QIBA Profile:
DCE-MRI Quantification (DCEMRI-Q)

Profile submitted for Stage 2: Consensus

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Change Log:

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

Date	Sections Affected	Summary of Change
2016.04.24	**All**	**Populated sections with content from profile 1.0**
2016.05.02	**3**	**Reviewed and sorted content to appropriate sections** **Added new actor 'Study coordinator' to profile table** **Resorted contents from Profile 1.0 to new structure and marked them in purple**
2016.06.07	**3**	**Executive Summary section updated and reviewed by TF**
2016.08.03	**3**	**Removed study coordinator section 3.0**
2017.10.12	**2**	**Added preliminary claim definition**
2017.11.09	**2**	**Updated claim definition based on feedback on poster content**
2018.01.05	**All**	**Updated profile to 2017 format**
2019.01.20	**All**	**Replaced AIF with VIF in the text**
		Parallel imaging statements
2019.10.14	**3**	**Moved sequence tables to Protocol Design**
2020.02.03	**All**	**B_1 correction details added**
2020. 08.03	**Appendices**	**Appendices updated**
2020.09.13	**All**	**Cleaned version with references in Endnote prepared for 'Public Comment'**

Open Issues:

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

Q. Does the conformance checklist include the necessary and feasible requirements for this profile? A. Requesting feedback from Public Comment
Q: Are there other body sites that should be prioritized for inclusion in the DCE profile? (i.e. sites with available test-retest data) A: Requesting feedback from Public Comment

Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues on.

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. How to validate software: DRO (Digital reference object) / comparing algorithm and technologies A. DRO should be used to validate T_1 mapping and PK mapping. Different DRO should be used for different PK model (e.g., TM, ETM, or SSM DRO)
Q. How to delineate ROIs for DCE-MRI? A. The ROI should be segmented on a T_1 or T2W anatomical image that is coregistered to the parameter map, not delineated on the parameter map. - Inter-observer variability may need to be measured for each cancer (e.g., inter-observer variability for prostate cancer may be different from that for glioblastoma). - There is some software, for example RAPID and IB Neuro, for brain tumors that have the capability to automate lesion segmentation
Q. Which VIF is recommended? Population average vs patient-specific? A. The profile recommends a population average VIF when the patient-specific VIF is not available. An alternative suggestion is population-based VIF modified for each individual patient, but test-retest data for this approach is not yet available (H Kim, Mag Reson Imaging, 2018).
Q. How to handle protocol parameters in claim definition from old publications with state-of-the-art protocols? (without test-retest) A. While the claims are tied to the published protocols (old publications) the profile includes a table of body-site specific recommended protocols that may include state-of-the art protocols. We also recommend working with the vendors on how to translate these test-retest data driven protocols into the modern protocols. As more test-retest data become available, we will plan to update the profile.

Q. How do we take dosage and relaxivity of the contrast agent into account A. While the standard dose is 0.1 mmol/kg, we ask for feedback about whether the dose of Gd could be reduced to account for GDD.
Q: How to include B_1 correction at 3T? A: B_1 correction is not available for all body sites. Since there is no publication with test-retest but B_1 correction for prostate is available, it will be a recommendation in the discussion without a link to the claim definition.
Q: Should parallel imaging be used for DCE-MRI? A: Our recommendation is to minimize the use of parallel imaging for DCE-MRI, if possible.
Q: Should view sharing, compressed sensing or radial imaging sequences be used to speed up DCE-MRI acquisition? A: Our recommendation is not to use view sharing techniques. There is insufficient information about compressed sensing and radial imaging for the DCE profile to provide a recommendation.

1. Executive Summary

The goal of the DCE-MRI quantification QIBA Profile version 2.0 is to provide an update from the Dynamic Contrast Enhanced MRI (DCE-MRI) Quantification profile (version 1.0, dated July 1, 2012) in order to include the use of 3 Tesla (T) MRI and the use of parallel imaging with receiver coil arrays. While many pharmacokinetic models have been described, this QIBA Profile (DCE-MRI Quantification) specifically addresses the physiological parameter K^{trans} derived from the Tofts or generalized kinetic model (GKM) (1), which is correlated with the vessel (surface/area product and permeability) and haemodynamic (flow) properties. Tofts et al. introduced an extended Tofts model or extended GKM (eGKM), including a signal contribution from the arteries to cover tissue with higher vascularization (1).

DCE-MRI is recognized as a potential method to provide predictive, prognostic, and/or physiological response biomarkers for cancer (2–10). This potential has been obtained despite considerable variation in the methods used for acquisition and analysis of the DCE-MRI data. This suggests there are substantial physiological differences (i.e., benign vs. malignant or non-responsive vs. responsive tumors) underlying these observations. Thus, there is potential value recognized in the integration of DCE-MRI for basic research, drug development, clinical research, and in routine clinical practice. However, in order to fulfill the promise of using DCE-MRI as a clinically useful tool, it is essential that common quantitative endpoints are used and that results are independent of imaging platforms, clinical sites, and time.

Update to include 3T: With the inclusion of 3T MRI, we have introduced "recommended" procedures to calibrate and compensate for radio frequency (RF) transmit (or B_1^+ field) inhomogeneity, described in the subsequent sections. At 3T, this calibration is ideally utilized to obtain the desired precision of the resulting DCE-MRI biomarkers in the breast and prostate, and this finding is expected to generalize to all other body parts (11,12). This profile also contains an Appendix with recommended vendor-specific procedures for acquiring the requisite calibration information.

Update to include Parallel Imaging: The inherent trade-offs between temporal and spatial resolution can be improved by using parallel imaging techniques to accelerate acquisition. But, the use of parallel imaging comes at the expense of signal-to-noise ratio (SNR) and potential artifacts. Nevertheless, modest acceleration factors are beneficial in the context of DCE-MRI and a range of acceleration factors are described in this profile.

Profile development is an evolutionary, phased process; version 2.0 of this Profile is in the 'public comment' 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 biomarker performance claims are derived from the body of scientific literature that have presented test-retest studies meeting scientific requirements. 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 to ensure acceptable performance. **Conformance** (Section 5) regroups Section 3 requirements by the Actor to conveniently check Conformance to the profile.

This document is intended to help imaging staff generating this biomarker, vendor staff developing related

products, purchasers of such products, clinicians who are using this biomarker to aid in clinical decisions, and researchers using this imaging biomarker as an endpoint measure within clinical trials.

Note that this document states requirements to achieve the specified Claims and does not reflect "standard of care" requirements for DCE-MRI. Due to the limited availability of test-retest studies, some of the Claims were achieved based on protocols that are outdated relative to the currently available imaging capabilities. Therefore, this profile also provides recommendations based on consensus by the DCE-MRI committee that reflect current quantitative DCE-MRI practices. Conformance to this Profile is secondary to properly caring for the patient.

2. Clinical Context and Claims

2.1 Clinical Context

The goal of this profile is to provide guidance towards gaining precise and reproducible measurements characterizing tissue vasculature. In this profile version, the focus lies on the contrast agent transfer constant, K^{trans} (1,13), which derives from pharmacokinetic modeling and is a promising, reproducible, parameter in DCE-MRI. The profile refers to DCE-MRI using standard extracellular contrast agents (e.g. Dotarem, Gadavist, ProHance), and not using liver-specific agents (e.g. Primovist).

One important clinical application of K^{trans} is to evaluate tumor response to treatment. The characterization of tumor vasculature is most important for evaluating the effects of anti-angiogenic tumor therapies but might also help to evaluate success of other therapies such as chemotherapy, hormonal therapy, immunotherapy, radiation therapy, irreversible electroporation, laser interstitial thermal therapy (LITT), or MR focused ultrasound. Moreover, DCE-MRI might prove helpful in management such as 'active surveillance' strategies, e.g., monitoring low-grade prostate cancer (14) or determining prognosis such as distinguishing between pseudo-progression and true progression in glioblastoma (15).

The requirement for measuring treatment response is a baseline scan prior to the treatment and repeated scan(s) sometime after initiation of treatment. A change in K^{trans} may reflect alteration of the vasculature following therapy. This change may serve as an early indicator for treatment response.

The goal of this Profile version is to provide general guidelines for the application of DCE-MRI to obtain reproducible and accurate K^{trans} specifically for brain, breast, prostate, and head & neck cancer. Moreover, it provides the expected level of variance of K^{trans} that are unrelated to biological changes. These levels of variance are described in the claim definitions below for brain and prostate cancer.

The described claims are held under several prerequisites, (e.g., temporal resolution, contrast agent, sequence used) which this profile describes and discusses. The profile tries to point out the possible consequences of variations from these prerequisites in terms of claims.

The intended audience for the Profile is healthcare professionals, scientists, and engineers involved in the process of extracting quantitative measures from DCE-MRI data. These include:

- Radiologists, technologists, engineers, scientists, and physicists developing and improving MRI protocols for DCE-MRI.

- Radiologists, technologists, engineers, scientists, physicists, and administrators at healthcare institutions considering specifications for purchasing MRI equipment, software or contrast agents.
- Developers of software and hardware creating products for conducting DCE-MRI.
- Biopharmaceutical companies.
- Imaging contract research organizations (CROs).
- Clinicians interested in quantitative therapy response assessment (including non-radiologists).
- Radiologists, health care providers, administrators, regulatory agencies, and government officials developing and implementing policies for cancer treatment and monitoring.

2.2 Claims

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

Claim 1 (brain configuration): At 1.5 T, measured change in K^{trans} of a brain lesion of 21% or larger indicates that a true change has occurred with two-sigma confidence (95%) confidence.

Claim 2a (prostate configuration a): At 1.5 T, measured change of K^{trans} of a prostate lesion of 56 % or larger indicates that a true change has occurred with two sigma confidence (GKM, individual vascular input function (VIF)) (16)**.**
Claim 2b (prostate configuration b): At 3 T, a measure change of K^{trans} of a prostate lesion of 95 % or larger indicates that a true change has occurred with two sigma confidence (GKM, individual VIF (17)**.**
Claim 2c (prostate configuration c): At 3 T, a measure change of K^{trans} of a prostate lesion of 105 % or larger indicates that a true change has occurred with two sigma confidence (eGKM, individual VIF) (17)**.**

Discussion:

Test-retest data from published scientific literature inform about these claims. We systematically searched literature for head & neck, brain, and prostate tumors and found test-retest data published for the latter two. The number of investigated subjects was limited. Jackson et al. (11) included 11 patients for brain tumors. Alonzi et al. (16) included 20 prostate cancer patients at 1.5 T, and Peled et al. (17) 11 patients at 3 T. The latter also did apply the eGKM to the data. Consequently, we can issue three claims, one for 1.5 T using the GKM (Claim 2a), one at 3T using GKM (Claim 2b), and one at 3 T using the eGKM (Claim 2c). With these data, we estimated the expected level of variance provided in the claim statements. The claims are specific to the protocol used in the publications used for the claim definition, as summarized in Appendix B. There was no test-retest data for breast or head and neck. The biomarker committee considers these applications very important in DCE-MRI and added recommendations even though a claim could not be defined.

As stated by Shukla-Dave et al. (18), the number of publications providing test-retest data is very limited for DCE-MRI, and these claims would be improved from further publications on the repeatability of K^{trans} measurements. The authors strongly encourage researchers to publish such data and for manuscript

reviewers to account for the importance of such publications in enabling quantitative imaging biomarker development and interpretation.

2.3 Clinical Interpretation

QIBA Claims describe the technical performance of the quantitative measurements. The clinical significance and clinical interpretation of those measurements is left to the clinician.

