QIBA Profile:

MRI-Based Proton Density Fat Fraction (PDFF) of the Liver

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Stage: 2: Consensus

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When referencing this document, please use the following format:

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Available at: https://qibawiki.rsna.org/index.php/Profiles

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Abbreviations

AUROC: area under receiver-operating characteristics curve; **CI:** confidence interval; **MRI:** magnetic resonance imaging; **CSE:** chemical-shift-encoded; **PDFF:** proton density fat fraction; **QA:** quality assurance; **ROI:** region-of-interest; **RC:** repeatability coefficient; **RDC:** reproducibility coefficient; **wSD:** within-subject standard deviation

1. Executive Summary

A QIBA Profile is an implementation guide to generate a biomarker with an effective level of performance, mostly by reducing variability and bias in the measurement.

The expected performance is expressed as Claims (Section 1.2). To achieve those claims, Actors, both human and equipment, (for example: scanners, data acquisition parameters, data reconstruction software and algorithms, image analysis tools, technologists and radiographers, medical physicists, radiologists) must meet the Checklist Requirements (Section 3) covering Periodic QA, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, and Image Analysis.

This Profile is at the Initial Draft stage (qibawiki.rsna.org/index.php/QIBA_Profile_Stages) so,

- Claim Confirmed: The requirements have been performed and found to be practical by multiple sites; The claim is verified in a multi-site, multi-vendor study; results are expected to be generalizable in similar settings.
- Technically Confirmed: The requirements have been performed and found to be practical by multiple sites; The claim is a hypothesis based on committee assessment of literature and QIBA groundwork.

QIBA Profiles for other CT, MRI, PET, and Ultrasound biomarkers can be found at qibawiki.rsna.org.

Consensus: The requirements are believed to be practical based on consensus of experts within and beyond the committee; The claim is a hypothesis based on committee assessment of literature and QIBA groundwork.

This document is intended to help clinicians and researchers basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints. Note that this document only states requirements to achieve the claim, not "requirements on standard of care." Conformance to this Profile is secondary to properly caring for the patient.

1.1 Clinical Context

This QIBA Proton Density Fat Fraction **(PDFF)** Profile primarily addresses the application of chemical-shift-encoded **(CSE)** Magnetic Resonance Imaging **(MRI)** for the standardized measurement of hepatic fat content, which can be used as a quantitative imaging biomarker of hepatic steatosis, or fatty liver (*PMID*: 22025886, 21094445, 29356032, 26848588). While PDFF can also be estimated using proton magnetic resonance spectroscopy, this Profile is intended for PDFF measured by MRI only. At present, this Profile is written for CSE MRI PDFF performed at clinical magnetic field strength of 1.5T and 3T.

In general, PDFF is a quantitative imaging biomarker that is measured as a percentage value from 0-100%. For liver applications, however, the physiological range of interest for PDFF is typically from 0-50%. To ensure harmonization, the Profile places requirements on acquisition devices (i.e., MRI scanners), data acquisition parameters of the pulse sequence, data reconstruction software and algorithms, image analysis tools, as well as participating staff, such as MRI technologists and radiographers, medical

physicists, image analysts, and radiologists. The Profile also places recommendations and requirements on MRI manufacturers, vendors, third-party developers involved in PDFF-related products, as well as imaging facilities.

The Profile additionally places requirements on PDFF-specific quality assurance **(QA)** procedures, in both phantom and human scans. The requirements of the Profile are aimed to achieve small biases and avoid unnecessary variability of the PDFF measurements across phantoms, human subjects, and acquisition devices. The requirements also aim to reduce variability potentially introduced by clinical and research staff. **The specific performance goals of the Profile include:**

i. **Bias within ±5% (absolute PDFF) as determined in highly controlled PDFF phantoms.**
ii. **Coefficient of reproducibility within 5% (absolute difference) as determined in liver PDFF of human subjects.**

These goals should be achieved within the clinically relevant liver PDFF range between 0-50%. The term "absolute" above, and henceforth referred to in this Profile, denotes the change in PDFF in absolute values, rather than relative units. For example, a change from 5% to 10% PDFF is an absolute change of 5%, whereas the relative change would be a two-fold increase in value (i.e., a 100% increase). Hence, the term "absolute" here does not refer to negative or positive changes. Thus, for example, a change from 10% to 5% PDFF is referred to as an absolute change of -5% in PDFF.

1.2 Claims

PDFF can be used in the clinical care of patients to quantify hepatic fat content for cross-sectional assessment (diagnosis, severity grading) as well as longitudinal assessment (monitoring, evaluation of response to treatment) on a per-subject basis, in those with suspected or known hepatic steatosis (i.e., fatty liver) of any etiology.

