST**

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1180 Reconstruction Software Checked - Make/Model/Version:
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Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Reading Paradigm		Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall re-process the first time point if it was processed by a different Reconstruction Software or Analyst.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Digital Reference Object		Shall demonstrate linear performance and has expected wCV on digital reference objects. See Section 4.2. Assessment Procedure: Digital Reference Object.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
AUC-TN and K2 maps		Shall record the image analysis tool version.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record AUC-TN and K2 images	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record parameters used for calculation of AUC-TN	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Data Reconstruction (section 3.10)			
AUC-TN and K2 maps calculation		Shall be able to calculate and save AUC-TN and K2 maps with either manual input data from the Image Analyst or automated calculation of above parameters. See Section 3.2.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

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IMAGE ANALYSIS TOOL CHECKLIST

Image Analysis Tool(s) Checked - Make/Model/Version:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Multiple Tumors		Shall allow multiple tumors to be measured.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall either correlate each measured tumor across time points or support the analyst to unambiguously correlate them.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
ROI Result Recording		Shall record the image analysis tool version.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record percentage AUC-TN change relative to baseline for each tumor.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record ROIs used.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record volume of regions of interests used.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
		Shall record the confidence interval of result for each AUC-TN change measurement.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image Analysis (section 3.13)			
Results Recording		Shall measure ROI metrics based on manually or automatically delineated ROIs and record results as specified in Section 3.2	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

Appendix F: Technical System Performance Evaluation using DSC Phantom

Procedures below are for basic assessment of MRI equipment in conformance to the quantitative DSC Profile. Conformance limits for performance metrics are suggested to ensure that technical measurement errors related to the MRI system do not unduly contribute to measurement variance.

F.1. ASSESSMENT PROCEDURE: ΔR2* QUALITIES AT/NEAR ISOCENTER

This activity describes criteria that are necessary for an MRI system to meet the quantitative DSC Profile Claims for evaluating DSC Phantom data.

F.1.1 Discussion

To assess an MRI system for AUC-TN measurement bias and precision, a phantom containing media having known susceptibility properties is required. The phantom should be filled with distilled water for at least 24 hours before expected scan date to allow air bubbles to settle. The assessor must transfer the phantom carefully to the scanner to avoid creation of air bubbles, ideally allowing sufficient time for the sample to achieve thermal equilibrium (>1 hour). Details for preparation and use of the QIBA DSC phantom are available in the QIBA DSC wiki, "DSC Phantom User Manual". This assessment procedure requires the assessor use the DSC-MRI scan parameters in Table F1 for the gradient echo (GRE) EPI acquisition and scan parameters in Table F2 for the Multi-Echo GRE acquisition.

Table F.1 Model-specific Parameters for DSC Gradient Echo Acquisition with Echo Planar Imaging readout

Acquisition Device	Settings Compatible with Conformance	
Siemens	TR	1500 ms
	TE	30 ms
	FA	60
	Acceleration	2 (GRAPPA)
	Timepoints	120
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
	Part Fourier	No
Philips	TR	1500 ms
	TE	30 ms
	FA	60

	Acceleration	2 (SENSE)
	Timepoints	120
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm
	Number of Slices	11
	Part Fourier	Yes (factor = 0.73)
General Electric	TR	1500 ms
	TE	30 ms
	FA	60
	Acceleration	2 (ASSET)
	Timepoints	120
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
	Part Fourier	No
Canon*	TR	1500 ms
	TE	30 ms
	FA	60
	Acceleration	2 (SPEEDER)
	Timepoints	120
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
	Part Fourier	No

*Not included as part of round-robin tests of phantom used to establish limits in Section F.2.

Table F.2 Model-specific Parameters for Multi-Echo GRE Sequence

Acquisition Device	Settings Compatible with Conformance	
Siemens	TR	750 ms
	TE	4/12/20/28/36/44/52/60 ms
	FA	60
	Head coil	32 channel

	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
Philips	TR	1500 ms
	TE	4.36/12.036/19.712/27.388/35.064/42.74/50.416/58.092 ms
	FA	60
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
General Electric	TR	700 ms
	TE	4.332/11.732/19.132/26.532/33.932/41.332/48.732/56.132 ms
	FA	60
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
	Number of Slices	11
	Part Fourier	Only if necessary to achieve TE requirements
Canon	TR	750
	TE	4.6/12.6/20.6/28.6/36.6/44.6/52.6/60.6 ms
	FA	60
	Head coil	32 channel
	Scan FoV	240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1mm
	Number of Slices	10

*Not included as part of round-robin tests of phantom used to establish limits in Section F.2.

