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

Stage: A. Initial Draft

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

16 **Table of Contents**

Change Log:

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

Date	Sections Affected	Summary of Change
2015.10.10	All	Major cleanup based on comments resolved in the Process Cmte. Also had to remove a few hundred extraneous paragraph styles.
2015.10.21	All	Approved by Process Cmte
2015.11.04	2 (Claims) 3 (Requirements)	Incorporating the more refined form of the claim language and referenced a separate claim template. Added Voxel Noise requirement to show example of the linkage between the requirement and the assessment procedure.
2015.12.16		Minor changes to remove reference to "qualitative" measurements, fix reference to guidance and clean some formatting.
2016.01.06	1, 3.8.1	Rewording to avoid the term "accuracy".
2017.05.12	1, 2, 3, 5, AppE	Explain profile stages. Update Claim examples to match guidance. Add Clinical Interpretation subsection to separate that topic from general discussion of the claims. Add Discriminatory text example. Add Section 3 activity requirement subsections with examples for Site Conformance, Staff Qualification, Product Validation, Protocol Design (some of these are to disentangle activities that happen at different times, i.e. product validation, protocol design and patient image acquisition, that were previously entangled Add Conformance section 5. Add Checklist appendix with requirements regrouped by actor.
2016.05.31	All	First draft created by an all-day teleconference by members of the DSC-TF
2016.06.07	All	Edits to ensure style conformance with template
2017.07.18	All	Removed K2 claims
2017.09.18	All	Updated to QIBA Profile Template 2017-07-26
2018.10.09	All	Added in claims from from Prah
2019.12.01	2	Added in claims from Kourosh, added in additional information to address reproducibility questions from NO.
2020.01.08	All	Removed “Scanner Operator” and replaced with “Technologist”or “Physicist” actor
2020.01.14	2,4	Corrected reproducibility questions. Added assessments for linearity and wCV using DRO

Open Issues:

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

Closed Issues:

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

Q. Is this template open to further revisions? A. Yes. This is an iterative process by nature. Submit issues and new suggestions/ideas to the QIBA Process Cmte.
Q. Is there a phantom that can be used to validate DSC measurements? A. There is no phantom available today that can be used to validate DSC measurements. There are discussions about creating a phantom that includes flow and which may prove useful in validating measurements, but at this time, no phantom is available.
Q. Shouldn't Contrast Agent actor be technologist or medical physicist? A.No, we consider contrast medium a separate actor since it has its own checklist
Q. Consolidate Actors (currently 7)? o **Perhaps combine into image analyst or scanner operator, as appropriate** o **Adjust checklists accordingly** · **Proposed actor consolidation:** o **Site** o **Acquisition Device** o **Reconstruction Software** o **Image Analysis Tools** o **Scanner Operator** o **Image Analyst**

○ **Power Injector?** **A. No, each checklist is separate. An individual can serve the role of multiple actors.**
Q. Every specification should have a matching partner in checklists **A.Done**
Q. Just saw this published(cant get full text yet): **https://www.ejcancer.com/article/S0959-8049(19)30203-5/fulltext** **A.Incorporated into reproducibility claims**
Q. Table 1 empty, needs fields to be filled ● **Inter-rater Reliability of ROI placement and effect on reproducibility of results** **A. Added Table to end of Discussion**

106
107
108
109

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 Initial 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 tissue-normalized first-pass area-under-the contrast-agent concentration curve (AUC-TN) which is often used as a biomarker of disease progression or response to treatment. It places requirements on Acquisition Devices, Technologists, Physicists, Radiologists, Image Analysts, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis.

The requirements are focused on achieving 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.

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.

DISCLAIMER: Technical performance of the MRI system can be assessed using a phantom having known susceptibility properties, such as the QIBA Delta Susceptibility Contrast phantom.

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

Quantifying the within tumor perfusion and measuring tumor longitudinal changes within subjects; i.e. evaluating progression or response with image processing of Dynamic Susceptibility Contrast perfusion MRI (hereafter referred to as DSC MRI) acquired at different time points. We will focus on measuring an imaging biomarker of tissue perfusion, the Area Under the contrast agent Curve-Tissue Normalized (AUC-TN), which has been normalized to reference tissue values.

DSC MRI is heavily used in clinical practice for the assessment of primary brain tumors, and the primary measure used is referred to as the relative Cerebral Blood Volume (rCBV). The rCBV is thought to reflect the blood volume within a region of tumor. While rCBV may indeed be the underlying marker, we will focus first on measuring the imaging biomarker, which is the Area Under the Curve-Tissue Normalized (AUC-TN), which has been normalized to normal-appearing white matter (NAWM), usually in the opposite hemisphere. We will investigate options for which tissue to use for normalization, and will more precisely describe that as part of this effort.

We note here, that we are not claiming to be measuring the cerebral blood volume. We are claiming a biomarker that is thought to be related to CBV, and therefore has merit as a potential biomarker for diseases or treatments that impact CBV. As such, we will not attempt to document CBV, but only to characterize the performance of DSC sequences to estimate the change in signal intensity with injection of a paramagnetic contrast material.

A second use for DSC MRI is to estimate the 'leakiness' of vessels within a tumor. This estimate is called 'K2' and is thought to be proportional to the slope of the line after the initial pass of contrast. Normal brain has an intact blood brain barrier (BBB), and thus should have a slope of 0. In areas of BBB disruption, DSC MRI will typically demonstrate slow increase in signal as contrast accumulates in the tissue, resulting in a slow change in the 'baseline' intensity. The K2 should be proportional to the leakage rate. We note that 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 is limited and therefore K2 claims will not be presented in the current profile.

In the setting of antiangiogenic therapy of high-grade glioma patients, it can be difficult to differentiate decreased contrast-enhancement due to antitumor effect from normalization of the BBB that is referred to as "pseudoresponse" (apparent response to therapy with the tumor actually continues to grow) [1]. Pseudoresponse could be a factor in the discordance seen between high response rates and prolonged progression free survival (PFS) without increased overall survival (OS) in GBM[2]. DSC MRI may provide the ability to assess true tumor viability after therapy, allowing differentiation of pseudoprogression (PsP) (apparent progression when tumor is actually responding to therapy) and pseudoresponse [3-5]. PsP refers to a temporary increase in contrast-enhancement that can appear identical to progressive disease (PD) high-grade glioma patients using conventional MRI [1]. It occurs in the first 6 months after

temozolomide chemoradiation and is associated with O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation as well as better survival [6, 7] Distinguishing PsP from progressive [7] diseases (PD) is critical to change therapies in the case of PD or mistakenly assuming treatment failure in the case of PsP. The biological mechanisms underlying PsP are still unclear, however, the increased contrast enhancement is thought to be due to a mix of tumor and necrosis with increased microvascular permeability and proinflammatory mediators and cytokines [8].

