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

Stage 1: Public Comment

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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. 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 publication 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. Does the conformance checklist include the necessary and feasible requirements for this profile? A. Requesting feedback from Public Comment
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: 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
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.

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. Which T_1 phantom should be used? **A. Got input from Ed. He will help including that information.**

1. Executive Summary

The goal of the DCE-MRI quantification QIBA Profile version 2.0 is to provide an update from Dynamic Contrast Enhanced MRI (DCE-MRI) Quantification profile (version 1.0, dated July 1, 2012) in order to include the use of 3 tesla (3T) MRI and the use of parallel imaging with receiver coil arrays. This QIBA Profile (DCE-MRI Quantification) predominantly addresses the K^{trans} parameter of the Tofts 1999 model (1), which is correlated with the vessel (surface/area product and permeability) and haemodynamic (flow) properties.

DCE-MRI is recognized as a potential method to provide predictive, prognostic and/or physiological response biomarkers for cancer (2-10). Remarkably, 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 appears to be a promising future for use of DCE-MRI for basic research, clinical research and in routine clinical practice. However, in order to fulfil this promise, 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 3 T MRI, we have introduced "recommended" procedures to calibrate and compensate for 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 (citation Kuhl et al, Krishna et al). 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 the expert suggested 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 the 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 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 characterising tissue vasculature. In this profile version, the focus lies on the contrast agent transfer constant, K^{trans} (1, 11), which derives from pharmacokinetic modelling and is a promising, reproducible parameter in DCE-MRI.

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 'watchful waiting' strategies, e.g., monitoring low-grade prostate cancer (12) or determining prognosis such as distinguishing between pseudo-progression and true progression in glioblastoma (13).

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 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 hold 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 claim.

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, and physicists developing and improving MRI protocols for DCE-MRI
- Radiologists, technologists, engineers and 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 organisations (CROs)
- Clinicians interested in quantitative therapy response assessment (including non-radiologists)
- Radiologists, health care providers, administrators 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): A measured change in K^{trans} of a brain lesion (glioblastoma multiforme, GBM) of 21 % or larger indicates that a true change has occurred with 95% confidence.

Claim 2 (prostate configuration a): A measured change of K^{trans} of a prostate lesion of 56 % or larger indicates that a true change has occurred with 95% confidence (GKM, individual AIF, 1.5T).
Claim 2 (prostate configuration b): At 3T, a measure change of K^{trans} of a prostate lesion of 95 % or larger indicates that a true change has occurred with 95% confidence. (GKM, individual AIF, 3.0T)
Claim 2 (prostate configuration c): At 3T, a measure change of K^{trans} of a prostate lesion of 95 % or larger indicates that a true change has occurred with 95% confidence. (eGKM, individual AIF, 3.0T)

Discussion:

Test-retest data from published scientific literature inform 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 and Alonzi et al. (14) included 20 patients for prostate. With these data we estimated the expected level of variance provided in the claim statements. The claims are specific for the protocol used in the publications used for the claim definition, as summarized in Appendix B.

As stated by Shukla-Dave et al. (15), the number of publications providing test-retest data is very limited for DCE, 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 interstitial space and the inflow of contrast agent from larger vessels. 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 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, then a later examination resulting 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 clinical interpretation with respect to the measured change in K^{trans} of a prostate lesion for claim configuration a:

Consider a prostate cancer patient undergoing radiation therapy. If the DCE-MRI in the examination prior to the intervention resulted in a K^{trans} of 0.9 min^{-1} in the tumor, then a later examination resulting in a K^{trans} of 0.2 min^{-1} (i.e., 100%*(0.2-0.9)/0.9 ≈ -78%) indicates a measurable decrease in K^{trans}, indicating a therapeutic success with 95% confidence. If K^{trans} is increased to 1.5 min^{-1} (100%*(1.5-0.9)/0.9 ≈ 67%, it can be considered as a true increase with 95% confidence based on Claim 2, pointing to a progressing disease or failing therapy.

Example clinical interpretation with respect to measured change in K^{trans} of a prostate lesion for claim configuration b and c: If the DCE-MRI in the examination prior to the intervention resulted in a K^{trans} of 1.4 min^{-1} in the tumor, then a later examination resulting in a K^{trans} of 0.01 min^{-1} (i.e., 100%*(0.01-1.4)/1.4 ≈ -99%) indicates a measurable decrease in K^{trans} of -99%, suggesting a therapeutic success with 95% confidence. A K^{trans} increased to 2.9 min^{-1} (100%*(2.9-1.4)/1.4 ≈ 107% 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 ROI drawn in the brain and prostate. For estimating the true change, the % Repeatability Coefficient (%RC) is used: 2.77 x wCV x 100%, or %RC=21.3% for brain and 55.7% for prostate. The wCV was obtained from the test-retest studies published in (11) and (14) and was 7.7% for brain and 20.1% for 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 is 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 MR scientist

**Image analyst may be a radiologist, technologist, physicist, or other MR 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.