The use of PDFF in patients and research participants may include determination of eligibility in a clinical trial; triaging eligible subjects into cohorts based on severity grade; assessing response to treatment as a primary or secondary endpoint; monitoring for adverse effects such as chemotherapy-induced fatty liver disease; or establishing a database for the development, optimization, and validation of other imaging biomarkers. Based on recent measurements of bias within ±5%, and within-subject standard deviation (wSD) of 1.5%, **conformance to this Profile by all relevant staff and equipment supports the following claim(s):**

Cross-Sectional Claim:	For a measured PDFF value, the 95% confidence interval for the true PDFF value is within bias ± 1.96 x wSD, i.e. within ±8% (absolute difference) of the measured value (*PMID*: 33464181).
Longitudinal Claim:	A measured absolute change in PDFF value of ±5% or more indicates that a true change has occurred with ≥ 95% confidence (*PMID*: 28892458).

These two claims hold when PDFF is measured at each relevant time point in accordance with the conformance requirements outlined in this Profile, including:

- Data acquisition by MRI scanner, data reconstruction, and subsequent PDFF image analysis follow conformance requirements (see flowchart in **Figure 1**).
- Periodic and routine QA scans are implemented to assess performance and maintain Profile conformance.
- No visible image artifacts are identified that may confound determination of liver PDFF values.
- No areas of severe liver iron overload or areas of high R2* values (beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T) are included in the PDFF regions-of-interest analysis.
- In the liver, ROIs with areas greater than that of 1 cm diameter circles are used on representative acquired slice(s) while avoiding non-tissue structures such as those from the vasculature and biliary system.
- For longitudinal assessment, PDFF measurements are made in the same area of the subject's liver across time points.

The flowchart below (**Figure 1**) summarizes this PDFF Profile as it relates to conformance by MRI manufacturers and vendors, third-party software developers, and end-users. For an MRI manufacturer or third-party developer to be certified as Profile conformant for a given implementation of PDFF (i.e., pulse sequence, data acquisition and reconstruction), evidence satisfying the Claims must be demonstrated using commercial hardware and software products as they would be supplied to a customer (i.e., an end-user site). An end-user should subsequently be able to further confirm Profile conformance onsite using the same product without modification from the source provider without the need to modify or augment the commercial product implementation. Should an end-user detect that the product PDFF implementation may not be conformant with the Profile requirements, it is recommended that the end-user report the error and provide feedback to the MRI manufacturer or third-party developer as a "Customer Complaint", as for example described in ISO 13485:2016 and 21 CFR Part 820.198.

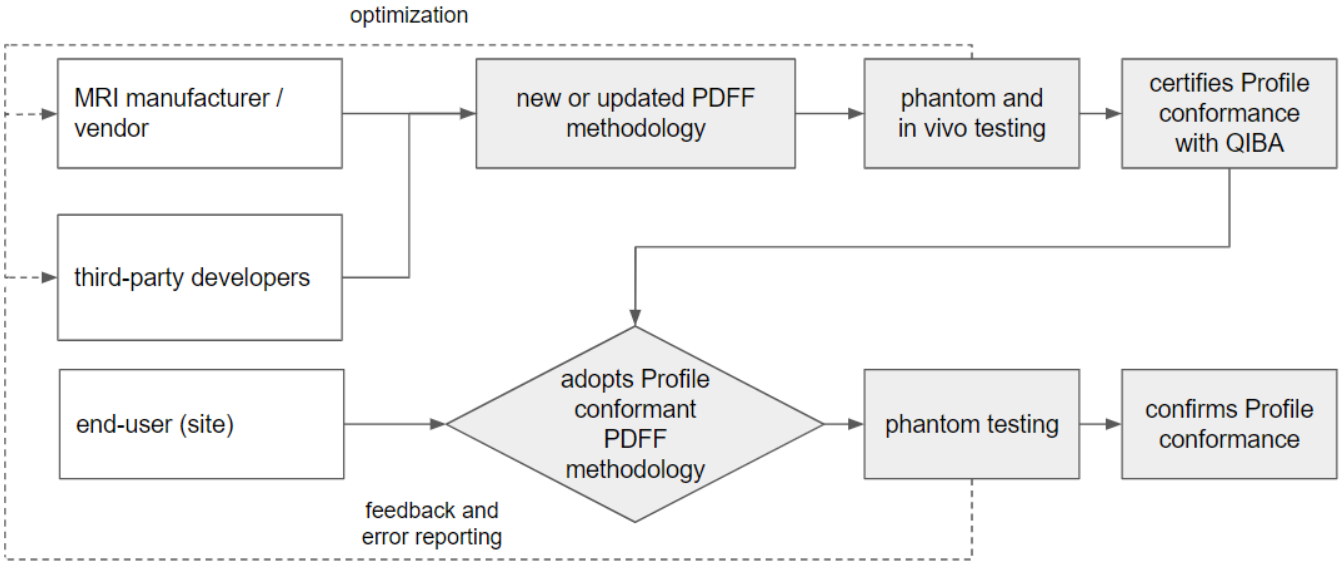


Figure 1. Flowchart for liver PDFF quantification method development and conformance testing.