The QIBA-NIST DSC phantom is centered at magnet isocenter, the point where the imaging gradients have no effect on the magnetic field strength. The acquisitions should be performed with the middle of the gadolinium filled vials (see Appendix G) aligned along the nasion in the

following order: localizer, DSC EPI, multi-echo GRE acquisitions. The phantom should then be taken out, rotated and localizer, DSC EPI, multi-echo GRE acquired again but new vial aligned along nasion. The phantom should then be rotated one last time and MRI sequences collected in this new rotation.

Software for analyzing the collected data is available on the QIBA DSC Wiki page and directions for use provided in the QIBA DSC wiki, “DSC Phantom User Manual”. For analyses, typically 5 mm radius region-of-interests measured at 3 midplane slices are utilized as described in the software manual. ROI placement is semi-automated.

F.2 Specification

The system is performing to specifications if the following hold true:

F.2.1. The 95% confidence interval for the correlation betweenΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging vs multi-echo gradient echo acquisition is 98.4 to 99.3% for both inner and outer vials.

F.2.2. The 95% confidence interval for the correlation betweenΔR2* values in the QIBA-NIST DSC phantom measured with echo-planar imaging across multiple time points is 95% or higher for both inner and outer vials.

F.2.3. Discussion

The 95% confidence intervals in Section F.2 are based on round-robin testing of the phantom across 6 sites involving 3-vendors (General Electric, Siemens, Philips). The phantom was scanned twice, one day apart using the protocols described in Section F.1 and steps detailed in the QIBA DSC wiki, “DSC Phantom User Manual”.

Appendix G: Recipe for making phantom components for Delta Susceptibility Contrast (DSC) MRI Phantom

G.1. OVERVIEW

The final configuration of the delta/dynamic susceptibility contrast phantom (DSC-MRI phantom) utilizes the same form factor as the DWI phantom shell (HPD) and consists of 13 vials. Ten of which are comprised of 0.01 mM $GdCl_3$, 0.02 mM EDTA and Agarose of different concentrations (Figure G1). Every two of those ten vials contain the same sample. The remaining three samples are reference vials consisting of 0.047 $MnCl_2$ to mimic the magnetic properties of blood without contrast agent. In the phantom shell, the vials are arranged in two rings. The inner and outer ring are both composed of six vials, five of which are filled with agarose concentrations ranging from 0.2% to 3% and a reference vial containing 0.047 mM MnCl2. The central vial is also filled with 0.047 mM $MnCl_2$. There are also three small reference tubes (blue arrows) filled with 1 mM $GdCl_3$ solution.

Figure G1: The open DSC-MRI phantom shell and vial layout (on left). Location of vials in phantom and corresponding concentration of agarose and $GdCl_3$ for each vial (on right).

Vial	Sample (% agarose)
1, 2, 3	0.047 mM $MnCl_2$
4, 5	0.2% Agarose + 0.01 mM $GdCl_3$
6, 7	0.5% Agarose + 0.01 mM $GdCl_3$
8, 9	1.0% Agarose + 0.01 mM $GdCl_3$
10, 11	2.0% Agarose + 0.01 mM $GdCl_3$
12, 13	3.0% Agarose + 0.01 mM $GdCl_3$

G.2. MATERIALS

- A microwave safe beaker or flask
- Microwave oven
- Agarose (A9539 SIGMA, BioReagent, for molecular biology)

We used: https://www.sigmaaldrich.com/catalog/product/sigma/a9539?lang=en&region=US

- Gadolinium(III) chloride hexahydrate (G7532 ALDRICH, $GdCl_3$)

We used: https://www.sigmaaldrich.com/catalog/product/aldrich/g7532?lang=en&region=USA

- Ethylenediaminetetraacetic acid (431788 ALDRICH, EDTA)

We used: https://www.sigmaaldrich.com/catalog/product/aldrich/431788?lang=en&region=US