On the spectrum of increased post-therapy enhancement is radiation necrosis (RN). RN necrosis can appear like PsP, although it appears months to years after radiation, much later than PsP. rCBV from DSC-MRI appears to be able to distinguish RN from PD, where PD has significantly higher rCBV, although thresholds vary by study [9, 10]. On the other hand, distinguishing PsP from PD with rCBV is more difficult. Some studies have been able to differentiate them, with PD having higher rCBV - again with different thresholds [3, 11, 12]. However, not all studies have not found a difference between PD and PsP [13, 14]. It could be that the mixture of tumor and necrosis may make mean rCBV a suboptimal metric for making this determination; perhaps longitudinal rCBV trends or histogram analysis aimed at capturing temporal or spatial variations might be more predictive of lesion destiny [13, 14]. There is also some preliminary evidence to suggest that methods like fractional tumor volume utilizing a single-voxel rCBV threshold hold of 1.0 might also hold promise in this context [8, 9].

Some work has shown that DSC-MRI might predict outcome following anti-angiogenic therapy where temporal changes in rCBV might predict OS [15, 16]. Furthermore, baseline rCBV might also be predictive of OS in patients treated with bevacizumab. rCBV might also be useful to distinguish nonenhancing tumor from vasogenic edema seen on FLAIR imaging [17-19]. DSC-MRI may be useful for classifying tumor grade [20]. Patel, et al. [21] found that thresholds separating viable tumor from treatment changes demonstrate relatively good accuracy in individual studies. Finally, AUC-TN 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[22].

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 $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times 0.31)^2 + (Y_2 \times 0.31)^2}$ [1, 23], where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

This claim holds when:

- **DSC-MRI is acquired on the same scanner equipment, using the same protocol at both timepoints**
- **The region of interest (ROI) is measured in enhancing brain tumor tissue as identified on the pre-contrast versus post-contrast T1-weighted images and placed by the same analyst**
    - **The ROI volume is at least a 1cm^2 area and less than 100cm^2 (1000cm^3 if volumetric)**

- **The same software is used to calculated AUC-TN**

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 $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times 0.40)^2 + (Y_2 \times 0.40)^2}$, where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

This claim holds when:

- **DSC MRI is acquired on the same scanner equipment, using the same protocol at both timepoints**
- **The region of interest is drawn on normal appearing brain tissue contralateral to enhancing brain tissue and placed by the same analyst**
  - **The ROI volume is at least a 1cm^2 area and less than 100cm^2 (1000cm^3 if volumetric)**
- **The same software is used to calculated AUC-TN**

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*. Similar interpretation can be applied to the 95% confidence interval in measurement of AUC-TN change in *normal tissue* [23]. 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 3T, on the same scanner, using same software, same analyst and with careful attention to repeating similar image planes and technique.

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 $100 \times (3.45 - 1.0) \pm 1.96 \times \sqrt{(1.0 \times 0.31)^2 + (3.45 \times 0.31)^2}$=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 $100 \times (3.45 - 1.0) \pm 1.96 \times \sqrt{(1.0 \times 0.40)^2 + (3.45 \times 0.40)^2}$=– 37% to 527% increase in AUC-TN again noting the assumption of a linear relationship and slope

of 1.0.

QIBA Profiles do not make claims of the clinical performance of a profiled measurement, such as clinically distinguishing groups of subjects (those with vs. without a particular disease, or those at different stages of disease) based on specific values (i.e., cut-points) of the measured biomarker. These boundaries can be thought of as "error bars" or "noise" around the measurement of AUC-TN change in tissue. Note that this does not address the biological significance of the change, just the confidence interval of the measured change. We reiterate here that the boundaries change assume the images are obtained at 3T, on the same scanner, using the same software, same analyst and with careful attention to repeating similar image planes and technique.

2.2 Discussion

The claims are based on estimates of perfusion AUC-TN coefficient of variation (wCV) for regions of interests 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 [23]. 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 [23, 24] based on automated standardization and normalization methods [25, 26] 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 [27]. Differences in performance compared to the above patient studies [23, 24] 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[28], wCV was 0.18, but results might have been confounded by multiple injections [29] 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 studies with test-retest DSC due to the risk of nephrogenic systemic fibrosis. In fact, the Jafari-Khouzani and Prah papers are derived from the same patient cohort, but because of differences in processing have different wCV. Furthermore, because DSC requires the injection of a contrast agent, 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 images to assure that all increased signal on post-contrast imaging is due to contrast enhancement. Once that has been determined, a region of interest (ROI) should be drawn to include at least a $1cm^2$ area and up to $100cm^2$ ($1000cm^3$ if volumetric).

QIBA Profiles do not make claims of the clinical performance of a profiled measurement, such as clinically distinguishing groups of subjects (those with vs. without a particular disease, or those at different stages of disease) based on specific values (i.e., cut-points) of the measured biomarker. These boundaries can be thought of as "error bars" or "noise" around the measurement of AUC-TN change in tissue. Note that this does not address the biological significance of the change, just the confidence interval of the measured change. We reiterate here that the boundaries change assumes the images are obtained at 3T, on the same scanner, using the same software, same analyst and with careful attention to repeating similar image planes and technique.

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

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 method variance is defined as endemic to the technique of measuring AUC of the DSC 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 [25] while others use automated NAWM selection [26] for standardization - both approaches decrease wCV [23, 24]. Expected variance in measurements of NAWM ROI (using 1.8 mm radius) was found to be approximately 20% [30]. Software variance could be measured using digital reference objects. ROI variance is variance related to interrater placement of ROI 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 [30]. Interobserver variance when using manual NAWM and tumor ROI was reported to be approximately 30% for maximum AUC-TN method [31]. 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
Acquisition Device	Product Validation	3.2.
	Pre-delivery	3.3.
	Installation	3.4
	Periodic QA	3.5.
Contrast Injector	Product Validation	3.2
	Pre-delivery	3.3
	Installation	3.4
	Periodic QA	3.5
Contrast Medium	Product Validation	3.2
	Installation	3.4
Technologist	Staff Qualification	3.1.
	Subject Handling	3.8.
	Image Data Acquisition	3.9.
	Image Data Reconstruction	3.10.
Radiologist	Staff Qualification	3.1
	Image QA	3.11
Physicist	Staff Qualification	3.1