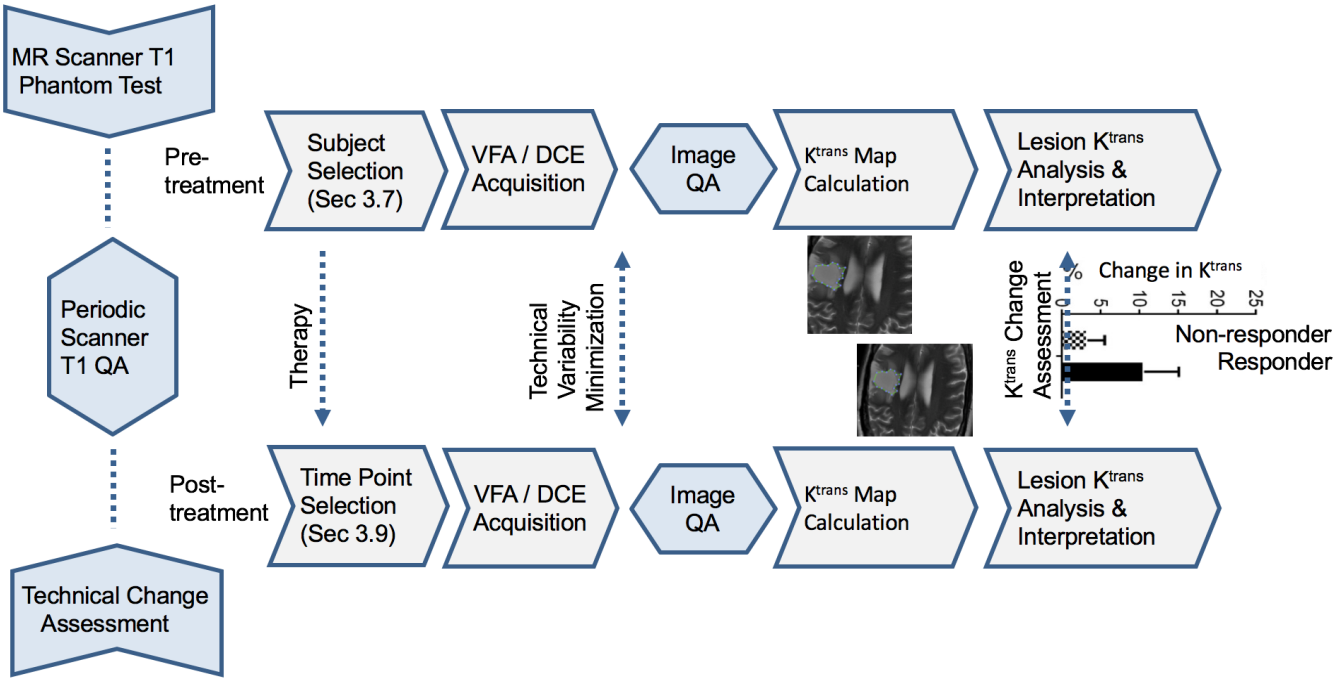

Figure 1: Typical quantitative Dynamic contrast-enhanced MRI (DCE-MRI) workflow for Treatment Response Assessment. Variable Flip Angle (VFA) denotes the recommended T_1-Mapping method, K^{trans}- map is determined using the General Kinetic Model (GKM) or extended GKM (eGKM).

3.1. Staff Qualification

This activity involves evaluating the human Actors (Radiologist, Physicist, and Technologist) prior to their

participation in the Profile. It includes training, qualification or performance assessments that are necessary to reliably meet the Profile Claim.

3.1.1 DISCUSSION

These requirements, as with any QIBA Profile requirements, are focused on achieving the Profile Claim. Evaluating the medical or professional qualifications of participating actors is beyond the scope of this profile. But the technician (or sometimes nurse involved in 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 E), procedures to confirm that the sequence, acquisition and DICOM metadata content is maintained along the network chain from scanner to 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 can be performed by a scanner operator, including a MR scientist or physicist.

3.1.2 SPECIFICATION

MR Technologists or other Site Personnel performing DCE-MRI studies

Parameter	Actor	Specification
Qualification	**MR 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 G, 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 adequate to meet the Profile Claim.

3.3.2 Specification

Parameter	Actor	Requirement
Performance metrics	Acquisition Device	Scanner shall meet established vendor performance metrics for given model
DCE sequence		Scanner shall be capable of obtaining proper temporal/spatial resolution and FOV with reasonable SNR for the target region.
DICOM conformance		DICOM Conformance Statement from Vendor will include DICOM tags for TE, TR, and 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. Site shall be capable of injecting contrast agent up to 4-5 mL/s with two bolus capability (for saline flush).

Coils

Parallel imaging allows to improve temporal resolution, which is very important to retrieve reliable vascular input function (VIF) and to conduct accurate image co-registration particularly in upper abdominal imaging. However, if the acceleration factor is too high, the images may be more vulnerable to noise and artifact, so it should be properly set (typically 2 or less).

3.5. Periodic QA

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

3.5.1 Discussion

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

DCE-MRI studies referenced in this QIBA Profile address imaging with either a 1.5 T or 3.0 T MRI scanner. The scanner hardware and software ideally should not be modified during a longitudinal study.

Phantom imaging for R_1 (see Assessment procedure 4.1): Phantoms with a range of R_1 values from *24* ms-1 to 1330 ms-1 shall be used. Examples of such phantoms include the QIBA DCE R_1 phantom and the NIST-ISMRM system phantom (or the system phantom lite). The phantoms will be available at the NIST phantom library *(https://www.nist.gov/programs-projects/medical-imaging-phantom-lending-library)*.