K^{trans} is the exchange rate of contrast agent from the blood vessels into the surrounding interstitial space. K^{trans} is generally increased in malignant tissue due to the increased number and greater permeability of the newly formed vessels due to neo-angiogenesis associated with malignant tumor growth. The claims in this Profile indicate that a change of K^{trans} is considered a true change when that change exceeds the statistical variation of the measurement process itself.

Example of clinical interpretation with respect to the measured change in K^{trans} of a brain lesion:

A patient with glioblastoma has DCE-MRI acquired before and after radiation therapy. We note that K^{trans} is 0.5 min^{-1} in the tumor prior to treatment, then a later examination after radiation therapy results in a K^{trans} of 0.9 min^{-1} (i.e., 100%*(0.9-0.5)/0.5 = 80%) indicates with 95% confidence that there was a measured change that is a true increase in K^{trans} based on Claim 1 and might indicate disease progression.

Example of clinical interpretation with respect to the measured change in K^{trans} of a prostate lesion for claim 2a:

Consider a prostate cancer patient undergoing radiation therapy. If the DCE-MRI in the examination prior to treatment results in a K^{trans} of 0.9 min^{-1} in the tumor, then a later examination after radiation therapy results in a K^{trans} of 0.4 min^{-1} (i.e., 100%*(0.4-0.9)/0.9 ≈ -65%) indicates with 95% confidence that there was a measurable decrease in K^{trans}, possibly indicating therapeutic success. If K^{trans} is increased to 1.4 min^{-1} (100%*(1.4-0.9)/0.9 ≈ 65%, it can be considered as a true increase with 95% confidence based on Claim 2, pointing to a progressing disease or failing therapy.

Example of clinical interpretation with respect to measured change in K^{trans} of a prostate lesion for claim 2b: If the DCE-MRI in the examination prior to treatment results in a K^{trans} of 1.4 min^{-1} in the tumor, then a later examination after radiation therapy results in a K^{trans} of 0.07 min^{-1} (i.e., 100%*(0.07-1.4)/1.4 ≈ -95%) indicates a measurable decrease in K^{trans} of 100%, suggesting a therapeutic success with 95% confidence. A K^{trans} increased to 2.73 min^{-1} (100%*(2.73-1.4)/1.4 ≈ 95% can also be considered as a true increase with 95% confidence based on Claim 2, pointing to a progressing disease or failing therapy.

Example of clinical interpretation with respect to measured change in K^{trans} of a prostate lesion for claim 2c: If the DCE-MRI in the examination prior to treatment results in a K^{trans} of 1.4 min^{-1} in the tumor, then a later examination after radiation therapy results in a K^{trans} of -0.07 min^{-1} (i.e., 100%*(-0.07-1.4)/1.4 ≈ -105%) indicates a measurable decrease in K^{trans} of 100%, suggesting a therapeutic success with 95% confidence. A K^{trans} increased to 2.87 min^{-1} (100%*(2.87-1.4)/1.4 ≈ 105% can also be considered as a true increase with 95% confidence based on Claim 2, pointing to a progressing disease or failing therapy.

Discussion:

These claims are based on estimates of the mean K^{trans} value from a region of interest (ROI) drawn in the brain and prostate. For estimating the true change, the % Repeatability Coefficient (%RC) is derived from the coefficient of variation (wCV). %RC can be derived from the latter using: 2.77 * wCV * 100%, or %RC = 21.3% for the brain and 55.7% for the prostate. The wCV was obtained from the test-retest studies published in (11) and (16) and was 7.7% for the brain and 20.1% for the prostate, respectively.

3. Profile Activities

The Profile is documented in terms of **Actors** performing **Activities**. Equipment, software, staff, or sites may claim conformance to this Profile as one or more of the Actors in the following table. Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced Section. For some activity parameters, we define three specifications. Meeting the ACCEPTABLE specification is sufficient to conform to the profile. Meeting the TARGET or IDEAL specifications are expected to achieve improved performance, but are not required for conformance to the profile.

ACCEPTABLE: Actors that shall meet this specification to conform to this profile.

TARGET: Meeting this specification is achievable with reasonable effort and adequate equipment and is expected to provide better results than meeting the ACCEPTABLE specification.

IDEAL: Meeting this specification may require extra effort or non-standard hardware or software but is expected to provide better results than meeting the TARGET.

Table 1: Actors and Required Activities

Actor	Activity	Section
Site	**Staff Qualification**	**3.1**
	Site Qualification	**3.2**
	Periodic QA	**3.5**
Acquisition Device	**Installation**	**3.4**
	Periodic QA	**3.5**
	Image Data Acquisition	**3.9**
Scanner Operator*	**Site Qualification**	**3.2**
	Periodic QA	**3.5**
	Protocol Design	**3.6**

	Image Data Acquisition	**3.9**
	Image Data Reconstruction	**3.10**
	Image Distribution	**3.12**
Technologist	**Subject Handling**	**3.8**
	Image Data Acquisition	**3.9**
Image Analyst[**]	**Subject Selection**	**3.7**
	Image QA	**3.10**
	Image Distribution	**3.12**
	Image Analysis	**3.13**
	Image interpretation	**3.14**
Image Analysis Tool	**Image Data Reconstruction**	**3.10**
	Image Analysis	**3.13**

[*]Scanner operator may be an MR technologist, physicist, or other MRI scientist.
[**]Image analyst may be a radiologist, technologist, physicist, or other MRI scientist.

The requirements in this Profile do not codify a Standard of Care. They only provide guidance intended to achieve the stated Claims. 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. Handling protocol deviations for specific trials/studies is at full discretion of the study sponsors and other responsible parties.

Example of a clinical workflow based on this DCE Profile is shown in Figure 1.

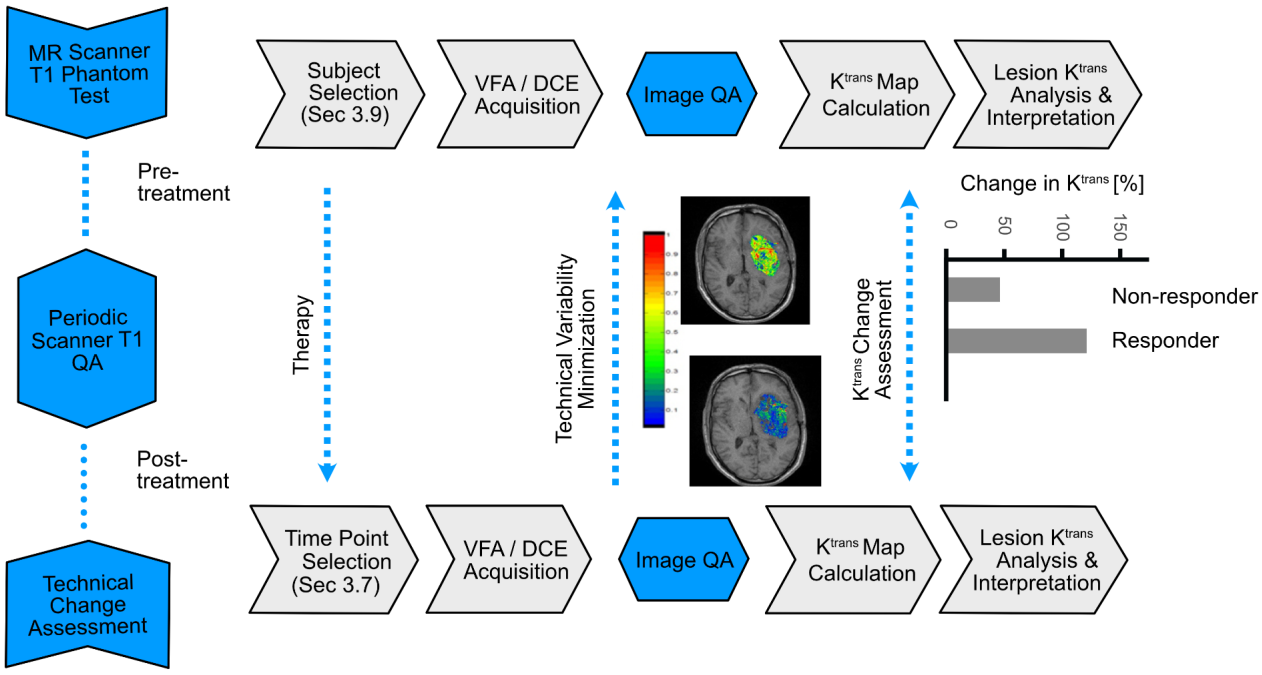

Figure 1: Typical quantitative DCE-MRI workflow for Treatment Response Assessment. Variable Flip Angle (VFA) denotes the recommended T_1-Mapping method, K^{trans}- map is determined using the General Kinetic Model or extended GKM.

3.1. Staff Qualification

This activity involves evaluating the human Actors (Radiologist, MRI Scientist, 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. But the technologist (or sometimes nurse involved in intravenous (IV) access) who is responsible for subject handling should have experience with DCE-MRI acquisition.

The image analyst can be a non-radiologist professional such as a medical physicist, biomedical engineer, or MRI scientist. The image analyst has to be trained in the key acquisition principles of DCE-MRI (Appendix C), procedures to confirm that the sequence, acquisition and Digital Imaging and Communications in Medicine (DICOM) metadata content is maintained along the network chain from scanner to picture archiving and communication system (PACS) and analysis workstation. The image analyst must be trained in using the specified image analysis software.

The Technologist is always assumed to be a Scanner Operator for subject scanning, while phantom scanning setup needs to be oversighted by a Physicist but can be conducted by an assistant and the evaluation of the phantom data should be conducted by the Physicist.

3.1.2 Specification

MR Technologists or other Site Personnel performing DCE-MRI studies

Parameter	Actor	Specification
Qualification	**MRI technologist**	**Should be a qualified individual with experience in clinical DCE-MRI acquisition**
Qualification	**Scanner Operator**	**Shall be a qualified Individual with experience in DCE-MRI acquisition, as defined by local regulations or institutional requirements**
Qualification	**Image Analyst**	**Shall undergo documented training by a qualified radiologist in terms of anatomical location and image contrast(s) used to select measurement target; and by qualified physicist, biomedical engineer or trained image analyst in understanding key elements in DCE acquisition and analysis**

3.2. Site Qualification

This activity involves evaluating performance of the product Actors (Acquisition Device, Reconstruction Software, and Image Analysis Tool) by the Scanner Operator and Image Analyst initially at the site to ensure acceptance to the trial and baseline cross-site protocol standardization, but not directly associated with a specific clinical trial subject, that are necessary to reliably meet the Profile Claim.

3.2.1 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 F, 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.

Technical details for MRI systems are complex. In the case of DCE-MRI, the need for contrast agent application, dynamic acquisition and the use of analysis software tools makes this even more complicated. Moreover, considering the costs of an MRI system, it is generally necessary to use equipment already available at the site. The suitability of the hardware needs to be aligned with the details described in the following sections.

The MR technologists should have prior experience in conducting DCE-MRI. Competence in the performance of DCE-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 DCE-MRI trial or in clinical practice.

While the specific protocols are not addressed here, the recommendations are included in section 3.6.2.

3.3 Pre-delivery

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

3.3.1 Discussion

Current clinical MR scanners equipped with 3D fast spoiled gradient recalled echo or equivalent are adequate to meet the Profile Claim.

3.3.2 Specification

Actor: Acquisition Device	
Parameter	**Requirement**
Performance Metrics	**Scanner shall meet established vendor performance metrics for given model**
DCE Sequence	**Scanner shall be capable of obtaining proper temporal/spatial resolution and field-of-view (FOV) with reasonable SNR for the target region.**
DICOM Conformance	**DICOM Conformance Statement from Vendor will include DICOM tags for echo time (TE), repetition time (TR), and flip angle (FA), whether standard or private data elements are used.**

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

The Site manager should ensure that MR scanners are 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. Power injector models should be noted, including date of their most recent calibration.