	Periodic QA	3.5
Site	Site Conformance	3.0
Image Analyst	Staff Qualification	3.1
	Image Data Reconstruction	3.10
	Image Analysis	3.10
	Image QA	3.11
Image Analysis Tool	Product Validation	3.2
	Image Analysis	3.10

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a "shall" 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:

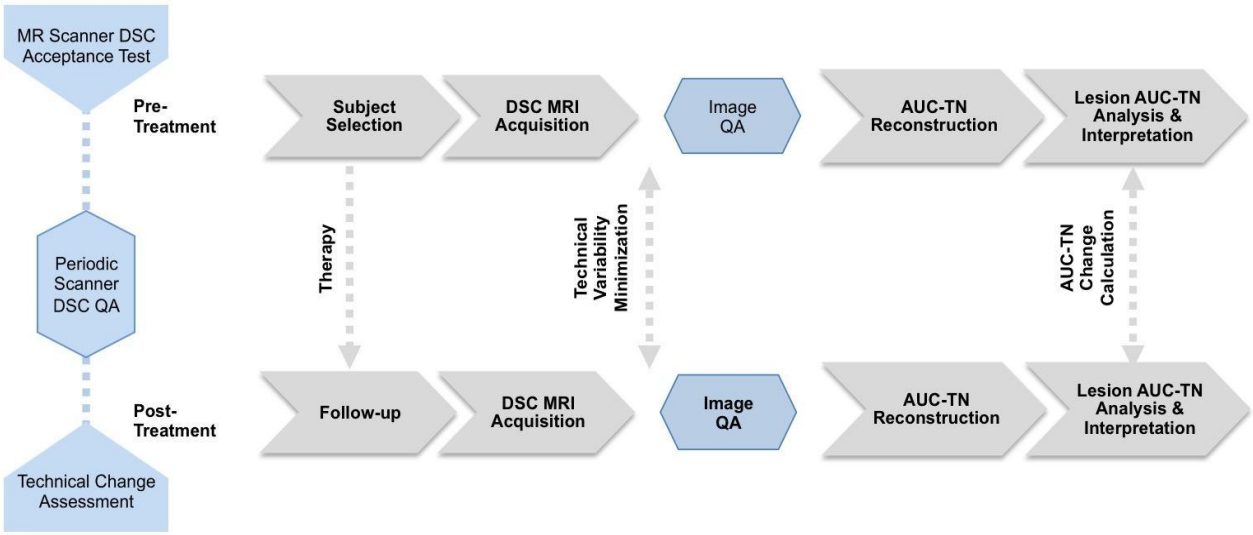

Figure 1: Dynamic Susceptibility Contrast MRI (DSC-MRI)- Activity Sequence

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.
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 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
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" and validate that protocol as described in section 3.6.2.
SiteImage 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".
Image Header	Acquisition Device	Shall record actual timing and triggers in the image header by including the Contrast/Bolus Agent Sequence (0018,0012).
Image Header	Acquisition Device	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”
Image Data Acquisition	Contrast Media	Shall confirm gadolinium based contrast agent (GBCA) used for study conforms with local and FDA safety guidelines.
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.
Reading Paradigm	Image Analysis Tool	● 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 Image Analysis Tool or Analyst.
Digital Reference Object	Image Analysis Tool	Shall be confirmed that performance is linear and has expected wCV on digital reference objects.

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 regions of interests used. • Shall record volume of regions of interests uses. • Shall record the confidence interval of result for each AUC-TN change measurement.

3.3. Pre-delivery

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

3.3.1 Discussion

DSC-MRI Acquisition Scanner

DSC-MRI studies as developed in this QIBA Profile address imaging with a 3.0 T MR scanner. It is beneficial to identify and qualify more than one MRI scanner with the same magnet strength at the site, if such are available for study use. This will ensure that if the primary MRI scanner is temporarily unavailable, the DSC-MRI study may proceed on a secondary scanner.

3.3.2 Specification

Parameter	Actor	Requirement
System performance benchmark	Acquisition Device	System shall perform within vendor-established performance benchmark ranges for the given model
Accreditation of site	Acquisition Device	Shall be qualified by a physicist as defined by appropriate accrediting bodies
Pulse sequence	Acquisition Device	Shall be qualified by a physicist as capable of acquiring gradient echo data with echo planar imaging readout within vendor-established performance benchmark ranges
System performance benchmark	Contrast Injector	System shall perform within vendor-established performance benchmark ranges for the given model and capable of injection rates as specified in section 3.9 “Image Data Acquisition”
Accreditation of site	Contrast Injector	Shall be qualified by a medical physicist as defined by appropriate accrediting bodies

3.4. Installation

This activity describes calibrations, phantom imaging, performance assessments or validations following installation of equipment at the site that are necessary to reliably meet the Profile Claim.

3.4.1 Discussion

Acquisition Device

Installation of acquisition device shall be done by a trained field service engineer as per manufacturers' specifications and supervised by a local MR physicist. MR scanners should be identified based on their manufacturer, model, and machine name. Hardware specifications (maximum gradient strength, slew rate, etc.) should be documented. Software versions in place at the time of trial initiation, and at all upgrades should be documented as well. Local receive coils to be used should be documented.

Contrast Injector

A power injector is required for DSC-MRI studies. It needs to be properly serviced and calibrated. Power injector models should be noted, including date of most recent calibration. Typical injection rates are 4-5 cc / second 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 20cc 'saline chaser' to push the contrast agent into the heart, rather than staying in peripheral veins.

3.4.2 Specification

Parameter	Actor	Requirement
System Performance Assessments	Physicist	System shall perform within vendor-established performance benchmark ranges for the given model after installation.
		Shall document and record hardware specifications, software version and calibration dates
Phantom Acquisition	Acquisition Device	System shall perform within specification on QIBA-NIST DSC phantom (Appendix)
Contrast Injector Performance Assessments	Physicist	• Shall ensure that system shall perform within vendor-established performance benchmark ranges for the given model.
		• Shall document and record hardware specifications, software version and calibration dates

3.5. Periodic QA

This activity describes calibrations, phantom imaging, performance assessments or validations

465 performed periodically at the site, but not directly associated with a specific subject, that are
466 necessary to reliably meet the Profile Claim.