Phantom imaging data analysis: If using the QIBA DCE R_1 phantom, data should be analyzed in a uniform manner using the software provided by QIBA. The software can be downloaded from the QIBA data warehouse:

https://qidw.rsna.org/#collection/594810551cac0a4ec8ffe574/folder/5781d9271cac0a118c64d841.

Assurance should be made by the central site that the phantom scan orientation is correct, and the 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. In particular, it is strongly recommended that patients undergoing a longitudinal study be scanned on the same MRI system with the same software version whenever possible. 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 gadolinium-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	**Physicist/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	**Physicist/ Scientist**	**Shall perform periodic system QCA that includes assessment of T_1 bias, random error, linearity, T_1, SNR, DCE image artifacts**
R_1 precision	**Physicist/ Scientist**	**Shall be verified by the use of an R_1 phantom. This needs to be performed after hard- 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.

R_1 Mapping sequence

The accurate determination of contrast agent concentration requires the knowledge of the local $\boldsymbol{R_1}$. Recommended for this purpose is the variable flip angle method. Use the same 3D T_1-weighted GRE sequence as the one used for the DCE MRI scan, and repeat sequence with multiple flip angles varying from 2° to 30°. It is advisable to run the gradient echo (GRE) sequences of the VFAs with 2 dynamic scans, and use the second dynamic scan for the analysis, as this allows to build up steady state in the signal.

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 H.

Temporal resolution and coverage

A sufficient temporal resolution is important for a valid quantitative DCE examination, especially when an individual 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 tissue with low vascularization without a VIF the temporal resolution could be lower. 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 4 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 R_1 mapping sequence should at least cover the whole tumor. The usage of an individual or adjusted VIF requires also the presence of a feeding vessel. The spatial resolution should be sufficient to resolve the tumor size and relevant heterogeneities (e.g., necrosis, enhancing rim).

Image Acquisition Considerations: Signal saturation and non-linearity

Depending on the sequence used, the relation between signal and concentration can become non-linear for high Ca concentrations. At 1.5T, the MRI parameter ranges should result in a sufficiently linear relation and prevent flattening of the curve. It is recommended to test the sequences using the R_1 phantoms and software by NIST (https://www.nist.gov/programs-projects/medical-imaging-phantom-lending-library) (see also section 4.1.2).

At 3.0T, signal linearity may be difficult to preserve due to a T_2^* effect and SAR limits that require the use of lower FAs and/or longer TRs, which then lower the T_1-weighting of the sequence.

Product sequences might make hidden modifications to acquisition parameters in order to mitigate SAR. For instance, the actual flip angle might be modified. Check the DICOM Tag FlipAngle (0018,1314) and

RepetitionTime (0018,0080) in the stored data if it is equal to the one in the sequence settings. On some scanners you might need to check some vendor tags to identify the FlipAngle used. Contact the technical support of the vendor if unsure.

3.6.2 Specification

Brain (16, 17)

	Parameter	Actor	Requirement	DICOM Tag
T_1-mapping Protocol (VFA Series)	Imaging sequence	Physicist/Technologist	3D fast spoiled gradient recalled echo or equivalent	0018,0024
	Flip Angles (FAs)	Physicist/Technologist	Multiple FAs ranging from 2-30° Numbers of FAs supported in the literature varies from 2-7.	0018,1314
	Repetition Time (TR)	Physicist/Technologist	Ensure TR stays constant for all flip angles	0018,0080
	Echo time (TE)	Physicist/Technologist	Ensure TE stays constant for all flip angles	0018,0081
	Number of signal averages (NSA or NEX)		NSA or NEX ≥ 1 recommended[A1]	0018,0083
DCE-MRI Protocol	Imaging sequence	Physicist/Technologist	3D fast spoiled gradient recalled echo or equivalent	0018,0024
	Flip Angles	Physicist/Technologist	Ranging from 25-35° (1.5T)/10-15° (3T)	0018,1314
	Repetition Time (TR)	Physicist/Technologist	Typical 3-8 ms, considering temporal resolution and coverage.	0018,0080
	Echo time (TE)	Physicist/Technologist	Minimal. Typical 1-3 ms. In phase at 1.5T=4.2 ms, in phase at 3T= 2.6 ms	0018,0081
	Number of baseline phases	Physicist/Technologist	≥ 5 phases	
	Temporal Resolution	Physicist/Technologist	< 10 sec (ideal ≤ 5 s)	
	Receiver Bandwidth	Physicist/Technologist	Greater or equal to 250 Hz/pixel	0018,0095
	Number of dynamics (phases)	Physicist/Technologist	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	Physicist/Technologist	The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent	0028,0101
Common Specification	Field Strength	Physicist/Technologist	Field Strength (1.5T)	0018,0087
	Receive Coil Name	Physicist/Technologist	≥ 8 channels recommended	0018,1250