Contrast Inject Device

DCE-MRI studies require a programmable power injector that the Site shall ensure is properly serviced and calibrated. The Site shall be capable of injecting a contrast agent up to 4-5 mL/s with two bolus capability (for saline flush).

Coils

Parallel imaging improves temporal resolution while retaining spatial resolution and coverage. The first is essential for retrieving reliable VIF, and the second is for conducting accurate image co-registration, particularly in upper abdominal imaging. Consequently, phased-array or multi-elements should be employed. However, if the acceleration factor is too high, the images may be more vulnerable to noise and artifacts, so they should be set appropriately (typically two or less).

3.5. Periodic Quality Assurance (QA)

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

3.5.1 Discussion

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

The scanner hardware and software should be kept as constant as possible for all patients imaged in longitudinal follow-up studies. Inevitably, data from patients imaged over many years will be subject to some upgrades in software and occasional change in hardware. The procedures in this profile aim at reducing these influences. Nonetheless, altering the scanner vendor, field strength, and software analysis package still increases the risk of changes in K^{trans} reflecting these technical factors rather than a genuine change in tumor physiology.

Phantom imaging for T_1 (see Assessment procedure 4.1): Phantoms with a range of T_1 values from 24 ms to 2000 ms shall be used. Examples of such phantoms include the QIBA DCE T_1 phantom and the National Institute of Standards and technology (NIST)- International Society for Magnetic Resonance in Medicine (ISMRM) system phantom (or the system phantom lite). The phantoms will be available at the NIST phantom library.

Phantom imaging data analysis: If using the QIBA DCE T_1 phantom, data should be analyzed in a uniform manner using the software provided by QIBA. The software can be downloaded from the Zenodo (19):

Assurance should be made by the central site that the phantom scan orientation is correct, and the local site performed appropriate image rotations or inversions (documented by the image analysis center).

Ongoing MRI scanner quality control

The phantom scans and analysis should be repeated at regular intervals (e.g., annually) during the course of the study. Any changes to scanner equipment, including major hardware changes or any software version change, need to be documented and will result in the need for imaging qualification renewal prior to repeat imaging. Sites performing DCE-MRI studies need to be informed of planned software upgrades, and when possible, such upgrades should be deferred until serial imaging of all currently enrolled patients is complete.

Signal stability

The signal stability test uses the same DCE-MRI acquisition sequence employed in the dynamic contrast-enhanced imaging. The duration of this scan should be at least 6 minutes to test magnet stability. A plot of the mean signal intensity (SI) in the ROI versus time should be linear and horizontal with no upward or downward trends. The root mean squared (rms) noise calculation should be similar across all aspects of the scan. Marked deviations or drift of signal intensity over time indicate magnet instability, and should initiate a thorough evaluation of the magnet by the on-site MR physicist or site engineer prior to use in the DCE-MRI trial.

3.5.2 SPECIFICATION

Parameter	Actor	Requirement
Accreditation of Site/System	**MRI Scientist**	**Shall have accreditation performed by a qualified MRI Medical Physicist/Scientist as performed in the hospital routine.**
System Performance Metrics	**Field Engineer/ Physicist**	**Shall periodically confirm the Acquisition Device performs within vendor-established performance benchmark ranges for the given scanner model**
Periodic T_1 QA	**MRI Scientist**	**Shall perform periodic (annually or more frequently depending on scanner or personnel availability) system quality control assessment (QCA) that includes assessment of T_1 bias, random error, linearity, T_1, SNR, DCE image artifacts**
T_1 Precision	**MRI Scientist**	**Shall be verified by the use of a T_1 phantom. This needs to be performed after hardware and software update. It is also required when changing the coil configuration.**

3.6. Protocol and Reconstruction 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.

Anatomic Imaging

In addition to the sequences listed in the protocol design section, it is common practice to obtain a localizer sequence followed by anatomical sequences as T_1- or T_2-weighted first.

T_1 Mapping sequence

The accurate determination of contrast agent concentration requires the knowledge of the local T_1.

Recommended for this purpose is the VFA method. The VFA is fast and can be acquired in a 3D fashion, and can therefore have exactly the same coverage and resolution of the DCE scan. Use the same 3D T_1-weighted gradient echo (GRE) sequence as the one used for the DCE MRI scan, and repeat the sequence with multiple flip angles varying from 2° to 30°. At 3T, the mapping of T_1 can be corrupted by the influence of B_1 inhomogeneities. Up to now, there are no standard sequences or evaluation tools available to correct for this influence. In order to minimize these errors, it is recommended to use 1.5T, if possible. A detailed discussion can be found in Appendix F. An error of 10% in T1 measurement can lead up to 20% error in the K^{trans} estimate (derived from (20)). It is therefore recommended to keep the T1 error below 10 %. The error should be tested using the phantom validation described in section 4.1.

Temporal resolution and coverage

A sufficient temporal resolution is important for a valid quantitative measurement of K^{trans}, especially when an individual vascular input function (VIF) is to be included. In general, temporal resolution should not be lower than 4 s in most cases; however, the tables below specify organ specific recommendations. In tissues with low vascularization the temporal resolution could be lower. When measuring a patient-specific VIF, the temporal resolution should be able to resolve the sharp peak at the beginning of the Dynamic scan. It is also important to cover a sufficiently long period of about 6 min for the permeability-dependent part of K^{trans}. In general, at least 5 baseline phases are acquired before the arrival of the contrast agent to allow the conversion from signal to contrast agent concentration; organ specific recommendations are included in the tables below.

Spatial resolution and coverage

The field of view of dynamic and T_1 mapping sequences should at least cover the whole tumor. The usage of an individual or patient normalized VIF also requires the presence of a feeding vessel in the FOV. The vessel used for the VIF, should, however, not be located at the edge of the imaging volume, to avoid inflow effects. The spatial resolution should be sufficient to resolve the tumor size and relevant heterogeneities (e.g., necrosis, enhancing rim), and in the case of a measured VIF (e.g. in the iliac artery of 10 to 14 mm of diameter, in or in sagittal sinus with 7 to 8 mm), be sufficient to resolve the vessel lumen. If no such vessel is available, consider using a population averaged VIF.

Image Acquisition Considerations: Signal saturation and non-linearity

The relation between signal and concentration in T1 weighted MRI sequences is non-linear but can be inferred using the matching mathematical relation (see Appendix C).

If the changes in signal induced by the changes in contrast agent concentration are too small, these might be masked by noise. In this case changes in contrast agent concentration will not be measurable. Therefore the sequence must be adjusted to the expected range of contrast agent concentration using a short TR and large FA to ensure sufficient T_1-weighting. If the maximum concentration exceeds the expected range, changes in concentration could be undetectable.

Additionally, high contrast agent concentration causes a significant T_2* effect, which results in a significant signal loss, e.g., in large vessels. These effects are more pronounced at 3 T, as the specific

absorption rate (SAR) limitations require lower FAs or longer TRs (21).
Consequently, new DCE sequences or applications should be tested using NIST's T1 phantoms and software. Comparing the T_1 measurements of the phantom T_1 calibrated containers ensures that differences in the expected concentration range are detectable by the sequence used. The required assessment procedure is described in section 4.1.2.

In configurations with T_2* weighting, high contrast agent concentration can result in significant T2 and T_2* effects. In those, the signal decreases with increasing contrast agent concentration resulting in an underestimation of contrast agent concentration. The measurement of the VIF is susceptible to this problem because of the inherently high concentration of contrast agents. This influence can be addressed by lowering the T_2* weighting of the sequence or by using a population-averaged VIF.

Validity of sequence parameters

Product sequences might make hidden modifications to acquisition parameters to mitigate SAR. For instance, the actual FA might be modified. Compare the DICOM Tag "FlipAngle" and "RepetitionTime" in the stored data with the ones in the sequence settings (but beware if 2D GRE sequences are used the TR, in the case of at least one manufacturer, is not the actual TR[1]). You might need to identify the appropriate vendor tags to determine the proper flip angle. Contact the technical support of the vendor if unsure.

3.6.2 Specification

Brain (16, 17)

Actor: Physicist/Technologist			
	Parameter	**Requirement**	**DICOM Tag**
***T_1*-mapping Protocol (VFA Series)**	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent[2, 3]**	**0018,0024**
	FAs	**Multiple FAs ranging from 2-25° Numbers of FAs supported in the literature vary from 2-7.**	**0018,1314**
	TR	**Ensure TR stays constant for all flip angles**	**0018,0080**
	TE	**Ensure TE stays constant for all flip angles**	**0018,0081**
	Number of Signal Averages (NSA or NEX)	**NSA or NEX ≥ 1 recommended**	**0018,0083**
	Phantom estimated error	**< 10 %, should be adjusted to site claim wCV.**	
DCE-MRI Protocol	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent[2, 3]**	**0018,0024**
	FA	**Ranging from 25-35° (1.5T)/10-15° (3T)**	**0018,1314**

[1] The TR for 2D GRE sequences on Siemens systems is not the true TR, the Echo Spacing contains the valid TR.
[2] It is recommended to use comparable sequence settings for the DCE and VFA sequences.
[3] Recently introduced view sharing techniques used to shorten temporal while retaining spatial resolution need further investigation since the relation of concentration and signal curve needs to be investigated.

	TR	**Typical 3-8 ms, considering temporal resolution and coverage.**	**0018,0080**
	TE	**Minimal. Typical 1-5 ms. In phase at 1.5T=2.2 ms, in phase at 3T= 4.4 ms**	**0018,0081**
	Number of Baseline Phases	**≥ 5 phases**	**No dedicated tag exists**
	Temporal Resolution	**< 10 sec (ideal ≤ 5 s)**	**0018,1060 0008,0032[4]**
	Receiver Bandwidth	**Greater or equal to 250 Hz/pixel**	**0018,0095**
	Number of dynamics phases	**Typical 40-80 phases. Sufficient to allow acquisition of at least 5 minutes of post injection data plus at least 5 phases acquired before contrast agent injection (baseline images)**	
	Bits Stored	**The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent**	**0028,0101**
Common Specification	**Field Strength**	**Field Strength (1.5 T or 3 T)[5]**	**0018,0087**
	Receive Coil Name	**≥ 8 channels recommended**	**0018,1250**
	Reconstruction Diameter	**FOV 22-24 cm**	**0018,1100**
	Number of Slices	**Number of slices - Acceptable: ≥10 prior to spatial interpolation. Ideal: Sufficient number of slices to cover the region of interest while maintaining the spatial and temporal resolution**	**0020,1002**
	Slice Thickness	**Slice Thickness (≤ 5mm)**	**0018,0050**
	Spacing Between Slices	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 5mm, i.e., no gap)**	**0018,0088**
	Acquisition Matrix	**256 x 128-160 (before applying rectangular FOV)**	**0018,1310**
	Pixel Size	**≤2 mm**	**0028,0030**
	Imaging Plane	**The acquisition plane should include the lesion of interest and a large vessel with in-plane flow in order to capture a VIF-DICOM attribute is Image Orientation (Patient).**	**0020,0037**
	Frequency Encoding	**Typical anterior-posterior (AP) for the axial plane. The frequency encoding direction should be adjusted based on the location of the tumor being investigated and its relationship to flow artifact. Row/column direction encoded in DICOM Acquisition Matrix.**	**0018,1310**

Prostate

Actor: Physicist/Technologist			
	Parameter	**Requirement**	**DICOM Tag**

[4] Temporal resolution can be derived from the "AcquisitionTime" or "TriggerTime" of the volume.