467 ### 3.5.1 Discussion

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

471 The QIBA NIST DSC-MRI phantom, or a similar multi-compartment phantom with range of
472 susceptibility (T2*) values appropriate for the DSC-MRI study to be performed, should be used if
473 the Profile Claim given above is to be assured. A recipe for creating such a phantom is provided
474 in Appendix G. Data should be acquired from the phantom using the same DSC-MRI acquisitions
475 that will be used in the proposed clinical application or clinical research protocol (see Section 6).

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

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

482 All scanner software version updates and changes must be documented.
483

484 ### 3.5.2 Specification

Parameter	Actor	Requirement
System performance benchmark	Physicist	• Shall assess system 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 for auditing.
Contrast Injector	Physicist	• 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 for auditing.
Scanner OperatorStability	Physicist	• Shall perform periodic system QA using QIBA-NIST DSC phantom, including assessment of temporal SNR and linearity (see Appendix). See 4.4 Assessment Procedure.
Image Analysis Tool	Image Analyst	• Shall document all software upgrades and shall confirm performance within benchmark on digital reference objects

485

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 same acquisition methods repeated on the same scanner using parameter settings tabulated below are necessary to reliably meet the Profile Claim. DSC scan protocols shall be built by the MR technologist and/or MR physicist with approval by the radiologist clearly labeled and stored on the MRI system for recall in repeatable serial scan of patients. Version control of edits to the protocol should be tracked with prior versions archived.

- The acquisition protocol shall cover the entire area of interest, and that can be a challenge, since most sequences today cannot cover the entire brain and get sufficient temporal resolution to be clinically useful.

- While there is a range of parameters that can produce acceptable DSC MRI data, it is very important to use the same values for longitudinal studies. 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 reproducibility and so GRE sequences are preferred. 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 [32].

- Clinical recommendations [33] for DSC do not recommend 90 degree FA, that was used to achieve our Profile claims [23] due to high T1 sensitivity that can contaminate the signal in conditions of disrupted BBB. Instead, the recommendations suggested FA of 60 to 70 degrees, 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 [32]:

FA	TE	TR	Preload Dose	Bolus Dose	Simulated

	(ms)	(s)	(fraction of standard dose)	(fraction of standard dose)	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 results using simulation approach as described by Semmineh et al [32]. 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, with the assumption that we will be able to meet our claims. If patients are unable to tolerate 2 full doses, then using a low FA, will likely have similar variability as that of our claims. Prospective test-retest studies at low FA will be needed to properly assess the RDC.

3.6.2 SPECIFICATION

Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Physicist	● Shall build a protocol that has been previously prepared and validated for this purpose. ● Shall report if any parameters are modified beyond the specifications below.	N/A
Acquisition Protocol	Radiologist	Shall approve protocol developed by Physicist to meet the requirements of this profile	N/A
Acquisition Protocol	Radiologist	Shall ensure technologists have been trained on the requirements of this profile.	N/A
Imaging sequence	Physicist	Shall confirm imaging sequence is a Gradient Echo acquisition with Echo Planar Imaging Readout	N/A
Number of slice locations	Physicist	Shall confirm number of slice locations provides optimal coverage of tumor	N/A
Total Acquisition TIme	Physicist	Shall confirm series acquisition duration is at least 180s.	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.	N/A
Pixel Spacing	Physicist	Shall confirm that in-plane resolution is between 1.72 and 1.9 mm2	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)=30 ms	0018,0081
Number of excitations	Physicist	Shall confirm Number of excitations: 1	0018,0083
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
Pixel Spacing	Physicist	Shall confirm that in-plane resolution is between 1.72 and 1.9 mm2	0028,0030

Sources: [32, 34]

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 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 gadolinium-based contrast media. The default recommendations for

intravenous contrast that follow assume there are no known contraindications in a particular patient other than the possibility of an allergic reaction to the gadolinium contrast agent. 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.

- Although the vascular half-life of the gadolinium-based contrast agents 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.

- 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 [35-37]. Bioimplants and devices having status "Safe" or "Conditional" for MRI shall 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 [38-40].

- 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.

- For specific study/trial, subject scan timing should be appropriately synchronized with the assayed subject condition (e.g., clinical state or therapeutic phase) per study design.

3.7.2 SPECIFICATION

Parameter	Actor	Requirement
Subject	Technologist	Shall confirm subject has no contraindication to MRI
Acquisition Protocol	Radiologist	Shall prescribe a protocol that is consistent with baseline acquisition (if applicable).
Use of	Technologist	Shall confirm subject has venous access that allows bolus injection

intravenous contrast		Shall confirm subject has no contraindication to gadolinium-based contrast agents (i.e. history of allergic reaction, poor renal output).

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.

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.
Use of intravenous contrast	Technologist	• Shall use the prescribed intravenous contrast medium parameters. • 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

- Image acquisition shall be based upon a protocol that has been previously prepared and validated for this purpose (See section 3.6.2 "Protocol Design Specification").
- Appendix tabulates a standardized DSC phantom scanning protocol in vendor-specific terms that may be useful to harmonize patient DSC protocol across platforms
- Suitable localizer (scout) images must be collected at the start of exam and used to confirm proper coil placement as well as selection of appropriate region to image.
- The acquisition protocol shall cover as much of the brain as possible for the specified TR.
- Longitudinal studies should be acquired on the same scanner using the same parameter settings to reliably meet the Profile Claim.
- DSC-MRI requires use of a power injector, which typically is remotely controlled; the injection must be started at least 60 s after the image acquisition begins.
- Once images are acquired, they shall be post-processed, either in-line if the acquisition device has available image analysis or images transferred to an off-line analysis workstation (see section 3.10).

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"). • Shall report if any parameters are modified beyond the specifications in section 3.6.	
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,	(0020,4000) or (0010,4000)

		subjects with chronic pain syndromes, etc.).	
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).	
Use of intravenous contrast injection delay	Technologist	Shall wait pre-specified number of phases (at least 60s) before bolus injection	
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	

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 will produce 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' images from the 4D series of images.

The basic steps required include determination of the baseline signal intensity (intensity prior to contrast appearance), conversion from acquired intensity to the R2* signal, correctly determining the intensity/shape of intensity curve as the bolus passes through the tissue, and determination of the intensity 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 material out of the intravascular space and into the tissue. Correctly characterizing this leakage rate is critical to characterizing the correct shape of the curve (because leakage starts during this phase) and because the slope of this 'baseline' may be biologically useful as a biomarker.

The AUC-TN image is computed by integrating the area under the R2* curve for the points from the Pre-Bolus to the Post-Bolus time point. There may be additional correction for leakage with integration of time points after the bolus.