	Reconstruction Diameter	**Physicist/Technologist**	**Field-of-view (FOV) 22-24 cm**	**0018,1100**
	Images in Acquisition	**Physicist/Technologist**	**Number of slices - Acceptable: ≥10 prior to zero fill. Ideal: as many as possible while maintaining ideal temporal resolution**	**0020,1002**
	Slice Thickness	**Physicist/Technologist**	**Slice Thickness (≤ 5mm)**	**0018,0050**
	Spacing Between Slices	**Physicist/Technologist**	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 5mm, i.e., no gap)**	**0018,0088**
	Acquisition Matrix	**Physicist/Technologist**	**256 x 128-160 (before applying rectangular FOV)**	**0018,1310**
	Pixel Spacing	**Physicist/Technologist**	**1-2 mm**	**0028,0030**
	Imaging Plane	**Physicist/Technologist**	**The acquisition plan should include the lesion of interest and a large vessel with in-plane flow in order to capture a vascular input function (VIF) - DICOM attribute is Image Orientation (Patient).**	**0020,0037**
	Frequency encoding	**Physicist/Technologist**	**Typical anterior-posterior (AP) for axial plane. The frequency encoding direction should be adjusted based on the location of the tumor being interrogated and its relationship to flow artifact. Row/column direction encoded in DICOM Acquisition Matrix.**	**0018,1310**

Prostate

	Parameter	Actor	Requirement	DICOM Tag
T_1 mapping Protocol (VFA Series	**Imaging sequence**	**Physicist/Technologist**	**3D fast spoiled gradient recalled echo or equivalent**	**0018,0024**
	Flip Angles (FAs)	**Physicist/Technologist**	**2° - 15°, use 3-5 FAs**	**0018,1314**
	Repetition Time (TR)	**Physicist/Technologist**	**Ensure TR stays constant for all flip angles: < 5 ms**	**0018,0080**
	Echo time (TE)	**Physicist/Technologist**	**Ensure TE stays constant for all flip angles: < 2 ms**	**0018,0081**
	Number of signal averages (NSA or NEX)		**NSA or NEX ≥ 1**	**0018,0083**
DCE-MRI Protocol	**Imaging sequence**	**Physicist/Technologist**	**3D fast spoiled gradient recalled echo or equivalent**	**0018,0024**
	Flip Angles	**Physicist/Technologist**	**Ranging from 15-25° (1.5 T)/10-15° (3 tesla)**	**0018,1314**
	Repetition Time (TR)	**Physicist/Technologist**	**Minimum (< 5ms)**	**0018,0080**
	Echo time (TE)	**Physicist/Technologist**	**Minimum (< 2ms)**	**0018,0081**
	Number of baseline phases	**Physicist/Technologist**	**≥ 5 phases**	

	Temporal Resolution	**Physicist/Technologist**	**~10 s**	
	Receiver Bandwidth	**Physicist/Technologist**	**Greater or equal to 250 Hz/pixel**	**0018,0095**
	Number of dynamics (phases)	**Physicist/Technologist**	**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	**Physicist/Technologist**	**The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent**	**0028,0101**
Common Specification	**Field Strength**	**Physicist/Technologist**	**Field Strength (1.5 or 3T)**	**0018,0087**
	Receive Coil Name	**Physicist/Technologist**	**endorectal and/or surface coil ≥ 4 channels**	**0018,1250**
	Reconstruction Diameter	**Physicist/Technologist**	**Field-of-view (FOV) to cover prostate with ≤1-2 mm in-plane resolution (~26-30 cm)**	**0018,1100**
	Images in Acquisition	**Physicist/Technologist**	**Number of slices - ~20 slices (full coverage of prostate and seminal vesicle if possible)**	**0020,1002**
	Slice Thickness	**Physicist/Technologist**	**Slice Thickness (≤ 5mm)**	**0018,0050**
	Spacing Between Slices	**Physicist/Technologist**	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 5mm, i.e., no gap)**	**0018,0088**
	Acquisition Matrix	**Physicist/Technologist**	**≤256 x 160 (before applying rectangular FOV) – in order to meet other requirements**	**0018,1310**
	Pixel Spacing	**Physicist/Technologist**	**≤1-2 mm**	**0028,0030**
	Imaging Plane	**Physicist/Technologist**	**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	**Physicist/Technologist**	**Anterior to posterior direction. Row/column direction encoded in DICOM Acquisition Matrix.**	**0018,1310**

Breast[1]

	Parameter	**Actor**	**Requirement**	**DICOM Tag**
T_1 mapping Protocol (VFA Series)	**Imaging sequence**	**Physicist/Technologist**	**3D fast spoiled gradient recalled echo or equivalent**	**0018,0024**
	Flip Angles (FAs)	**Physicist/Technologist**	**2-30°, use 3-5 FAs**	**0018,1314**

[1] No test-retest data is available for Tofts K^{trans} and breast therefore this table gives values derived from the literature review. Note, that there is no claim definition for breast yet.