[5] A field strength of 1.5 T shows a lower $B1^+$ influence but 3 T is commonly used. This influence should be taken into account (see Appendix E for a detailed discussion).

T_1-mapping Protocol (VFA Series)	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent [2, 3]**	**0018,0024**
	FAs	**2° - 20°, use 4-5 FAs**	**0018,1314**
	TR	**Ensure TR stays constant for all flip angles: < 5 ms**	**0018,0080**
	TE	**Ensure TE stays constant for all flip angles: < 2 ms**	**0018,0081**
	NSA or NEX	**NSA or NEX ≥ 1**	**0018,0083**
	Phantom phantom estimated error	**< 10 %, should be adjusted to site claim wCV.**	
DCE-MRI Protocol	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent[2, 3]**	**0018,0024**
	FAs	**Ranging from 15-25° (1.5T)/10-15° (3 T)**	**0018,1314**
	TR	**Minimum (< 5ms) However, relaxing to 7ms would allow Dixon imaging at 1.5T**	**0018,0080**
	TE	**Minimum (< 2ms)**	**0018,0081**
	Number of Baseline Phases	**≥ 5 phases**	**No dedicated tag exists**
	Temporal Resolution	**~10 s**	**0018,1060 0008,0032[3]**
	Receiver Bandwidth	**Greater or equal to 250 Hz/pixel**	**0018,0095**
	Number of dynamics phases	**Sufficient to allow acquisition of at least 5 minutes of post injection data plus at least 5 phases acquired before contrast agent injection (baseline images)**	**No dedicated tag exists**
	Bits Stored	**The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent**	**0028,0101**
Common Specification	**Field Strength**	**Field Strength (1.5 or 3T)[3]**	**0018,0087**
	Receive Coil Name	**surface coil ≥ 4 channels with/without endorectal**	**0018,1250**
	Reconstruction Diameter	**FOV to cover prostate with ≤1-2 mm in-plane resolution (~26-30 cm)**	**0018,1100**
	Number of Slices	**Number of slices - ~20 slices (full coverage of prostate and seminal vesicle if possible)**	**0020,1002**
	Slice Thickness	**≤ 5mm**	**0018,0050**
	Spacing Between Slices	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 5mm, i.e., no gap)**	**0018,0088**
	Acquisition Matrix	**≤256 x 160 (before applying rectangular FOV) – in order to meet other requirements**	**0018,1310**
	Pixel Size	**≤2 mm**	**0028,0030**
	Imaging Plane	**Axial plane (or AX-oblique plane, perpendicular to the feet-head (FH) [i.e. superior-inferior (SI)] axis of prostate) - DICOM attribute is Image Orientation (Patient)**	**0020,0037**
	Frequency encoding	**Anterior to posterior direction. Row/column direction encoded in DICOM Acquisition Matrix.**	**0018,1310**

Breast[6]

[6] No test-retest data are available for GKM K^{trans} and breast, therefore this table gives values derived from the literature

Actor: Physicist/Technologist			
	Parameter	**Requirement**	**DICOM Tag**
T_1 mapping Protocol (VFA Series)	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent [2, 3]**	**0018,0024**
	FAs	**2-30°, use 3-5 FAs**	**0018,1314**
	TR	**Ensure TR stays constant for all flip angles: < 8 ms**	**0018,0080**
	TE	**Ensure TE stays constant for all flip angles: < 3 ms**	**0018,0081**
	NSA or NEX	**NSA or NEX ≥ 1**	**0018,0083**
	T1 phantom estimated error	**< 10 %, should be adjusted to site claim wCV.**	
DCE-MRI Protocol	**Imaging Sequence**	**3D fast spoiled gradient recalled echo or equivalent[2, 3]**	**0018,0024**
	Flip Angles	**Ranging from 10-30°**	**0018,1314**
	TR	**< 8 ms**	**0018,0080**
	TE	**TE < 3 ms**	**0018,0081**
	Number of Baseline Phases	**Number of Phases before bolus injection: at least 2 phases or frames**	**No dedicated tag exists**
	Temporal Resolution[2]	**< 20 s**	
	Receiver Bandwidth	**Greater or equal 250 Hz/pixel**	**0018,0095**
	Number of dynamics phases	**Sufficient to allow 8 min or more of total acquisition time with at least 2 phases acquired before contrast agent injection (baseline images)**	**0018,1060 0008,0032[3]**
	Bits Stored	**The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent**	**0028,0101**
Common Specification	**Field Strength**	**Field Strength (1.5 or 3T)**	**0018,0087**
	Receive Coil Name	**Phase array, bilateral, ≥ 4 channels**	**0018,1250**
	Reconstruction Diameter	**Field-of-view (FOV) to cover the entire breast whether it is a unilateral or bilateral data acquisition. Generally, 18-24 cm for sagittal unilateral acquisition and 32-38 cm for axial bilateral acquisition.**	**0018,1100**
	Number of Slices	**Number of slices - Sufficient to cover the whole breast(s).**	**0020,1002**
	Slice Thickness	**<= 2.5mm**	**0018,0050**
	Spacing Between Slices	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 2.5mm, i.e., no gap)**	**0018,0088**
	Acquisition Matrix	**Use appropriate matrix size to meet 1-1.5 mm in-plane spatial resolution.**	**0018,1310**
	Pixel Size	**≤ 2 mm**	**0028,0030**
	Imaging Plane	**Sagittal for single breast coverage; axial for bilateral coverage - DICOM attribute is Image Orientation (Patient).**	**0020,0037**
	Frequency Encoding	**The frequency encoding direction should be adjusted so as to minimize motion artifacts. Recommend anterior-posterior (AP) for both sagittal and axial acquisitions. Row/column direction encoded in DICOM Acquisition Matrix.**	**0018,1310**

review. Note, that there is no claim definition for breast yet.

3.7. Subject Selection

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

3.7.1 Discussion

All subjects considered suitable for clinical contrast-enhanced MRI may be considered for a DCE study. If a patient needs adjustment in contrast-agent dose and bolus injection rate beyond the recommended conditions listed in this profile, the claims of the profile may not apply.

The technologist or nurse shall confirm that the patient has no contraindication to Gadolinium-based contrast agents (GBCA) and has venous access that allows bolus injection at the rate required to meet profile claim(s). Further guidelines on the safety profile of contrast agents, and in particular Gadolinium-based, can be seen in the ACR Manual on Contrast Media (22,23).

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

- The major regulatory agencies (Food and Drug Administration (FDA), European Medicines Agency (EMA)) and scientific societies have amended their guidelines regarding the use of GBCAs. The DCE-MRI committee advises reference to these documents when developing and considering DCE-MRI clinical trial protocols.
    - Recent FDA safety communications highlight recent concerns regarding the accumulation of gadolinium in the brain and other tissues (24,25).
    - The presence of metal, air or large hemorrhage may result in significant susceptibility artifacts that can influence the quantitative value of DCE-MRI measurements such that the claims made in this profile may not be achievable in some patients and clinical situations. For this reason, we recommended that quantitative DCE-MRI examinations should not be performed shortly after surgical procedures or biopsies near or within the lesions of interest.
    - Although the vascular half-life of the GBCAs addressed by the Profile is approximately 90 min, it is a contraindication for the use of the Profile (i.e. claims cannot be met) if patients receive ANY GBCA within 24 hours before a DCE-MRI procedure, as some residual CA may remain in the lesion(s) of interest and the impact of such residual CA on the within-patient coefficient of variation in enhancing tumors is unknown.

3.7.2 Specification

Parameter	Actor	Requirement

Prescription of GBCA	**Physician**	**Patient has no contraindication to GBCA**
Administration of GBCA	**Technologist or Nurse**	**Confirm that the patient has no contraindication to GBCA and has venous access that allows bolus injection at the rate required to meet profile claim(s)**

3.8. Subject Handling

This activity describes details of handling imaging subjects that are necessary to meet these Profile Claims. General MRI subject safety considerations apply but are beyond the scope of this Profile.

This activity describes details of handling imaging subjects to ideally meet the Profile Claim.

- Size and position of IV catheter placement should be noted and maintained in all successive scans.
- Positioning (depends on body part).
- Speed of injection should be noted and maintained in all successive scans.
- No GBCA shall have been administered within 24 hours before a DCE-MRI procedure as some residual GBCA may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation is unknown.
- Ideally, scanning is conducted on the same machine with the same scanner software.

3.8.1 Discussion

Beyond a clear, simple language description of the image acquisition procedure, patient preparation will include the placement of an intravenous catheter. Ideally the catheter is no smaller than 20 gauge (0.8 mm inner diameter) and should be ideally placed in the right antecubital fossa. However, what is critical is that the same injection site (whenever possible) and catheter size needs to be used for repeated studies. Under ideal circumstances the hematocrit should also be taken into account. Investigations show that this effect is neglectable (26).

3.8.2 Specification

Actor: Technologist	
Parameter	**Requirement**
Administration of Contrast Agent	**No GBCA shall have been administered within 24 hours before a DCE-MRI procedure**
Documentation of Injection Parameters	**Store or note the contrast agent (0018, 0010), volume (0018, 0041) , rate (0018, 0046) being used. Preferably in the appropriate DICOM tags.**

3.9. Image Data Acquisition

This activity describes details of the data acquisition process that are necessary to reliably meet the Profile Claim (such as adjusting certain protocol parameters for this specific patient study). It includes 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

The acquisition of quantitative DCE-MRI data requires rapid and consistent injection of IV contrast material and therefore requires a power injector, which typically is remotely controlled. The injection must start after the acquisition of adequate baseline images (see tables on protocol design for organ specific information) to measure and model the uptake of contrast.

This section describes the imaging protocols and procedures for conducting a quantitative DCE-MRI exam. Suitable localizer (scout) images shall be collected at the start of the exam and used to confirm proper coil placement as well as selection of appropriate regions to image. This is typically followed by routine non-contrast agent-enhanced sequences to delineate the number, location, and limits of the tumor extent.

For the VFA and DCE-MRI protocols, the scanner pre-scan calibration must remain constant during the acquisition of the imaging sequences. If an option to choose manual or auto pre-scan is available, it is advisable to run a sequence with the highest flip angle with auto pre-scan first and run the others, including DCE scan, with manual pre-scan to ensure constant pre-scan parameters. The VFA and DCE-MRI protocols shall be constructed with the same sequence, with identical geometric parameters like slice positioning and orientation, slice thickness and distance, FOV, and matrix size. If available, using copy reference functionality of the scanner is advisable.

The acquisition protocol must cover the entire area of interest, and that can be a challenge to maintain, since most sequences today cannot cover the entire brain and get sufficient spatial resolution to be clinically useful. Once images are acquired, they must be post-processed, typically requiring the images be sent to an analysis workstation.

The contrast agent brand, dose, volume and injection speed should be documented. Ideally in DICOM information in the images. The analysis software should also be adapted to those parameters.

3.9.2 Specification

Parameter	Actor	Requirement
Scan Procedure	**Acquisition Device**	**Study of individual patients shall be performed on the site pre-qualified scanner using the approved receiver coil and pre-built profile-conformant scan protocol (3.6.2).**
Patient Positioning	**Scanner Operator (Technologist)**	**Predefined positioning procedures and receiver coils (e.g., always head-first or always feet-first) shall be used for all study subjects. Subject-specific landmarks shall be centered on the target organ, which shall be located as close as is feasible to the magnet isocenter.**

Scan Parameters	**Scanner Operator (Technologist)**	**Subject-specific adjustments within allowed parameter ranges (3.6.2) shall be made to suit body habitus. Parameter adjustments for a given subject shall be constant for serial scans.[7]**
Contrast Media	**Scanner Operator (Technologist)**	**Document brand, dose, volume and injection speed of contrast agent.**
Acquisition Device	**Scanner Operator**	**The same scanner shall be used for baseline measurement and a subsequent longitudinal measurement for detecting change in K^{trans}.[7]**

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

In MRI, the scan and reconstruction methods are generally combined in the MRI sequence, therefore the reconstruction software shall be used per vendor specification for all imaging data reconstruction, including coil sensitivity profiles. Image post-processing such as image intensity-based normalization should not be applied. Other user-selected filters should be used with caution. In some scanners (e.g., Philips) the original floating-point values of the images should be used by rescaling the image with appropriate fields available in the DICOM headers if phased-array receiver coils are used. Image combination and reconstruction should be according to standard manufacturer algorithms and image analysis software.