The K2 value is computed by fitting a line to the post-bolus baseline, which requires identification of the end of the bolus, and a sufficient number of points to accurately fit the slope of the line. The slope of that line is the K2 value. In areas of intact BBB, the slope is 0, but with increasing leakage, the slope may increase or decrease depending on the relative T1 and T2 effects and can also vary depending on the tumor.

Increasingly, the Reconstruction Software for DSC MRI analysis is automated. Early versions of Reconstruction Software required manual identification of the pre-bolus baseline and of the post-bolus baseline as well as the white matter sample or vessel to normalize against. This is increasingly automated. For Reconstruction Software that requires user input to define one or more of these, the procedure is:

- Pre-Bolus Baseline: The Image Analyst shall visually identify the last point prior to a definite change in signal due to bolus passage. (An increase if viewing an R2* image).

- Post-Bolus Baseline: The Image Analyst shall visually identify the first point after the change in [23] signal due to bolus passage. The baseline after bolus may show continued gradual change with small peaks due to recirculation.

- Normalization: The Image Analyst shall create a region of interest that is at least 2x2cm in the normal appearing white matter of the brain opposite from the lesion of interest on the same slice. In the case that the lesion is in both hemispheres, the ROI may be placed more posteriorly, as far from the lesion as possible. The ROI must NOT include gray matter.

    - Automated approaches which automatically standardize images [23] and/or select ROIs for tissue normalization [41, 42] may improve reproducibility of results. In the study by Bell et al [41], the NAWM coefficient of variation across subjects for the radiology-drawn ROIs was 0.30, whereas it decreased to 0.18 when automated approaches were used [30, 31, 41, 43]. However, since many centers may not have access to specialized software required to do this, we have provided specifications to generate ROIs to satisfy the claims in this profile.

The software used to produce parametric images from the DSC 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 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.

3.10.2 Specification

Parameter	Actor	Requirement
Pre-Bolus Baseline	Image Analyst	Shall identify the last point prior to a definite change in signal due to bolus passage
Post-Bolus Baseline	Image Analyst	Shall identify the first point after the change in signal due to bolus passage
Normalization	Image Analyst	Shall create a region of interest that is at least 2x2cm in the normal appearing white matter of the brain opposite from the lesion of interest on the same slice or use automated approaches
AUC-TN and K2 map generation	Image Analyst	Shall use the same procedural steps for image reconstruction of AUC-TN and K2 map generation for all subjects and time points.

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. 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: At the time of image acquisition and review, quality of DSC data shall be

checked for the following issues. Poor quality due to sources below may be grounds to reject individual datasets.

- Susceptibility Effects can compromise the ability to measure either AUC-TN or K2. These may be due to metal or blood near the surgical site (including small metal filings that may be imperceptible) as well as normal structures like bone and air that can compromise values near the periphery of the brain.
- Gross patient motion not correctable with motion-correcting algorithms
- Low Temporal SNR – if the temporal SNR is not sufficient to detect bolus profile in individual voxels compared to signal fluctuation
- Ghost/parallel imaging artifacts – Discrete ghosts from extraneous signal sources along phase-encode direction can obscure tissue of interest leading to unpredictable AUC-TN maps
- Severe spatial distortion – Some level of spatial distortion is inherent to SS-EPI, although distortion can be severe near high susceptibility gradients in tissues or metallic objects; or due to poor magnet homogeneity [44, 45]. Severe distortion can alter apparent size/shape/volume of tissues of interest thereby confound ROI definition, as well as adversely affect AUC-TN values.
- Failure of the imaging site to replicate the imaging parameters within acceptable standards of deviation from protocol specifications

3.11.2 SPECIFICATION

Parameter	Actor	Requirement
Patient Motion Artifacts	Image Analyst	Shall confirm the images containing the tumor are free from artifact due to patient motion.
Susceptibility or Other Artifacts	Image Analyst	Shall confirm the images containing the tumor are free from artifact due to paramagnetic objects, materials or anatomic positioning.
Tumor Size	Image Analyst	Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 cm^3 and 524 cm^3.)
Tumor Margin Conspicuity	Image Analyst	Shall confirm the tumor margins are sufficiently conspicuous to place ROIs.
Use of intravenous contrast	Image Analyst	Shall confirm adequate signal reduction in response to bolus of contrast agent
AUC-TN Measurability	Image Analyst	Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement.

		Conversely, if artifacts are present but the analyst is confident and prepared to edit the regions of interest to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.
Consistency with Baseline		Shall confirm that the tumor is similar in both timepoints in terms of all the above parameters and shall reprocess the images if first time point if it 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 regions of interest 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 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
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

The image analysis software typically processes the 4D DSC 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 [46]. Commonly, the multiple 3D images in the 4D set are summed together, and that is used to create the transformation matrix that is used to match the DSC MRI to the T1-weighted image. Once that is done, the contrast-enhancing component is then used for measurement. In some cases, the user selects a threshold or draws an ROI that matches the contrast-enhancing portion, while other software automatically produce a contrast-enhancing lesion segmentation.

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) [30]. 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 the 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).

- Automated approaches which automatically select ROIs for analyses can potentially improve reproducibility. One study showed that errors due to

interrater differences in ROI measures can vary from 0.3 to 0.43 depending on method [30].

3.13.2 Specification

Parameter	Actor	Requirement
ROI Determination	Image Analyst	Shall segment the contrast-enhancing portion from the T1 post-contrast image.
Image Registration	Image Analyst	Shall align the AUC-TN image to the T1 post-contrast image
Mean value	Image Analyst Image Analyst	Shall measure the mean value of the ROI

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

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 dynamic susceptibility contrast (DSC) perfusion-weighted imaging performance requires additional tests detailed in Appendix F. Key quantitative DSC 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 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: Patient Motion

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

4.3. Assessment Procedure: Bolus Quality

The assessor shall measure the mean signal drop in the whole brain. The assessor shall indicate that the bolus is of poor quality it the signal drop is less than 10% [47].

4.4. Assessment Procedure: Temporal SNR

The assessor will measure the temporal signal to noise ratio as the mean signal in a region of interest (ROI) divided by the standard-deviation over multiple timepoints focusing on baseline data points prior to arrival of contrast agent.

4.5 Assessment Procedure: Artifacts

The assessor will identify artifacts regions of signal dropout or signal increases that is not anatomically consistent.

4.6. 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).

4.6a. 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" [48]. 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 will 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.

4.6b. 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 [24]. 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).

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.