	Repetition Time (TR)	**Physicist/Technologist**	**Ensure TR stays constant for all flip angles: < 8 ms**	**0018,0080**
	Echo time (TE)	**Physicist/Technologist**	**Ensure TE stays constant for all flip angles: < 3 ms**	**0018,0081**
	Number of signal averages (NSA or NEX)		**NSA or NEX ≥ 1**	**0018,0083**
DCE-MRI Protocol	**Imaging sequence**	**Physicist/Technologist**	**3D fast spoiled gradient recalled echo or equivalent**	**0018,0024**
	Flip Angles	**Physicist/Technologist**	**Ranging from 10-35°**	**0018,1314**
	Repetition Time (TR)	**Physicist/Technologist**	**< 8 ms**	**0018,0080**
	Echo time (TE)	**Physicist/Technologist**	**Echo Time (TE) < 3 ms**	**0018,0081**
	Number of baseline phases	**Physicist/Technologist**	**Number of Phases before bolus injection: at least 2 phases or frames**	
	Temporal Resolution	**Physicist/Technologist**	**< 20 s[2]**	
	Receiver Bandwidth	**Physicist/Technologist**	**Greater or equal 250 Hz/pixel**	**0018,0095**
	Number of dynamics (phases)	**Physicist/Technologist**	**Sufficient to allow 8 min or more of total acquisition time with at least 2 phases acquired before contrast agent injection (baseline images)**	
	Bits Stored	**Physicist/Technologist**	**The maximum dynamic range should be utilized, e.g., "extended dynamic range" or equivalent**	**0028,0101**
Common Specification	**Field Strength**	**Physicist/Technologist**	**Field Strength (1.5 or 3T)**	**0018,0087**
	Receive Coil Name	**Physicist/Technologist**	**Phase array, bilateral, ≥ 4 channels**	**0018,1250**
	Reconstruction Diameter	**Physicist/Technologist**	**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**
	Images in Acquisition	**Physicist/Technologist**	**Number of slices - Sufficient to cover the whole breast(s) with considerations of slice thickness and guidelines of ACR breast MRI accreditation.**	**0020,1002**
	Slice Thickness	**Physicist/Technologist**	**<= 2.5mm, following guidelines of ACR breast MRI accreditation.**	**0018,0050**
	Spacing Between Slices	**Physicist/Technologist**	**Center-to-center distance (not gap) (same as Slice Thickness and ≤ 2.5mm, i.e., no gap)**	**0018,0088**

[2] 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.

	Acquisition Matrix	**Physicist/Technologist**	**use appropriate matrix size to meet 1-1.5 mm in-plane spatial resolution**	**0018,1310**
	Pixel Spacing	**Physicist/Technologist**	**1-2 mm**	**0028,0030**
	Imaging Plane	**Physicist/Technologist**	**Sagittal for single breast coverage; axial for bilateral coverage - DICOM attribute is Image Orientation (Patient).**	**0020,0037**
	Frequency encoding	**Physicist/Technologist**	**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**

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. (based on kidney function). If a patient needs adjustment in gadolinium 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 agent and has venous access that allows bolus injection at the rate required to meet profile claim(s).

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 (GCP) will be substituted for the default in cases where there are known risks.

- The major regulatory agencies (FDA, 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: http://www.fda.gov/drugs/drugsafety/ucm455386.htm
    - The presence of metal, air or large hemorrhage may result in significant susceptibility artifact 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 gadolinium-based contrast agent within 24 hours before a DCE-MRI procedure, as some residual contrast agent may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation in enhancing tumors is unknown.

3.7.2 SPECIFICATION

Parameter	Actor	Requirement
Administration of contrast agent	**Technologist (or nurse)**	**Patient has no contraindication to gadolinium-based contrast agent 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 this 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 gadolinium-based contrast agent shall have been administered within 24 hours before a DCE-MRI procedure as some residual contrast agent may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation is unknown.

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 (0.8mm inner diameter) and should be ideally placed in the right antecubital fossa, but what is critical is that the same injection site (whenever possible) and catheter size needs to be used for repeated studies.

3.8.2 SPECIFICATION

Parameter	Actor	Requirement
Administration of contrast agent	**Technologist**	**No gadolinium-based contrast agent shall have been administered within 24 hours before a DCE-MRI procedure**

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 region 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. 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.

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 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 landmarks shall be centered on the target organ, which shall be located as close as is feasible to magnet isocenter.
Scan Parameters	Scanner Operator (Technologist)	Subject-specific adjustments within allowed parameter ranges (Section 3.6.2) shall be made to suit body habitus. Parameter adjustments for a given subject shall be constant for serial scans. †
Acquisition Device	Scanner Operator	The same scanner shall be used for baseline measurement and a subsequent longitudinal measurement for detecting change in K^{trans}. †

† 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.

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. Image intensity-based normalization should not be applied. Coil sensitivity profiles should be included into the reconstruction. 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.

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**	**Spatial misalignment due patient motion shall be corrected by image registration prior to generation of K^{trans} maps.**

3.11. Image QA

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

3.11.1 Discussion

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

The image analyt shall check each volume for pulsatory effects 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.