- Manganese (II) chloride tetrahydrate (203734 SIGMA-ALDRICH, MnCl2)
  We used:
  https://www.sigmaaldrich.com/catalog/product/sigald/203734?lang=en&region=US
- Precision balance
- Thermometer
  We used https://www.thermoworks.com/Reference-Thermapen
- Plastic Wrap
- Thick gloves or potholders
- HPD vials, or any other vials used in the phantom
  Vials we used: https://www.amazon.com/Azlon-301705-0001-Plastic-Narrow-Sample/dp/B0046A8YTY?ie=UTF8&redirect=true&ref_=s9_simh_gw_p328_d11_i1

G.3. GEL PREPARATION

G.3.1. Preparing chelated $GdCl_3$ master solution

For 100 ml of 1 mM of $GdCl_3$ chelated with 2 mM of EDTA*

Master solution	$GdCl_3$	EDTA
MW (g/mol)	371.7	292.24
Volume (L)	0.1	0.1
Molarity mol/L	0.001	0.002
g	0.03717	0.058448

For 2 HPD vials (70 ml of the gel)

Percentage of the gel	Agarose (g)	$GdCl_3$ master +EDTA (ml)
0.20%	0.14	0.7
0.50%	0.35	0.7
1%	0.7	0.7
2%	1.4	0.7
3%	2.1	0.7

The last 3 samples (90 ml in total) contain 0.047 mM $MnCl_2$ as a reference solution, comprised of 0.008371593 g of $MnCl_2$ in diH_2O.

G.3.2. Melting agarose using a Microwave Oven

1. Use a beaker or flask that is 2-4x the volume you are making. Add 0.7 ml of $GdGl_3$ master solution and fill with diH_2O to approximately 50 ml.
NOTE: Volume of 2 vials is 60 ml. To make sure one has enough gel to avoid forming bubbles while filling one needs to prepare 70 ml of the gel for 2 vials.

2. Weigh out the agarose and add it to the flask. Fill to 70 ml with degassed diH_2O.

3. To hydrate, swirl the beaker and suspend the agarose in solution. Alternatively, you can use a stir bar and stirring plate to rapidly mix the solution. Remember to remove the stir bar before microwaving!
    a. Let the agarose hydrate a minute or two before proceeding, this allows for a quicker dissolution and can reduce foaming. Let higher percentage gels (>1.5%) hydrate longer than lower percentage gels.

4. Cover the mouth of the beaker with plastic wrap and make a small hole in the top to allow the solution to vent.

5. Weigh the beaker and record the starting weight.

6. Heat the beaker in the microwave for 15-30 second intervals until the solution begins to boil. Stir after each heating interval.

7. Remove the beaker from the microwave and very gently swirl.

WARNING: THE MICROWAVED SOLUTION CAN BECOME SUPERHEATED AND FOAM OVER QUICKLY WHEN AGITATED. USE CAUTION AND ALWAYS WEAR APPROPRIATE PROTECTION.

8. If solid agarose or gel pieces remain, return the flask to the microwave and continue heating in 15 second intervals until all product is in solution. This may take a few minutes depending on the strength of your microwave and the gel concentration you are making.

9. Once the gel is fully melted (at around 95 °C), reweigh the solution and add diH_20 to the beaker to reach the starting weight. Mix thoroughly.

10. Let the solution sit for several minutes to provide time for the bubbles to go out of it. Then mix deliberately, but carefully, while swirling along the sides and bottom of the beaker. Once there are no bubbles present in the solution, you may pour the gel into the HPD vials. NOTE: The heating intervals depend on the volume of gel heated. Adjust accordingly.

11. Rinse the vials with IPA (isopropyl alcohol) prior to filling and let them dry to ensure that the inner surface is clean. The gel will stick to it better. Fill up ¾ of the vials first, then shake out bubbles that formed while pouring. When filling the last ¼ of vial, tilt it to avoid bubbles that get stuck on the upper edge. You can intentionally leave one big bubble on the edge and spin it around the upper edges to gather all small bubbles confined there. Then, you can then easily shake the big bubble out. Fill the rest of the vials to the very top leaving a convex meniscus on the top of it. Pour some of the gel into vial caps also. Once the gel cools down and gets stiffer, close the vials.