References

1. Boxerman, J.L., et al., *Dynamic Susceptibility Contrast MR Imaging in Glioma: Review of Current Clinical Practice.* Magn. Reson. Imaging Clin. N. Am., 2016. **24**(4): p. 649-670.

2. Gilbert, M.R., et al., *A randomized trial of bevacizumab for newly diagnosed glioblastoma.* N. Engl. J. Med., 2014. **370**(8): p. 699-708.

3. Prager, A.J., et al., *Diffusion and perfusion MRI to differentiate treatment-related changes including pseudoprogression from recurrent tumors in high-grade gliomas with histopathologic evidence.* AJNR Am. J. Neuroradiol., 2015. **36**(5): p. 877-885.

4. Wen, P.Y., et al., *Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.* J. Clin. Oncol., 2010. **28**(11): p. 1963-1972.

5. Tsien, C., et al., *Parametric response map as an imaging biomarker to distinguish progression from pseudoprogression in high-grade glioma.* J. Clin. Oncol., 2010. **28**(13): p. 2293-2299.

6. Gerstner, E.R., et al., *Mgmt methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma.* Neurology, 2009. **73**(18): p. 1509-1510.

7. Brandes, A.A., et al., *A Randomized Phase II Trial (TAMIGA) Evaluating the Efficacy and Safety of Continuous Bevacizumab Through Multiple Lines of Treatment for Recurrent Glioblastoma.* Oncologist, 2018.

8. Fatterpekar, G.M., et al., *Treatment-related change versus tumor recurrence in high-grade gliomas: a diagnostic conundrum--use of dynamic susceptibility contrast-enhanced (DSC) perfusion MRI.* AJR Am. J. Roentgenol., 2012. **198**(1): p. 19-26.

9. Barajas, R.F., Jr., et al., *Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging.* Radiology, 2009. **253**(2): p. 486-496.

10. Hu, L.S., et al., *Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements.* AJNR Am. J. Neuroradiol., 2009. **30**(3): p. 552-558.

11. Young, R.J., et al., *MRI perfusion in determining pseudoprogression in patients with glioblastoma.* Clin. Imaging, 2013. **37**(1): p. 41-49.

12. Kong, D.S., et al., *Diagnostic dilemma of pseudoprogression in the treatment of newly diagnosed glioblastomas: the role of assessing relative cerebral blood flow volume and oxygen-6-methylguanine-DNA methyltransferase promoter methylation status.* AJNR

Am. J. Neuroradiol., 2011. **32**(2): p. 382-387.

13. Boxerman, J.L., et al., *Longitudinal DSC-MRI for Distinguishing Tumor Recurrence From Pseudoprogression in Patients With a High-grade Glioma.* Am. J. Clin. Oncol., 2017. **40**(3): p. 228-234.

14. Di Chiro, G., et al., *Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies.* American Journal of Roentgenology, 1988. **150**(1): p. 189-197.

15. Harris, R.J., et al., *MRI perfusion measurements calculated using advanced deconvolution techniques predict survival in recurrent glioblastoma treated with bevacizumab.* J. Neurooncol., 2015. **122**(3): p. 497-505.

16. Schmainda, K.M., et al., *Dynamic susceptibility contrast MRI measures of relative cerebral blood volume as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 multicenter trial.* Neuro. Oncol., 2015. **17**(8): p. 1148-1156.

17. Artzi, M., et al., *Differentiation between vasogenic-edema versus tumor-infiltrative area in patients with glioblastoma during bevacizumab therapy: a longitudinal MRI study.* Eur. J. Radiol., 2014. **83**(7): p. 1250-1256.

18. Akbari, H., et al., *Pattern analysis of dynamic susceptibility contrast-enhanced MR imaging demonstrates peritumoral tissue heterogeneity.* Radiology, 2014. **273**(2): p. 502-510.

19. Jain, R., et al., *Outcome prediction in patients with glioblastoma by using imaging, clinical, and genomic biomarkers: focus on the nonenhancing component of the tumor.* Radiology, 2014. **272**(2): p. 484-493.

20. Server, A., et al., *Measurements of diagnostic examination performance and correlation analysis using microvascular leakage, cerebral blood volume, and blood flow derived from 3T dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in glial tumor grading.* Neuroradiology, 2011. **53**(6): p. 435-447.

21. Patel, P., et al., *MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: a systematic review and meta-analysis.* Neuro-Oncology, 2017. **19**(1): p. 118-127.

22. Cho, H.R., et al., *Assessment of bevacizumab resistance increased by expression of BCAT1 in IDH1 wild-type glioblastoma: application of DSC perfusion MR imaging.* Oncotarget, 2016. **7**(43): p. 69606-69615.

23. Prah, M.A., et al., *Repeatability of Standardized and Normalized Relative CBV in Patients with Newly Diagnosed Glioblastoma.* AJNR Am. J. Neuroradiol., 2015. **36**(9): p. 1654-

1661.

24. Jafari-Khouzani, K., et al., *Repeatability of Cerebral Perfusion Using Dynamic Susceptibility Contrast MRI in Glioblastoma Patients.* Transl. Oncol., 2015. **8**(3): p. 137-146.

25. Bedekar, D., T. Jensen, and K.M. Schmainda, *Standardization of relative cerebral blood volume (rCBV) image maps for ease of both inter-and intrapatient comparisons.* Magn. Reson. Med., 2010. **64**(3): p. 907-913.

26. Emblem, K.E., et al., *Histogram analysis of MR imaging-derived cerebral blood volume maps: combined glioma grading and identification of low-grade oligodendroglial subtypes.* AJNR Am. J. Neuroradiol., 2008. **29**(9): p. 1664-1670.

27. Shin, K.E., et al., *DCE and DSC MR perfusion imaging in the differentiation of recurrent tumour from treatment-related changes in patients with glioma.* Clin. Radiol., 2014. **69**(6): p. e264-72.

28. Grandin, C.B., et al., *Absolute CBF and CBV measurements by MRI bolus tracking before and after acetazolamide challenge: repeatabilily and comparison with PET in humans.* Neuroimage, 2005. **26**(2): p. 525-535.

29. Levin, H.S., et al., *Serial MRI and neurobehavioural findings after mild to moderate closed head injury.* J. Neurol. Neurosurg. Psychiatry, 1992. **55**(4): p. 255-262.

30. Wetzel, S.G., et al., *Relative Cerebral Blood Volume Measurements in Intracranial Mass Lesions: Interobserver and Intraobserver Reproducibility Study.* Radiology, 2002. **224**(3): p. 797-803.