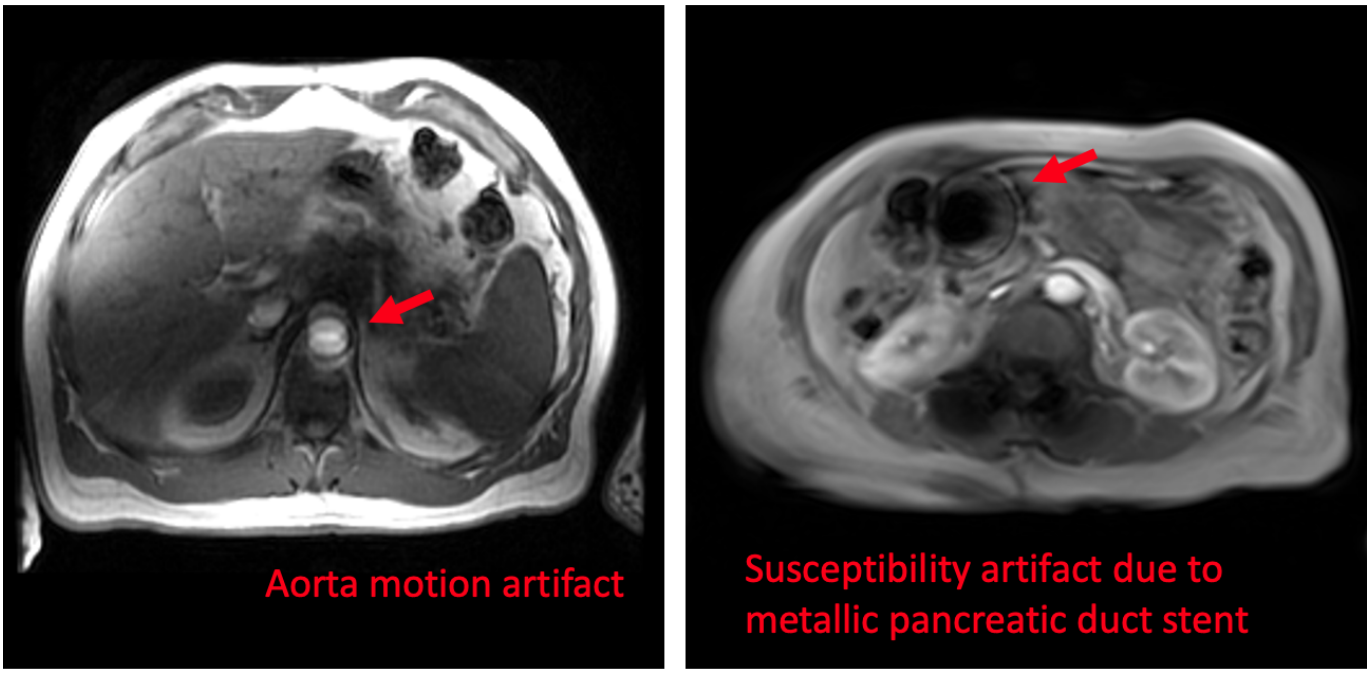

Figure 2: Example images for in-volume motion and susceptibility artefacts in MRI images. Left: a movement in the aorta during volume acquisition (GE VIBE image) and signal destruction due to metallic stenting in the pancreas (Siemens FSPGR). Images courtesy Harrison Kim, UAB, Birmingham, AL, USA.

Whenever possible, a clear description of the image quality assurance (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: pulsation artifacts, susceptibility artifacts, motion artifacts - within volume artefacts, volume-to-volume artefacts).

3.11.2 SPECIFICATION

Parameter	Actor	Requirement
Patient Motion Artifacts	**Image Analyst**	**Shall confirm the images containing no within-volume motion artifacts and volume-to-volume motion artifacts are corrected.**
No Contrast Agent visible	**Image Analyst**	**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	**Image Analyst**	**Shall confirm that the tumor and feeding vessel is present in the acquired volume over the whole sequence of images.**
Cardiac Pulsatility Artifact	**Image Analyst**	**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

- **Regions of Interest (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 (http://dicom.nema.org/medical/dicom/current/output/chtml/part03/sect_A.75.html). 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 (e.g., https://www.mevislab.de) (18-20).

3.12.2 Specification

Parameter	Actor	Requirement

Parameter Maps	**Image Analyst**	**Store parameter maps of K^{trans}, T_1 and B_1 into floating point data format**
ROI definition	**Image Analyst**	**Archive ROI selection for analysis of tissue data and VIF measurement.**
Medical interpretation	**Image Analyst**	**Archive medical interpretations**
Metadata	**Image Analyst**	**Store metadata along with non-DICOM files and store non-DICOM data (e.g., 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.

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. A comprehensive list can be found on the web page of the open source initiative for perfusion imaging (OSIPI) https://www.osipi.org/task-force-1-2/.

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 digital reference objects (DRO). Tofts 1999 GKM and eGKM based DROs are available at the QIBA data warehouse (https://qidw.rsna.org/) or at the QIBA wiki (https://qibawiki.rsna.org/index.php/Synthetic_DCE-MRI_Data).

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 data.
B. Generate a native tissue T_1 map using the VFA data.
C. Convert tissue DCE-MRI signal intensity time-course data, SI(t), to tissue contrast agent concentration, C(t) (or Delta R_1).
D. Determine a vascular input function.
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.

618

619 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.
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.

620

621 ## 3.14. Image Interpretation

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

624 3.14.1 DISCUSSION

625 A lack of reproducibility of DCE-MRI remains an impediment to its use in clinical trials and clinical practice
626 (21). Various factors such as differences in MRI scanners, image acquisition sequences, choice of AIF,
627 pharmacokinetic methods and choice of post-processing software can result in variability in DCE-MRI
628 metrics (22-28). One other factor that can result in variability is the method tumor of segmentation.
629 Currently, automated methods of ROI selection of tumor have been validated and so user-defined ROIs are
630 employed. Recent work by Barboriak et al. in gliomas has shown that inter-reader variation in DCE-MRI
631 metrics can vary by more than 16% attributable due to differences in user-defined ROIs (29). Future
632 validation of automated methods of tumor segmentation may improve reproducibility of DCE-MRI.