3.10.2 Specification

Parameter	Actor	Requirement
Image Reconstruction	**Reconstruction Software**	**Image combination and reconstruction needs to be according to manufacturer standards. An intensity-based normalization is not to be applied.**
Spatial Registration	**Image Analyst**	**Following motion correction, spatial registration should be performed prior to generation of T_1 and K^{trans} maps. Prior to generating any inference on specified ROIs, spatial registration must be performed between the post-contrast T1 (for ROI definition), VFA T_1 and dynamic scan images.**

3.11. Image QA

[7] Not using the same scanner and image acquisition parameters for baseline and subsequent measurements does not preclude clinical use of the measurement but will exclude meeting the requirements of the profile claim.

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

3.11.1 Discussion

A quality review by the image analyst shall confirm correct:

- imaging parameters
- data structure before the data are submitted for analysis
- administration of the contrast agent by reviewing the contrast change resulting from the appearance of contrast agent in vessels and tissue
- contrast presence in tissue of interest and vessel for VIF definition
- compare the measured T_1 values of known tissue with the values published in earlier studies.

The image analyst shall check each volume for imaging artifacts (e.g., phase-encoded motion artifacts) or within-volume motion (smearing) in the area of interest (e.g., tumor), or the vessel required to define the VIF. They shall correct volume-to-volume motion with appropriate motion correction algorithms and correct for inflow effects when selecting a ROI for determining the VIF.

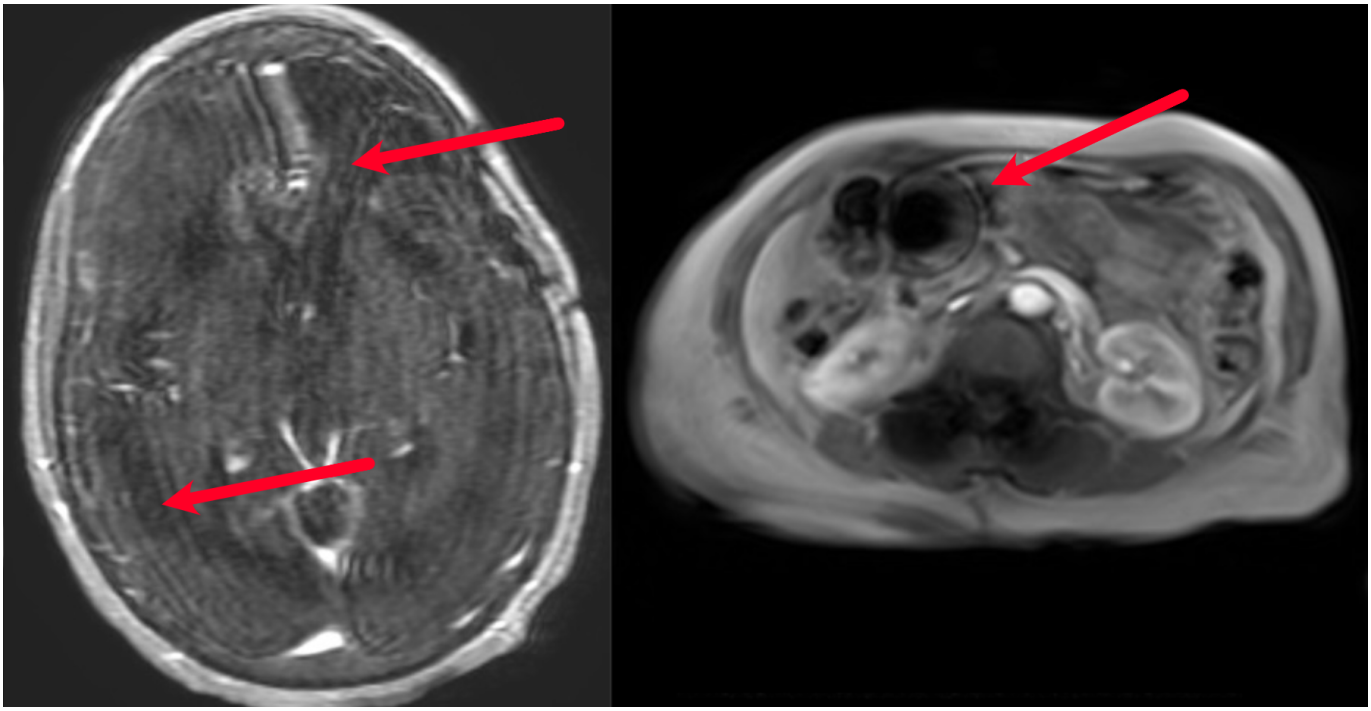

Figure 2: Example images for in-volume motion and susceptibility artifacts in MRI images. Left: a movement during a T_1 weighted brain scan. Right: signal destruction due to metallic stenting in the pancreas (Siemens fast spoiled gradient echo, FSPGR). Images courtesy Mark Shiroishi, USC, Los Angeles, CA, USA and Harrison Kim, UAB, Birmingham, AL, USA.

Whenever possible, a clear description of the image QA requirements should be pre-specified in the DCE-MRI protocol and all anticipated reasons for excluding individual DCE-MRI data from the final analysis should be defined (e.g. Figure 2: susceptibility artifacts, motion artifacts - within volume artifacts).

3.11.2 Specification

Actor: Image Analyst	
Parameter	**Requirement**
Patient Motion Artifacts	**Shall confirm the images containing no within-volume motion artifacts and volume-to-volume motion artifacts are corrected.**
No Contrast Agent Visible	**Shall confirm that a sufficient dose of contrast agent has been applied in the patient and that there is at least one non-contrast containing image volume at the beginning of the sequence.**
Tumor Present in Volume	**Shall confirm that the tumor and feeding vessel are present in the acquired volume over the whole sequence of images.**
Cardiac Pulsatility Artifact	**Shall confirm ROI under investigation is not affected by pulsatory effects. In case of an individual VIF, this also needs to be the case for the VIF defining region.**

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. All acquired reconstructed images as encoded by the scanner vendor in DICOM format shall be archived, including private data elements.

Post-processed data needs to be generated by the scanner, with scanner-vendor supplied software, or using third-party software. It is mandatory that post-processed images and data are stored in DICOM or other suitable medical image formats (See Appendix F).

Post-Processed Data

- **ROI:** Manually or automatically defined ROIs used for lesion and VIF definition need to be stored.
- **VIF:** Detailed specification of the VIF selection needs to be archived, either the population averaged VIF or the definition of ROI used for VIF measurement.
- **Lesions:** The ROI defining the lesion, either for ROI-averaged or voxel-by-voxel analysis, needs to be archived.

- **Registration:** When a motion correction is applied or the DCE data is aligned to images from other sequences or modalities, the reformatted DCE data needs to be stored. Alternatively, the deformation vector fields can be stored.
- **Parameter maps:** Maps of K^{trans}, T_1 and B_1 (if available) should be stored as images. If a non-DICOM format is used, the parameter maps are required to include the metadata required to generate the maps.

Interpretation Results

All medical interpretation of the results should be saved for purposes of verification and audit.

Image Analysis Results

We strongly recommend using standard representation for communicating parametric maps produced by the DCE-MRI analysis tools (both the pixel data and the accompanying metadata) to enable interoperability and reuse of the data. DICOM Parametric map object is the recommended representation of DCE analysis results. DICOM Parametric map can be converted easily into a range of research formats, and is supported by the growing number of commercial and open source imaging tools (27–29).

3.12.2 SPECIFICATION

Actor: Image Analyst	
Parameter	**Requirement**
Parameter Maps	**Store parameter maps of K^{trans}, T_1 and B_1 into floating point data format**
ROI Definition	**Archive ROI selection for analysis of tissue data and VIF measurement.**
Medical Interpretation	**Archive medical interpretations**
Metadata	**Store metadata along with non-DICOM files and store non-DICOM data (e.g., Hematocrit (HCT), population averaged VIF, etc)**

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. For longitudinal studies that are evaluating change in DCE parameters over time, the same software package should be used to analyze the data at each time point. Similarly, for multi-institutional studies, it is recommended that all the DCE data from all institutions are analyzed using the same software package. In clinical practice, the software package should not be changed for individual patients. New packages should be checked using the Digital reference object (DRO) assessment procedure described in 4.2 before being introduced in the clinical routine.

3.13.1 DISCUSSION

The extraction of quantitative DCE-MRI parameters requires a software package that addresses the algorithmic steps described below. The evaluation and validation of these packages is beyond the scope

of this profile. There are several commercial, open-source and possibly an in-house solution available for the required tasks. The OSIPI – Open Science Initiative for Perfusion Imaging (ismrm.org) has investigated several software packages and made a comprehensive list available. In addition, a lexicon and a code repository were developed to improve standardization (30,31).

Based on the algorithmic steps described below, the applicability of the software should be discussed with the vendors, developers or maintainers of the software. The software can be validated by DRO. Tofts 1999 GKM and eGKM based DROs are available at here (19) or at the QIBA wiki.

Algorithmic steps for parametric image calculation

Analysis of DCE-MRI data is carried out in a series of distinct steps. A detailed discussion of those steps can be found in Appendix C.

A. When required, apply time-series motion correction to the dynamic and T_1 mapping data.
B. Generate a native tissue T_1 map using the VFA data.
C. Determine a VIF or use population average VIF.
D. Convert tissue DCE-MRI signal intensity time-course data, S(t), to tissue contrast agent concentration, C(t) (or Delta T_1).
E. Calculate the DCE-MRI imaging biomarker parameter maps, K^{trans} using GKM or extended GKM
F. Identify the region or regions of interest as described in Appendix C.

3.13.2 SPECIFICATION

Parameter	Actor	Requirement
Motion Correction	**Radiologist / Image Analyst**	**A time-series motion correction needs to be applied when motion is present in the data. Both the original and corrected data should be archived.**
T_1 Map	**Acquisition Device**	**The native T_1 of the tissue needs to be determined using the VFA method.**
VIF	**Radiologist / Image Analyst**	**A VIF needs to be determined from the acquired dynamic images or the use of population-averaged VIFs needs to be documented.**
ROI-Determination	**Radiologist / Image Analyst**	**Shall segment the ROI consistently across time points using the same software / analysis package guided by a fixed set of image contrasts and avoiding artifacts. The ROI should be stored, preferably to the PACS system. Ideally, a high resolution post-contrast image is used.**
K^{trans} Analysis	**Image Analysis Tool**	**Software performance should be evaluated using the QIBA DRO at baseline and after any major software upgrade to ensure consistent results (Appendix C). The K^{trans} map or parameters for a ROI based curve must be calculated with the validated software and stored. The same software should be used across all time points for the same patient to evaluate change over time.**

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

A lack of reproducibility of DCE-MRI remains an impediment to its use in clinical trials and clinical practice (32). Various factors such as differences in MRI scanners, image acquisition sequences, choice of VIF, pharmacokinetic methods and choice of post-processing software can result in variability in DCE-MRI metrics (33–39). One other factor that can result in variability is the method of tumor segmentation. Currently, automated methods of ROI selection of tumors have been validated and so user-defined ROIs are employed. Recent work by Barboriak et al. in gliomas has shown that inter-reader variation in DCE-MRI metrics can vary by more than 16% due to attributable differences in user-defined ROIs (40). Future validation of automated methods of tumor segmentation may improve reproducibility of DCE-MRI.