31. Smits, M., et al., *Repeatability and reproducibility of relative cerebral blood volume measurement of recurrent glioma in a multicentre trial setting.* Eur. J. Cancer, 2019. **114**: p. 89-96.

32. Semmineh, N.B., et al., *Optimization of Acquisition and Analysis Methods for Clinical Dynamic Susceptibility Contrast MRI Using a Population-Based Digital Reference Object.* AJNR Am. J. Neuroradiol., 2018. **39**(11): p. 1981-1988.

33. Welker, K., et al., *ASFNR recommendations for clinical performance of MR dynamic susceptibility contrast perfusion imaging of the brain.* AJNR Am. J. Neuroradiol., 2015. **36**(6): p. E41-51.

34. Leu, K., J.L. Boxerman, and B.M. Ellingson, *Effects of MRI Protocol Parameters, Preload Injection Dose, Fractionation Strategies, and Leakage Correction Algorithms on the Fidelity of Dynamic-Susceptibility Contrast MRI Estimates of Relative Cerebral Blood Volume in Gliomas.* American Journal of Neuroradiology, 2017. **38**(3): p. 478-484.

1022 35. Shellock, F.G. and J.V. Crues, *MR procedures: biologic effects, safety, and patient care.*
1023 Radiology, 2004. **232**(3): p. 635-652.

1024 36. Shellock, F.G. and A. Spinazzi, *MRI safety update 2008: part 1, MRI contrast agents and*
1025 *nephrogenic systemic fibrosis.* AJR Am. J. Roentgenol., 2008. **191**(4): p. 1129-1139.

1026 37. Shellock, F.G. and A. Spinazzi, *MRI safety update 2008: part 2, screening patients for*
1027 *MRI.* AJR Am. J. Roentgenol., 2008. **191**(4): p. 1140-1149.

1028 38. Shinbane, J.S., P.M. Colletti, and F.G. Shellock, *Magnetic resonance imaging in patients*
1029 *with cardiac pacemakers: era of" MR Conditional" designs.* J. Cardiovasc. Magn. Reson.,
1030 2011. **13**(1): p. 63.

1031 39. Ciet, P. and D.E. Litmanovich, *MR safety issues particular to women.* Magn. Reson.
1032 Imaging Clin. N. Am., 2015. **23**(1): p. 59-67.

1033 40. Enders, J., et al., *Reduction of claustrophobia during magnetic resonance imaging:*
1034 *methods and design of the" CLAUSTRO" randomized controlled trial.* BMC Med. Imaging,
1035 2011. **11**(1): p. 4.

1036 41. Bell, L.C., A.M. Stokes, and C.C. Quarles, *Analysis of postprocessing steps for residue*
1037 *function dependent dynamic susceptibility contrast (DSC)-MRI biomarkers and their*
1038 *clinical impact on glioma grading for both 1.5 and 3T.* J. Magn. Reson. Imaging, 2019.

1039 42. Emblem, K.E., et al., *A generic support vector machine model for preoperative glioma*
1040 *survival associations.* Radiology, 2015. **275**(1): p. 228-234.

1041 43. Korfiatis, P., et al., *Dynamic Susceptibility Contrast-MRI Quantification Software Tool:*
1042 *Development and Evaluation.* Tomography, 2016. **2**(4): p. 448-456.

1043 44. Bastin, M.E., *Correction of eddy current-induced artefacts in diffusion tensor imaging*
1044 *using iterative cross-correlation.* Magn. Reson. Imaging, 1999. **17**(7): p. 1011-1024.

1045 45. Chen, N.-K. and A.M. Wyrwicz, *Removal of EPI Nyquist ghost artifacts with two-*
1046 *dimensional phase correction.* Magn. Reson. Med., 2004. **51**(6): p. 1247-1253.

1047 46. Ellingson, B.M., et al., *Consensus recommendations for a standardized Brain Tumor*
1048 *Imaging Protocol in clinical trials.* Neuro. Oncol., 2015. **17**(9): p. 1188-1198.

1049 47. Benner, T., et al., *Cerebral MR perfusion imaging: first clinical application of a 1 M*
1050 *gadolinium chelate (Gadovist 1.0) in a double-blinded randomized dose-finding study.* J.
1051 Magn. Reson. Imaging, 2000. **12**(3): p. 371-380.

1052 48. Obuchowski, N.A., et al., *Statistical Issues in Testing Conformance with the Quantitative*
1053 *Imaging Biomarker Alliance (QIBA) Profile Claims.* Acad. Radiol., 2016. **23**(4): p. 496-506.

1054 49. Sullivan, D.C., et al., *Metrology Standards for Quantitative Imaging Biomarkers.*

Radiology, 2015. **277**(3): p. 813-825.

50. Raunig, D.L., et al., *Quantitative imaging biomarkers: a review of statistical methods for technical performance assessment.* Stat. Methods Med. Res., 2015. **24**(1): p. 27-67.

Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America [49], 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:

Daniel Barboriak
Laura Bell
Michael Boss
Jerrold Boxerman
Slavka Carnicka
Thomas Chenevert
Caroline Chung
Benjamin Ellingson
Kyrre Emblem
Bradley J. Erickson
Alexander Guimaraes
Brandon L. Hancock
Leland Hu
Edward Jackson
Katy Keenan
John Kirsch
Hendrik Laue
Dariya Malyarenko
Elizabeth Mirowski
Matthias JP van Osch
Nancy Obuchowski
Chad Quarles
Luis Rodriguez
Mark Rosen
Kathleen Schmainda
Mark Shiroishi
Daniel Sullivan
Ona Wu
Gudrun Zahlmann

We also acknowledge the extraordinary efforts by RSNA QIBA staff in making this Profile possible.

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 [50], 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 [50].