633 3.14.2 SPECIFICATION

Parameter	Actor	Requirement
Lesion coverage	**Scanner Operator**	**The FOV shall completely cover the lesion.**

Absence of substantial artefacts	**Scanner Operator**	**No substantial artefacts shall overly the target lesion.**
Slab placement documentation	**Scanner Operator**	**The routine anatomic image shall document 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: R_1/T_1 Mapping accuracy and signal saturation

4.1.1 Testing T_1 mapping sequence and algorithm validity and accuracy

The requirements form periodic QA (section 3.5) a static T_1 phantom should be used. An evaluation software and a manual are available at the QIDW:
https://qidw.rsna.org/#collection/594810551cac0a4ec8ffe574/folder/5781d9271cac0a118c64d841

A physical R_1/T_1-mapping phantom can evaluate the suitability of MRI hardware and sequence for DCE-MRI. NIST offers a phantom lending service (https://www.nist.gov/programs-projects/medical-imaging-phantom-lending-library), and also make available evaluation software.

Other phantoms have been developed and are commercially available (https://www.ultrasoundenterprises.com/mritext.html). 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 prostate also less than 2000 ms (30). 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 (31).

4.1.2 Testing sequence for signal quantification errors

R_1/T_1 precision

The fidelity of R_1 measurement should be assessed based on phantom imaging. As uncertainty in the measurement of R_1 is an important contributor to concentration measurement bias (32), the measured phantom R_1 values based on the VFA method (see Section 5) should be compared within the known R_1 values calibrated based on non-flip angle dependent methods (such as IR imaging with multiple TIs). Simulation studies suggest that variation in the R_1 value by greater than 15% from actual may severely affect the reliability of the DCE-MRI quantification when R_1-dependent modelling of tumor gadolinium concentration in DCE-MRI studies is used. Therefore, if accurate R_1 values cannot be reproduced, it is recommended that R_1-dependent modelling not be performed.

R_1/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 R_1 and R_2 relaxation rate values appropriate for DCE-MRI (16). With the exceptions noted below, imaging of the phantom should otherwise be performed using the same R_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. (33) in the prostate, Sengupta et al. for brain (17) and Sung for breast (34), 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 F 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 the data QIDW (https://qidw.rsna.org/#collection/594810551cac0a4ec8ffe574/folder/578021181cac0a118c5fa12f) It is recommended to use the sigma=2 dataset with the lowest noise level.
- Download the DCE Tofts data (QIBA_v12_Tofts). There are versions for mimicking GE and Siemens scanners.
- Download the QDET software evaluation tool msi installer from https://qidw.rsna.org/#collection/594810551cac0a4ec8ffe574/folder/578021041cac0a118c5fa128 .
- Import the T_1 DRO data into your processing software and calculate the R_1/T_1 map. 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 images. 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 1.

- 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 E.

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

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

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

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

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Appendices

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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 are already outdated by today and would not be used in an up to date study. 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 Jackson et al. (11). 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 T_1 map was acquired with FA=2, 10, 35°.
- 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 temporal resolution of 5.1 to 8.7 s was used
- The duration of the scan was 10.6 to 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 Alonzi et al. (14) and a study by Peled et al. (35). The imaging requirements for this study and the related claim are listed as follows, for Alonzi et al:

- The scan was conducted at 1.5T (Siemens with phased array pelvic coil)
- A FLASH sequence (TE=5 ms, TR=74ms, FA=70°, 8 mm slice thickness)
- A bolus of 0.1 mmol/kg of Gd-DTPA with a 20 ml saline flush was applied
- The GKM with a Fritz-Hansen population based VIF was used (36)
- The temporal resolution is 12 s over 8 minutes of DCE-MRI acquisition
- Neither T_1 nor B_1 map were acquired

for Peled et al:

- 0.15 mmol/kg Gd-DTPA with a rate of 3 ml/s and a 20 ml saline flush.
- 3T GE with a receiver endorectal coil

- TR 3.74.1 ms; flip angle 12° or 15°; TE = 1.31.4 ms; time per frame 58.4 seconds; scan time 4.55.5 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 AIF
- The ROI is 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 [https://qibawiki.rsna.org/index.php/Synthetic_DCE-MRI_Data] as a benchmark.

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.

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 reducing the motion would improve the image stability.

Breast: Non-linear motion correction may be applied to the data in order to improve image quality. Generally, an algorithm is included in the DCE analysis software. Elastix, open-source software based on ITK, is available at https://elastix.lumc.nl.

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 j 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).

$$S_{i,j} = M_0 \sin \alpha_j \frac{1-E_{1,i}}{1-\cos\alpha_1 E_{1,i}} \text{with } E_{1,i} = exp\,(-TR/T_{1,i}) \quad (1)$$

Alternatively, the method proposed by Cheng et al. (37) can be used by converting equation 1 to:

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

The linear from $Y_i = m\,X_i + b$ of this equation can yield 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 (37).

C: 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-contrastT_{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 (eqs 2-4): 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 flip angle, TR is the repetition time, and SI(t) and SI(0) are the signal intensities at time t and pre-contrast baseline respectively in the DCE-MRI sequence (eq 5). 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 1 the concentration curve C(t) can be determined by:

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

D: DETERMINE A VASCULAR INPUT FUNCTION.