3.14.2 Specification

Actor: Scanner Operator	
Parameter	**Requirement**
Lesion Coverage	**The FOV shall completely cover the lesion in both the transverse and slice directions.**
Absence of Substantial Artifacts	**No substantial artifacts shall cover the target lesion.**
Slab Placement Documentation	**The routinely acquired anatomical images shall be used to identify the slab position.**

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: T_1 Mapping accuracy and signal saturation

4.1.1 Testing T_1 mapping sequence and algorithm validity and accuracy

The requirements from periodic QA (section 3.5) a static T_1 phantom should be used. An evaluation software and a manual are available at DRO data on Zenodo (19).
A physical T_1-mapping phantom can evaluate the suitability of MRI hardware and sequence for DCE-MRI. NIST offers a phantom lending service, and also provides an evaluation software.

Other phantoms have been developed and are commercially available. The T_1 reference values should be in the range of 50 to 2000 ms. In the brain T_1 values vary between 500 and 5000 ms, but only 2000 ms if excluding ventricles), pre contrast, in the prostate also less than 2000 ms (41). Note that the concentration in highly perfused organs or tumors, i.e., kidneys, pancreas or breast lesions, might also become non-linear for the initial phases (42).

4.1.2 Testing sequence for signal quantification errors

T_1 precision

The fidelity of T_1 measurement should be assessed based on phantom imaging. As uncertainty in the measurement of T_1 is an important contributor to concentration measurement bias (43), the measured phantom T_1 values based on the VFA method (see Section 4) should be compared within the known T_1 values calibrated based on non-flip angle dependent methods (such as inversion recovery (IR) imaging with multiple inversion times (TIs))[8]. Simulation studies suggest that variation in the T_1 value by greater than 15% from actual may severely affect the reliability of the DCE-MRI quantification when T_1-dependent modeling of tumor gadolinium concentration in DCE-MRI studies is used. Therefore, if accurate T_1 values cannot be reproduced, it is recommended that T_1-dependent modeling not be performed.

T_1 Phantom imaging

To qualify the MRI scanner, phantom imaging QA is required using either the QIBA DCE-MRI phantom, or a similar multi-compartment phantom with a range of T_1 and T_2 relaxation rate values appropriate for DCE-MRI (44). With the exceptions noted below, imaging of the phantom should otherwise be performed using the same T_1 mapping and DCE-MRI acquisitions that are to be used in the clinical research protocol. Coil placement should approximate that which would be used for the purposes of the DCE-MRI studies.

4.1.3.1 Discussion

B_1 mapping: Nonuniformity of the transmit radiofrequency field (B_1^+) can lead to flip angle variations from the nominal value. Phantom studies have demonstrated that B_1^+ at 3T can be more inhomogeneous than at 1.5T. Although this inhomogeneity may be different *in vivo* than in phantoms, performing B_1^+ mapping at 3T to correct the flip angles using the scaling factors provided by the B_1^+ mapping sequence has potential value to improve quantitative DCE analysis. Without B_1^+ correction, the VFA T_1 maps at 3T will likely contain error and added uncertainty to the quantitative measurement. B_1^+ mapping *in vivo* in the head and knee are not mandatory at 1.5T, as the B_1^+ field is expected to be rather homogeneous, but publications suggest that B_1^+ can be inhomogeneous at 3T. As published by Rangwala et al. (45) in the prostate, Sengupta et al. for brain (46) and Sung for breast (47), B_1^+ maps in these areas indicate that values of the effective flip angle is in the range of 80-125% of the nominal value in all the three areas (brain, breast, prostate). B_1^+ mapping sequences are available as clinical products on many scanners (see Appendix E for details).

4.2 Assessment Procedure: Image Analysis Software

The requirements for the software in Image Analysis (section 3.13) can be evaluated using digital reference object data and an evaluation software comparing the calculated results. The assessment procedure will be performed in the following steps (for further details refer to Appendix C):

- Download the variable flip angle DRO data QIBA_T1_v03 from Zenodo (19). It is recommended to use the sigma 2 dataset with the lowest noise level.

[8] Methods such as IR and TR variation sequences should only be used for phantom validation since the native T_1 in the dynamic sequence is influenced by B_{1+}.

- Download the DCE Tofts data (QIBA_v12_Tofts). There are versions for mimicking General Electric (GE) and Siemens scanners. At this point for most tissues and field strength a T_1 of 2000 ms and a noise level of 5% should be selected, however the DRO database will be updated with more tissue specific T_1 ranges in the near future.
- Download the QIBA DRO Evaluation Tool (QDET) MSI installer from Zenodo (48) .
- Import the T_1 DRO data into your processing software and calculate the T_1 map. Disable motion correction in software if present. Store the map to your local disk.
- Import the DCE Tofts DRO into your processing software. The VIF can be obtained from the lowest row in the DRO dataset[9]. Set the $T_{1,0}$ parameters of the processing software to 1500 ms and the contrast agent relaxivity to 0.0037 $mmol^{-1}$ $msec^{-1}$. Select a spoiled gradient echo sequence. The sequence parameters are stored in the DICOM files.
- Calculate the pharmacokinetic parameters with your software package and store the results as a DICOM or binary file.
- Import the T_1 data using the T_1 mode of the QDET software and perform the evaluation.
- Import the Tofts results using the GKM mode of the QDET software and compare the K^{trans} values. The assessor shall fit an ordinary least squares (OLS) regression of the measured T_1 values on the known T_1 values. A quadratic term is first included in the model to rule out non-linear relationships. The assessor shall fit a linear model and estimate R^2. The R^2 should be above 0.95 and the slope of the linear model should be between 0.95 and 1.05.
- If higher deviations are encountered, contact the vendor/developer of the software package. The deviations should be documented.

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 F.

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 comments on models and implementations used as well as performance in DRO tests (as shown in sections 4.2) describing how

[9] Consult the authors of the QDET software if the used DCE analysis software automatically determines the VIF from the data.

their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing (see section 4.2).

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Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (49), Dynamic Contrast Enhanced Imaging Biomarker Committee. The 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. During the last four years, the following individuals have made critical contributions in the development of this Profile:

Hendrik Laue, PhD (Co-chair)	Sina Nazemi, MD	Wei Huang, PhD
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Ararat Chakhoyan, PhD	Zahra Hosseini, PhD	

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Alexander Guimaraes, MD, PhD	Thomas Chenevert, PhD	Richard J Martin, PhD
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Gudrun Zahlmann, PhD	Elizabeth Mirowski, PhD	Jinnan Wang, PhD

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Appendix B: Claim definition details

The claim definitions are based on test-retest data from 3 different studies. The protocols used in these studies shall be used as minimum bars which, nevertheless, would further decrease the variance and/or increase the accuracy of DCE when compared with current methods. Still, the statistics used for the claim definitions are linked to these experiments. Therefore, we give a summary of the protocols used in these experiments. To our estimation, the protocols proposed in this profile would lead to comparable or better results in reproducibility but since the availability of test-retest data for DCE is very limited, we cannot prove it.

BRAIN

For the brain, these claims are based on a study of 11 patients by (50). The imaging settings for this study are:

- A 1.5 T ACS Gyroscan NTPT6000 (Philips Medical Systems) scanner with a birdcage head coil was used
- A 16 G catheter was placed in the ante-cubital vein and 0.1 mmol/kg of Gd-DTPA-BMA was injected manually over 3-4 seconds following the seventh dynamic scan
- A T_1 map was acquired with FAs 2, 10, and 35°
- A temporal resolution of 5.1-8.7 s was used
- The duration of the scan was 10.6-17.4 minutes
- A measured VIF fitted with a bi-exponential

PROSTATE

For the prostate, these claims are based on a study of 20 patients by (16) and an 11 patient study by (17). The imaging requirements for this study and the related claim are listed as follows, from Alonzi et al:

- The scan was conducted at 1.5T (Siemens with phased array pelvic coil)
- A bolus of 0.1 mmol/kg of Gd-DTPA with a 20 ml saline flush was applied
- A T_1-weighted GRE fast low angle shot (FLASH) sequence (TE=5 ms, TR=74 ms, FA=70°, 8 mm slice thickness)
- The GKM with a Fritz-Hansen population based VIF was used (36)
- The temporal resolution was 12 s over the 8 minute DCE-MRI acquisition

- Neither T_1 nor B_1 map were acquired

From Peled et al:

- The scan was conducted at 3 T (GE with body-array and endorectal coil)
- 0.15 mmol/kg Gd-DTPA with a rate of 3 mL/s and a 20 mL saline flush
- TR=3.7-4.1 ms; FAs=12 and 15°; TE=1.3-1.4 ms; time per frame 5-8.4 s; scan time 4.5-5.5 minutes; matrix either 256×256×16 with resolution 1×1×6 mm, or 512×512×32 with resolution 0.55×0.55×2.5 mm
- Neither T_1 nor B_1 correction were used
- Assuming linear signal
- The GKM and eGKM models were used with a study based averaged VIF
- The ROI was defined on the T2* and DWI image of the same region

Appendix C: Detailed description of Image Analysis

Quantitative DCE-MRI requires dedicated software, either provided by the MRI manufacturer or by a third-party provider. In order to ensure the validity of the Claim statements in this profile, it is necessary that the algorithm used for analysis provide comparable results to the methods referenced for the Claim statements. Below, the steps recommended for data analysis are described in this section. In addition to ensuring these steps are taken, an approach for testing the validity of the algorithm used for analysis is to use the QIBA DRO data as a benchmark (19).

Methods to Be Used

A: Apply time-series motion correction to the dynamic data

In dynamic imaging, movement of the patient or body parts might corrupt the measurement. Data corrupted with motion must be either corrected before analysis or discarded for subsequent pharmacokinetic analysis. Guidance for the handling of movement during acquisition for the body sites or organs highlighted within this profile can be found below. Generally, an algorithm is included in DCE analysis software such as Elastix (51).

Brain: Motion correction is usually not necessary. If a patient moved the head during the acquisition, a shear restricting affine (rotation and translation, no shearing) correction might be applied.

Prostate: Motion correction is not necessary in the majority of cases; an endorectal coil or the use of Levsin or Glucagon for inhibiting gastrointestinal movement would improve image stability.

Breast: Non-linear motion correction may be applied to the data in order to improve image quality.

Head and neck: Many DCE-MRI studies have focused on metastatic cervical lymph nodes rather than primary head and neck tumors given that nodal regions are less prone to motion artifacts. If analysis of the primary tumor is desired and there is significant motion artifact, then a motion correction algorithm is recommended, if at all possible.