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 will 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 Acquisition Devices

Acquisition Device	Settings Compatible with Conformance	
Siemens	*Submitted by: Massachusetts General Hospital*	
	TR	1500 ms (maximum)
	TE	30 ms
	FA	60
	Acceleration	iPAT 2 (no PF)
	Timepoints	120
	Head coil	32 channel
	Scan FoV	220-240
	Acquisition Matrix	128x128
	Slice Thickness	5 mm skip 1 mm
General Electric	*Submitted by: Mayo Clinic*	
	TR	1500 ms (maximum)
	TE	30 ms
	FA	60
	Averages	1
	Timepoints	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
Philips	*Submitted by: Barrow Neurological Institute*	
	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 (or 30)
	Acceleration (SENSE)	Yes, (P reduction (AP) = 2.29)
	Halfscan	Yes (factor = 0.73)
	Timepoints	120
	Head coil	32 channel
	FOV	220-240
	Acquisition Matrix (M x P)	128x128
	Slice Thickness	5 mm

1144

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

Name of Site Checked:

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
Image Analyst		Shall confirm all participating analysts conforms 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

ACQUISITION DEVICE CHECKLIST

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

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
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
Image Header		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
Image Header		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
Image Header		Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column in section 3.4.2 "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve compliance.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Pre-delivery (section 3.3)			
System performance benchmark		System shall perform within vendor-established performance benchmark ranges for the given model	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Accreditation of site		Shall be qualified by a physicist as defined by appropriate accrediting bodies	□ 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 imaging readout within vendor-established performance benchmark ranges	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Installation (section 3.4)			

Phantom Acquisition		System shall perform within specification on QIBA-NIST DSC phantom (Appendix)	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

188
189

CONTRAST INJECTOR CHECKLIST

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

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Product Validation (section 3.2)			
Image Data Acquistion		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)			
System performance benchmark		System shall perform within 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
Accreditation of site		Shall be qualified by a medical physicist as defined by appropriate accrediting bodies	□ 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
Protocol Design (section 3.6)			
Acquisition Protocol		Shall approve protocol developed by Physicist to meet the requirements of this profile	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Protocol		Shall ensure technologists have been trained on the requirements of this profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Subject Handling (section 3.8)			
Acquisition Protocol		Shall prescribe a protocol that is consistent with baseline acquisition (if applicable).	□ 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
Installation (section 3.4)			
System Performance Assessments		System shall perform within vendor-established performance benchmark ranges for the given model after installation.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
System Performance Assessment		Shall document and record hardware specifications, software version and calibration dates	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast Injector Performance Assessments		Shall ensure that system shall perform within vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast Injector Performance Assessments		Shall document and record hardware specifications, software version and calibration dates	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Periodic QA (section 3.5)			
System performance benchmark		Shall assess system performance are within vendor-established performance benchmark ranges for the given model.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
System performance benchmark		Shall document all hardware/software upgrades.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
System performance benchmark		Shall record the date/time of calibrations as recommended by the vendor.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
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
Contrast		Shall document all hardware/software upgrades.	□ Routinely do already

Injector			□ Feasible, will do □ Feasible, will not do □ Not feasible
Contrast Injector		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
Stability		Shall perform periodic system QA using QIBA-NIST DSC phantom, including assessment of temporal SNR and linearity (see Appendix). See 4.4 Assessment Procedure.	□ 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
Acquisition Protocol		Shall report if any parameters are modified beyond 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
Acquisition Protocol		Shall confirm pre-specified DICOM tags meet specifications	□ 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 mm2	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Total Acquisition TIme		Shall confirm series acquisition duration is at least 180s	□ 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 base line when using specified contrast agent and dosage.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible

1225

1226 **TECHNOLOGIST CHECKLIST**

1227

1228

1229 Technologist(s) Checked:

1230

Parameter	Conforms (Y/N)	Specification	Site Opinion
Subject Selection (section 3.7)			
Subject		Shall confirm subject has no contraindication to MRI	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous contrast		Shall confirm subject has venous access to allow bolus injection	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous contrast		Shall confirm subject has no contraindication to gadolinium-based contrast agents (i.e. history of allergic reaction, poor renal output).	□ 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
Use of intravenous contrast		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
Use of intravenous contrast		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
Use of intravenous contrast		Shall document the total volume of contrast medium administered, the concentration, the injection rate, and volume of saline flush used.	□ Routinely do already □ Feasible, will do □ 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		□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Acquisition Protocol		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
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 Slices		Shall set Consistent with baseline (if applicable).		□ Routinely do already □ 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
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

1231
1232

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
Multiple Tumors		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
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
Reading Paradigm		Shall be able to re-process the first time point (e.g. if it was processed by a different Image Analysis Tool or Analyst).	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Digital Reference Object		Shall be confirmed that performance is linear and has expected wCV on digital reference objects.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Result Recording		Shall record the image analysis tool version.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Result Recording		Shall record percentage AUC-TN change relative to baseline for each tumor.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Result Recording		Shall record regions of interests used.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Result Recording		Shall record volume of regions of interests used.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Result Recording		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

1237
1238

1239 **IMAGE ANALYST CHECKLIST**

1240

Parameter	Conforms (Y/N)	Specification	Site Opinion
Periodic QA (section 3.5)			
Image Analysis Tool		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 Data Reconstruction (section 3.10)			
Pre-Bolus Baseline		Shall identify the last point prior to a definite change in signal due to bolus passage	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Post-Bolus Baseline		Shall identify the first point after the change in signal due to bolus passage	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
White Matter Identification		Shall create a region of interest that is at least 2x2cm in the normal appearing white matter of the brain opposite from the lesion of interest on the same slice	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
AUC-TN and K2 map generation		Shall use the same procedural steps for image reconstruction of AUC-TN and K2 map generation for all subjects and time points.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Image QA (section 3.11)			
Patient Motion Artifacts		Shall confirm the images containing the tumor are free from artifact due to patient motion.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Susceptibility or Other Artifacts		Shall confirm the images containing the tumor are free from artifact due to paramagnetic objects, materials or anatomic positioning.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Tumor Size		Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor this would roughly correspond to a volume between 0.5 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 regions of interest.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Use of intravenous		Shall confirm adequate signal reduction in response to bolus of contrast agent	□ Routinely do already □ Feasible, will do

contrast			□ Feasible, will not do □ Not feasible
AUC-TN Measurability		Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the analyst is confident and prepared to edit the regions of interest to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Consistency with Baseline		Shall confirm that the tumor is similar in both timepoints in terms of all the above parameters and shall reprocess the images if first time point if it 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 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	□ 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 contrast-enhancing portion from the T1 post-contrast image.	□ 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	□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible
Mean value		Shall measure the mean value of the ROI	□ Routinely do already □ Feasible, will do □ Feasible, will not do

			□ Not feasible

1241

Appendix F: Technical System Performance Evaluation

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.

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 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	20
	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

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

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.

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

G.1. OVERVIEW

The final configuration of the delta/dynamic susceptibility contrast phantom (DSC 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 GdCl3, 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 MnCl2 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 MnCl2. There are also three small reference tubes (blue arrows) filled with 1 mM GdCl3 solution.

Figure G1: The open DSC 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.