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

In some cases, data-driven vascular input functions 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 (26, 39-41) or reference-tissue-based vascular input functions (42) 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 (43), 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 FlipAngle in these cases might help. The selection of AIF is organ and sequence specific (44),
- **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 (43, 45). The VIF should be determined from the slice located at least 3 cm away from the first slice to prevent VIF unsaturation (Roberts et al, Mag Res Med, 2011), when blood flows from the first slice.
- **A population averaged VIF** using values derived from previous studies (26, 46). Common VIF are the Weinman- [Weinman et al,], the Parker-population averaged AIF is used. [Parker et al,] Fritz-Hansen published measured AIFs, 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 to change the VIF used (26, 36, 47)
- **Fully Automated VIF selection** There are fully automated methods available (48-50). These are organ and sequence specific and possibly need some adjustments.

E: CALCULATE THE DCE-MRI IMAGING BIOMARKER PARAMETER MAPS

Parameter K^{trans} will be calculated based on the standard Tofts model (1). Equation 7 represents the tissue concentration in the GKM and equation 8 the tissue concentration for the extended GKM:

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

$$C_t(t) = v_p C_p(t) + K^{trans} \int_{\tau=0}^{t} C_p(\tau)\ exp\ (-\frac{k^{trans}(t-\tau)}{v_e})d\tau \qquad (11) \qquad (8)$$

where K^{trans} is the volume rate constant between blood plasma and extra-cellular extra-vascular space (EES) 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 (51). 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 a lesion by placing regions of interest on correlative 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). Correlative images should be obtained in the same imaging plane as the DCE-MRI series, with similar or higher spatial resolution.
- 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, 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 (21). Various factors such as differences in MRI scanners, image acquisition sequences, choice of AIF, pharmacokinetic methods and choice of post-processing software can result in variability in DCE-MRI metrics (22, 24, 25, 28, 52). One other factor that can result in variability is the method tumor of segmentation. Currently, automated methods of ROI selection of tumor 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 by differences in user-defined ROIs (29). 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

- CROs contract research organizations
- DCE-MRI: Dynamic contrast enhanced magnetic resonance imaging
- DICOM: Digital Imaging and Communications in Medicine; Medical imaging information standard https://www.dicomstandard.org/.
- DROs digital reference objects
- eGFR: estimated Glomerular Filtration Rate
- eGKM: extended General Kinetic Model
- EMA European Medicines Agency
- FA flip angle
- FDA Food and Drug Administration(21)
- FOV field-of-view
- FSPGR fast spoiled gradient echo
- GBCAs gadolinium-based contrast agents
- Gd-DTPA: Gadolinium-diethylene triamine pentaacetic acid
- GKM: General Kinetic Model
- GRE gradient echo
- Hct hematocrit
- IAUGCBN: Initial area under the Gadolinium concentration blood normalized
- K^{trans}: Permeability transfer constant
- LITT laser interstitial thermal therapy
- NIST National Institute of Standards and Technology
- NSA number of signal averages
- OSIPI: open source initiative for perfusion imaging
- QA quality assurance
- QIBA: Quantitative Imaging Biomarkers Alliance
- ROI: Region of Interest
- SAR Specific Absorption Rate
- SI: signal intensity
- SNR signal-to-noise ratio
- SPGR: Spoiled Gradient Recalled
- 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 (ROI) coefficient of variation

Appendix F: Vendor-specific B_1^+ Mapping information for 3 tesla

3 tesla (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 modelling.

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. (53). 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" in MRI phantoms, similar to the validation performed in Bliesener et al.(53)

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	MRM 63:1315, 2010	MRM 57:192, 2007 MRM 55:1326, 2006 MRM 68,1517, 2012	MRM 64:439, 2010	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 pharmacokinetic modelling	Offline tool available from vendor

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Appendix G: 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 E).	□ **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 SW, image analysis tool and phantom R_1 performance metrics as specified in Table xxx 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 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 the 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/MR scientist shall perform periodic system QA that includes assessment of T_1 bias, random error, linearity, T_1 SNR, DCE image artifacts.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
R_1 precision	□ **Yes** □ **No**	Shall be verified by the use of an R_1 phantom. This needs to be performed after hard- and 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/MR 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**

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.170 # SCANNER OPERATOR CHECKLIST

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.172 Name of Scanner Operator:

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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** □ **Variations**	A sequence to acquire the native T_1/ R_1 of the ROI should be applied. Recommended is a variable flip angle sequence as specified in the Table in section 3.6.2 depending on the site investigated. Multiple FAs ranging from 2-30 degrees Numbers of FAs supported in the literature varies from 2-7.	□ **Routinely do already** □ **Feasible, will do** □ **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 R_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**	Remove metal implant close to imaging vicinity.	□ **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 to magnet isocenter.	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**
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**

.174 # IMAGE ANALYST CHECKLIST

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.176 Name of Image Analyst:

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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 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 to 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 CT volumes.**	□ **Routinely do already** □ **Feasible, will do** □ **Feasible, will not do** □ **Not feasible**

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.179 # IMAGE ANALYSIS TOOL CHECKLIST

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

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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 Tofts 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**
Vascular Input Function	□ **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 Tofts 1999 model or the extended Tofts model in case of highly perfused tissue.	□ **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**

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