B: GENERATE A NATIVE TISSUE T_1 MAP USING THE VFA DATA

A complete map of pre-contrast T_1 for the imaged slab needs to be determined. The slice locations, orientation, and resolution of these images are to match those of the dynamic series. The series should be acquired immediately before the dynamic series. Consider the use of motion correction if the images show movement for different flip angles or the dynamic series. Voxel-based $T_{1,i}$ values are calculated and then used to perform an accurate signal to contrast agent concentration calculation for each voxel location i. Consider the use of motion correction if the images show movement for different flip angles or the dynamic series. The T_1 for the signal $S_{i,j}$ for flip angle αj at each voxel location can be calculated using the Levenberg-Marquardt optimization of T_1 with α_j as independent and $S_{i,j}$ as dependent variable (equation 1).

$$S_{i,j} = M_0 \sin\alpha_j \frac{1-E_{1,i}}{1-\cos\alpha_j E_{1,i}} \text{with } E_{1,i} = \exp(-TR/T_{1,i}) \quad (1)$$

Alternatively, the method proposed by Cheng and Wright (52) can be used by converting equation 1 to:

$$\frac{S_{i,j}}{\sin\alpha_j} = E_{1,i}\frac{S_{i,j}}{\tan\alpha_j} + M_0(1 - E_{1,i}) \quad (2)$$

Written in linear form $Y_i = m X_i + b$, this relation yields T_1 by fitting using a linear least mean square error method or by Levenberg-Marquardt. Fitting then yields T_1:

$$T_1 = -TR/\ln(m) \quad (3)$$

Note that the latter algorithm models the noise distribution of the MRI system less accurately (52).

C: DETERMINE A VIF.

The intent of this step is to generate an accurate, patient-specific VIF to serve as an input to the vascular model (38). The signal for the VIF can then be converted into concentration using the method described in Section C in this Appendix.

In some cases, data-driven VIFs may be difficult to measure accurately due to anatomy, motion, flow effects, and T2* effects. In these situations, alternative methods of using population-averaged VIF (37,53–55) or reference-tissue-based VIFs (56) may be used. These methods in general lead to poorer characterization of subject-specific physiology and lead to poorer reproducibility.

Proposal: The selection of the VIF is of central importance for the correct determination of K^{trans}. It frequently depends on the software package used but it might be possible to choose an option. Four methods are generally used:

- **A fully manual VIF selection** by using a drawn ROI is a feeding of or adjacent to the tumor in question. It has been demonstrated previously that this method has significant variability associated with it (57), due primarily to the spatially- and temporally-varying flow artifacts found in major arteries. Within the ROI it is advisable to select the most enhancing pixels (e.g., 5% most enhancing pixels in the ROI). Note that for high contrast agent concentrations the signal-to-concentration relation might become inaccurate, usually notable by a reduced first pass

peak in the VIF. Consider reducing the Flip Angle in these cases might help. The selection of VIF is organ and sequence specific (58),

- **A semi-automatic local optimal VIF** A better option is to make use of an automated search technique to generate a locally optimal VIF. Several methods of accomplishing this have been described (57,59). The VIF should be determined from the slice located at least 3 cm away from the first slice to prevent VIF unsaturation (60), when blood flows from the first slice.
- **A population averaged VIF** using values derived from previous studies (37,61). Common VIF are the Weinman- (62), the Parker-population averaged VIF is used. Fritz-Hansen published measured VIFs, which can also be parameterized and used as VIF. The use of the Weinman function is not recommended as it does not take into account the initial VIF peak. Software packages might allow changing the VIF used (37,62,63).
- **Fully Automated VIF selection** There are fully automated methods available (64,65). These are organ and sequence specific and possibly need some adjustments.

D: CONVERT TISSUE DCE-MRI SIGNAL INTENSITY TIME-COURSE DATA TO CONCENTRATION

The arbitrary signal intensity units in the dynamic data must be converted into units of contrast agent concentration. This step should be applied after the regions of interest for analysis have been defined, but prior to the calculation of vascular parameters. Two methods for accomplishing this are defined below.

Conversion using a signal formation model to contrast agent concentration at each image pixel is given by the relation of change of $T_1(t)$ over time with a pre-contrast, T_{10}:

$$\frac{1}{T_1(t)} - \frac{1}{T_{10}} = C(t)\, R_{Ca} \quad (4)$$

R_{Ca} is the relaxivity of the contrast agent (obtained from contrast agent manufacturer's specifications).

T_1(t) can be derived from the SPGR signal equation (neglecting T_2^* effects, assuming T_2^*>>>TE) and is given by the following expressions 5-7: Let

$$E_{10} = \exp(-TR/T_{10}) \quad (5)$$

$$B = \frac{1-E_{10}}{1-\cos\alpha\, E_{10}} \quad (6)$$

$$A = B\, S(t)/S(0) \quad (7)$$

where α is the FA, TR is the repetition time, and S(t) and S(0) are the signal intensities at time t and pre-contrast baseline respectively in the DCE-MRI sequence. Then,

$$R_1 = \frac{1}{T_1(t)} = -\frac{1}{TR}\ln\left(\frac{1-A}{1-\cos\alpha * A}\right) \quad (8)$$

With equation 4 the concentration curve C(t) can be determined by:

$$C(t) = (\frac{1}{T_1(t)} - \frac{1}{T_{10}})/R_{Ca} \quad (9)$$

E: CALCULATE THE DCE-MRI IMAGING BIOMARKER PARAMETER MAPS

Parameter K^{trans} will be calculated based on the GKM and eGKM (1). Equation 10 represents the tissue concentration in the GKM and equation 11 the tissue concentration for the eGKM:

$$C(t) = K^{trans} \int_{\tau=0}^{t} C_p(\tau) \exp(-\frac{k^{trans}(t-\tau)}{v_e}) d\tau \quad (10)$$

$$C_t(t) = v_p C_p(t) + K^{trans} \int_{\tau=0}^{t} C_p(\tau) \exp(-\frac{k^{trans}(t-\tau)}{v_e}) d\tau \quad (11)$$

where v_e is the fractional volume of the extracellular extravascular space. K^{trans} is the volume rate constant between blood plasma and v_e. Given the tissue uptake curve $C_t(t)$ and the VIF $C_p(t)$, K^{trans} are estimated using a gradient-descent energy minimization scheme, by using already established Levenberg-Marquardt or Minpack-1 curve fitting algorithms (66). Delay correction should be performed to shift the VIF curve to match the arrival time of the tumor curve for each voxel prior to curve fitting. A full parameter set will be calculated for each voxel within the defined tumor boundaries. Parameters may be reported out either as mean or median statistics per tumor.

F: IDENTIFY THE REGION OR REGIONS OF INTEREST

The first step in the extraction of quantitative parameter K^{trans} associated with a particular lesion is to segment this lesion from adjacent tissues. Which techniques of segmentation are ideal or even acceptable for a given application is the subject of on-going research, but it is clear that the segmentation techniques used must be tailored to the particular organ system being studied with DCE-MRI. The following guidelines are proposed:

- The committee recommends an analysis scheme where an operator defines regions of interest on anatomical images obtained at the same imaging session as the DCE-MRI that are co-registered to the DCE images (i.e. not directly on the K^{trans} maps). The correlative anatomical images should be obtained in the same imaging plane as the DCE-MRI series, with similar or higher spatial resolution. If feasible for smaller target organs, the anatomical images should be prescribed to match the DCE[10].
- Because of the presence of image noise on source images of the dynamic series, along with time-dependent changes in signal intensity which may blur or even obliterate the border between lesion and background tissue, analysis schemes in which lesions are segmented independently on each image of the dynamic series should be avoided where possible. In the case of moving organs,

[10] ROIs should be checked for coverage of the dynamic sequence if the whole tumor volume is evaluated. The ROI should be resampled to the grid used by the dynamic sequence to ensure a valid parameter evaluation.

it may be necessary to segment the lesion of interest on early (preferably, before the arrival of the contrast bolus) or late dynamic images and estimate the position of the segmented lesion in intermediate time points.

- A lack of reproducibility of DCE-MRI remains an impediment to its use in clinical trials and clinical practice (32). Various factors such as differences in MRI scanners, image acquisition sequences, choice of VIF, pharmacokinetic methods and choice of post-processing software can result in variability in DCE-MRI metrics (33,35–37,39). One other factor that can result in variability is the method of tumor segmentation. Currently, automated methods of ROI selection of tumors have been validated and so user-defined ROIs are employed. Recent work by Barboriak et al. has shown that interreader variation in DCE-MRI metrics can vary by more than 16% attributable to differences in user-defined ROIs (40). Future validation of automated methods of tumor segmentation may improve reproducibility of DCE-MRI.
- Several techniques are available that allow a semi-automated approach to be used. The training of the operator or operators in performing segmentations should be documented, preferably with training sets.

Appendix D: Conventions and Definitions

D.1 List of Abbreviations

- AP: Anterior-posterior
- CROs: Contract research organizations
- DCE-MRI: Dynamic contrast enhanced magnetic resonance imaging
- DICOM: Digital Imaging and Communications in Medicine; Medical imaging information standard
- DREAM: dual refocusing echo acquisition mode
- DROs: Digital reference object
- eGKM: Extended Generalized Kinetic Model
- EMA: European Medicines Agency
- FA: Flip angle
- FDA: Food and Drug Administration
- FLASH: fast low angle shot
- FOV: field-of-view
- FSPGR: fast spoiled gradient echo
- GBCA: gadolinium-based contrast agent
- Gd-DTPA: Gadolinium-diethylene triamine pentaacetic acid
- GKM: Generalized Kinetic Model
- GE: General Electric
- GRE: gradient echo
- HCT: hematocrit
- IR: Inversion Recovery
- TI: Inversion Time
- IV: Intravenous
- K^{trans}: contrast agent transfer constant
- MR: magnetic resonance

- MRI: magnetic resonance imaging
- LITT: laser interstitial thermal therapy
- NIST: National Institute of Standards and Technology
- NEX: Number of excitations
- NSA: number of signal averages
- OSIPI: open science initiative for perfusion imaging
- PACS: picture archiving and communication system
- QA: quality assurance
- QCA: quality control assessment
- QIBA: Quantitative Imaging Biomarkers Alliance
- QDET: QIBA DRO Evaluation Tool
- RF: radio frequency
- RMS: root means square
- ROI: region of interest
- SAR: specific absorption rate
- SI: signal intensity
- SNR: signal-to-noise ratio
- SPGR: spoiled gradient recalled
- T: Tesla
- TE: echo time
- TR: repetition time
- VEGF: vascular endothelial growth factor
- VFA: variable flip angle
- VIBE: volumetric interpolated breath-hold examination
- VIF: Vascular input function
- wCV: within-region-of-interest coefficient of variation
- %RC: repeatability coefficient

Appendix E: Vendor-specific B_1^+ Mapping information for 3 T

3T and higher field MRI systems are becoming more and more common. They are attractive primarily due to increased signal-to-noise ratio. Unfortunately, higher field strength increases the spatial heterogeneity in the images due to B_1^+ inhomogeneity. This leads to preventable errors in quantitative DCE-MRI measurements. Although the direct effect on reproducibility has not been investigated in clinical DCE-MRI, the effects are well characterized from phantom measurement and knowledge of the underlying physics. Based on this, we strongly recommend the use of advanced B_1^+ mapping techniques for DCE scans at 3T and higher field strengths. This B_1^+ information should then be used to correct pre-contrast T_1 maps and also be considered during quantitative DCE-MRI modeling.

The required B_1^+ mapping sequences are readily available; however, the best available imaging methods differ among MRI manufacturers and the optimal parameters are subject to change. Therefore, specific technical recommendations are difficult to provide in this document.

We recommend using B_1^+ mapping sequences and parameters used by Bliesener et al. (67). If these specific sequences are not available, we recommend working with the MRI manufacturer to obtain comparable sequences and settings. Such sequences and settings should be cross-validated against the double angle method (DAM) in MRI phantoms, similar to the validation performed in Bliesener et al (67).

Below are sequences and parameters that are available from four MRI manufacturers, as of Q1 2020.

Vendor Name	**GE**	**Philips**	**Siemens**	**Canon**
Usable Models	**MR750, MR750w**	**Achieva, Ingenia**	**Skyra, Prisma, Vida, Lumina, Spectra**	**Vantage Titan 3T, Vantage Galan 3T**
Required Software Version	**DV23.0 or never**	**DREAM: R5.2, DAM: RS 3.2** **AFI: 2.5**	**VB19, VD13, VE11, , VA10A and above**	**MPower 2.5 and above**
Sequence name	**FastB1Map**	**DREAM, Dual TR, Dual FA**	**tfl_b1Map**	**RSDE FASE2D (enable Pulse->Mapping)**
Sequence type	**Bloch-Siegert-Mapping, 2D**	**DAM, AFI, DREAM, 2D + 3D**	**pre-SAT-TFL, 2D multi-slice**	***k*-space spatial domain filtering, 2D**
Recommended Parameters	**FA=20**	**FA=0-90**	**pre-SAT FA = 80 (product protocol)**	**Tag FA-40, Tag Pitch=10**
Recommended Matrix			**64x64 (product protocol)**	**256x256**
Reference/Patent	**Sacolick et al, 2010** (68)	**Yarnykh, 2007** (69) **Cunningham et al, 2006** (70) **Nehrke and Böhnert, 2012** (71)	**Chung et al, 2010** (72)	**US Patent: US 8,077,955 B2**
Post-Processing	**External Software**	**Part of the reconstruction software**	**Inline correction of T_1 map as part of MapIt Corrected T_1 map can be loaded into Tissue4D for**	**Offline tool available from vendor**

			pharmacokinetic modeling	

Appendix F: Conformance Checklists

QIBA Checklist:

DCE-MRI Quantification (DCEMRI-Q)

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
Staff Qualification (section 3.1)			
Qualification	□ **Yes** □ **No**	May be a non-radiologist professional such as a medical physicist, biomedical engineer, MRI scientist or image analyst. The Scanner Operator for subject scanning should be a Technologist. The analyst has to be trained in technical aspects of DCE, including understanding key acquisition principles of DCE-MRI (Appendix C).	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Site Qualification (section 3.2)			
Qualification activities	□ **Yes** □ **No**	Shall perform qualification activities for Acquisition Device, Scanner Operator, and Image Analyst to meet equipment, reconstruction software, image analysis tool and phantom T_1 performance metrics as specified in tables in section 3.6.2 by protocol.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Coils	□ **Yes** □ **No**	Shall conform to the specifications given in tables in section 3.6.2 depending on the body site to be investigated.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Equipment	□ **Yes** □ **No**	The same, pre-qualified equipment and SW is recommended to be used over the length of a trial, and all preventive maintenance shall be documented over the course of the trial. Re-qualification shall be performed in case of major SW or hardware upgrade.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**

ACQUISITION DEVICE CHECKLIST

Name of Device Checked:

Parameter	Conforms (Y/N)	Requirement	Site Opinion
Pre-Delivery (section 3.2)			
Performance metrics	□ **Yes** □ **No**	Scanner shall meet established vendor performance metrics for given model.(vendor specific, factory)	□ **Routinely do already** □ **Feasible, will do**

			□ Feasible, will not do **□ Not feasible**
VFA-Sequence	**□ Yes** **□ No**	Scanner and coils should be capable of acquiring the variable flip angle sequences as defined in Table 3.6.2.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
DCE-Sequence	**□ Yes** **□ No**	Scanner and coils should be capable of acquiring the dynamic sequence as defined in Table 3.6.2.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
DICOM conformance	**□ Yes** **□ No**	Shall be capable of performing reconstructions and producing images with all the parameters set as specified in 3.6.2 "Protocol Design Specification".	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Installation (section 3.4)			
Contrast Injection Device	**□ Yes** **□ No**	A programmable power injector that is capable of injecting contrast agent up to 4-5 ml/s and has two bolus capability (for saline flush) must be properly serviced and calibrated.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Coils	**□ Yes** **□ No**	Coils need to satisfy the requirements specified in Tables in section 3.6.2 for the different sites.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Periodic QA (section 3.5)			
Periodic T_1 QA	**□ Yes** **□ No**	Physicist/MRI scientist shall perform periodic system QA that includes assessment of T_1 bias and SNR, random error, linearity, DCE image artifacts.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
T_1 precision	**□ Yes** **□ No**	Shall be verified by the use of an T_1 phantom. This needs to be performed after a hard- or software update. It is also required when changing the coil configuration.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**

System performance metrics	**□ Yes □ No**	Physicist/MRI scientist shall periodically confirm the Acquisition Device performs within vendor-established performance benchmark ranges for the given scanner model	**□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible**

SCANNER OPERATOR CHECKLIST

Name of Scanner Operator:

Parameter	Conforms (Y/N)	Requirement	Scanner Operator Opinion
Site Qualification (section 3.2)			
Acquisition Protocols	**□ Yes □ No**	Shall prepare scan protocols conformant with section 3.6.2 "Protocol Design Specification" and phantom qualification	**□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible**
Acquisition Protocols	**□ Yes □ No**	Shall perform assessment procedures for site qualification (section 3.2) and periodic QA (section 3.5)	**□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible**
Periodic QA (section 3.5)			
Reconstruction Software	**□ Yes □ No**	Shall confirm all participating reconstruction software conforms to this Profile.	**□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible**
Protocol design (section 3.6)			
Localizer	**□ Yes □ No**	A localizer sequence should be acquired to set the field of view to the appropriate region	**□ Routinely do already □ Feasible, will do □ Feasible, will not do □ Not feasible**
VFA-Mapping (see 3.9 for details)	**□ Yes □ No □**	A sequence to acquire the native T_1 of the ROI should be applied. Recommended is a variable flip angle sequence as specified in the Table 3.6.2 depending on the site investigated.	**□ Routinely do already □ Feasible, will do**

	Variations	Multiple FAs ranging from 2-30 degrees Numbers of FAs supported in the literature vary from 2-7.	**□ Feasible, will not do** **□ Not feasible**
B_1-Mapping	**□ Yes** **□ No**	A B_1 map should be acquired at 3 T field strength (and above). It is recommended that the VFA map be corrected with the acquired B_1 map.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
DCE: Signal linearity	**□ Yes** **□ No**	The sequence needs to be designed such that the signal enhancement by the contrast agent does not become saturated for high contrast agent concentrations. This can be checked using a T_1 phantom with the sequence first.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
DCE Imaging sequence	**□ Yes** **□ No**	3D fast spoiled gradient recalled echo or equivalent	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
DCE Number of baseline phases	**□ Yes** **□ No**	The number of baseline phases will depend on the body site (see section 3.6.2)	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Subject Handling (section 3.8)			
Use of intravenous contrast (Gd)	**□ Yes** **□ No**	It should be confirmed that no gadolinium-based contrast agent shall have been administered within 24 hours before a DCE-MRI procedure	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Use of intravenous contrast	**□ Yes** **□ No**	NFS, check blood tests for creatinine level	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Artifact Sources	**□ Yes** **□ No**	Move metal implants away from imaging vicinity, if possible. If not, align the longest extent with the B0 field.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Patient Positioning	**□ Yes** **□ No**	Predefined positioning procedure and receiver coil (e.g., always head-first or always feet-first, torso phased-array) shall be used for all study subjects. Subject specific landmark shall be centered on the target organ, which shall be located as close as is feasible	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**

		to magnet isocenter.	
Image Data Acquisition (section 3.9)			
Contrast-based Acquisition Timing	**□ Yes** **□ No**	Use 1 to 5 pre-contrast baseline scans for dynamic sequence depending on body site (per section 3.6.2)	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Scan Parameters	**□ Yes** **□ No**	Subject-specific adjustments within allowed parameter ranges (Table 3.6.2) shall be made to suit body habitus. Parameter adjustments for a given subject shall be constant for serial scans.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Acquisition Device	**□ Yes** **□ No**	The same scanner shall be used for baseline measurement and a subsequent longitudinal measurement for detecting changes and if this is not possible, this should be documented.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Image Reconstruction (section 3.10)			
Post-processing filters	**□ Yes** **□ No**	No post processing filters or normalization algorithms shall be applied.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**

IMAGE ANALYST CHECKLIST

Name of Image Analyst:

Parameter	Conforms (Y/N)	Specification	Technologist Opinion
Image Data Reconstruction (section 3.10)			
Image reconstruction	**□ Yes** **□ No**	Image combination and reconstruction needs to be according to manufacturer standards. An intensity-based normalization is not to be applied.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Spatial Registration	**□ Yes** **□ No**	Spatial misalignment due patient motion shall be corrected by image registration prior to generation of K^{trans} maps.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Image QA (section 3.11)			

Patient Motion Artifacts	□ **Yes** □ **No**	Shall confirm the images containing no within-volume motion artifacts and volume-to-volume motion artifacts are corrected.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
No Contrast Agent visible	□ **Yes** □ **No**	Shall confirm that a sufficient dose of contrast agent has been applied in the patient and that there is at least one non-contrast containing image volume at the beginning of the sequence	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Tumor present in volume	□ **Yes** □ **No**	Shall confirm that the tumor and feeding vessel is present in the acquired volume over the whole sequence of images.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Image Distribution (section 3.12)			
Regions of Interest (ROI)	□ **Yes** □ **No**	Manually or automatically defined ROIs used for lesion and VIF definition need to be stored.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Input function	□ **Yes** □ **No**	Detailed specification of the VIF selection needs to be archived, either the population averaged VIF or the defining ROI.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Lesion location	□ **Yes** □ **No**	The ROI defining the lesion, either for ROI-averaged analysis or statistics on voxel-by-voxel analysis needs to be archived.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Parameter maps	□ **Yes** □ **No**	Maps of K^{trans}, T_1 and B_1 (if available) should be stored as images. If a non-DICOM format is used, the parameter maps are required to include metadata required to generate the maps.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
Registration	□ **Yes** □ **No**	When a motion correction is applied or the DCE data is aligned to images from other sequences or modalities, the reformatted DCE data needs to be stored. Alternatively, the deformation vector fields can be stored.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not**

			do **□ Not feasible**
Image Analysis (section 3.13)			
Software	**□ Yes** **□ No**	The software should either be tested with the digital reference objects provided by QIBA or at least conform to the requirements described in section 3.13 and appendix C.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Image Interpretation (section 3.14)			
Artifact Sources	**□ Yes** **□ No**	**Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads and other metal equipment) such that they will not degrade the reconstructed volumes.**	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**

IMAGE ANALYSIS TOOL CHECKLIST

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

Parameter	Conforms (Y/N)	Requirement	Operator Opinion
Image Analysis (section 3.13)			
DRO Test	**□ Yes** **□ No**	Should give acceptable results when processing the DRO data for VFA and GKM/eGKM model provided by QIBA.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Motion correction	**□ Yes** **□ No**	Should be capable of applying a motion correction to dynamic and VFA data, if necessary.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
T_1 Map	**□ Yes** **□ No**	It should be capable of generating a T_1 map and include it into the Toft model calculation.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Signal to concentration	**□ Yes** **□ No**	It should convert the signal to concentration as described in appendix C.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not**

			do **□ Not feasible**
VIF	**□ Yes** **□ No**	A method to determine the VIF in the images or to use a population based VIF should be available.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
GKM or eGKM	**□ Yes** **□ No**	The calculation should be based on the GKM for moderately or the eGKM in case of highly perfused tissue (1).	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Highly Desirable but Not Required			
B_1 Map	**□ Yes** **□ No**	In case of a field strength of 3 T (above is not recommended), the software is ideally capable of importing or generating B_1 maps for a corrected T_1 map for the MRI scanner model used.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**
Storage of processing parameters	**□ Yes** **□ No**	Specific parameters used for calculation should be stored to allow reproducibility of results and to document the processing. This includes the VIF, initial values for fitting routines.	**□ Routinely do already** **□ Feasible, will do** **□ Feasible, will not do** **□ Not feasible**