1.2.1 CURRENT PERFORMANCE

Based on the groundwork studies and literature review carried out by the QIBA PDFF Biomarker Committee, the use of conventional two-echo water-fat imaging methods can result in poor performance when compared to methods that are conformant with this Profile. Specifically, we will consider a two-echo acquisition (nominally in-phase and opposed-phase), followed by water-fat separation without correction for R2* decay and multi-peak fat signals. The corresponding fat fraction contains systematic bias, as demonstrated in refs (*PMID*: 21212366, 23172799). In these works, a regression slope of 0.85 was determined between the two-echo fat fraction and the reference PDFF (measured using MR spectroscopy) (*PMID*: 21212366). In contrast, PDFF quantification using a six-echo acquisition including correction for R2* decay and multi-peak fat signals had a regression slope close to 1.0 (0.98) and minimal bias compared to the reference. Similarly, in PDFF phantoms a two-echo method led to a mean underestimation of -5.4% (absolute PDFF measurement of 23.6%) compared to a six echo method (absolute PDFF measurement of 29.0%) (*PMID*: 23172799).

Figure 2 shows simulated bias and variability using two-echo (in-phase and opposed-phase) methods without correction for R2* or multi-peak fat signals. Bias is calculated with respect to the ground truth PDFF. Variability is calculated between protocols that acquire TE = (1.2,2.4) msec, and TE = (2.4,3.6) msec, respectively. No noise or other sources of variability are included: the substantial bias and variability observed in these simulations are due purely to the lack of correction for these two confounding factors.

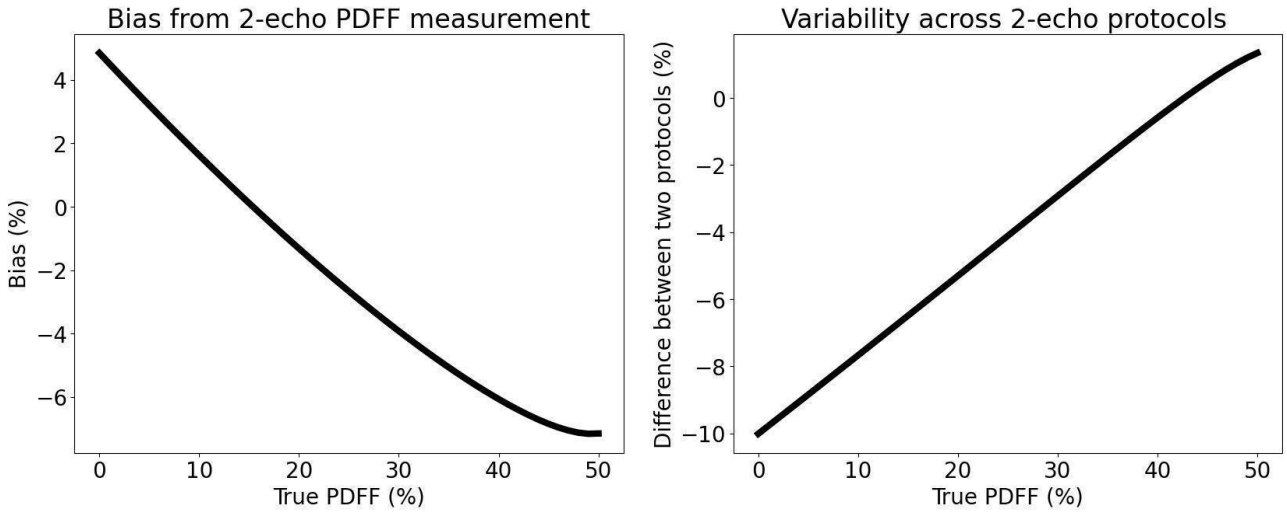


Figure 2. In highly controlled 3.0T simulations, substantial bias (left) and variability (right) are obtained from two-echo (in-phase and opposed-phase) acquisitions without correction for R2* or multi-peak fat signals. No other sources of error are included in these simulations (T1, noise, artifacts, etc.). Bias is calculated with respect to the ground truth PDFF. Variability is calculated between protocols that acquire TE = (1.2,2.4) msec, and TE = (2.4,3.6) msec, respectively, to mimic the realistic scenario where the first opposed-phase echo (1.2 msec) may or may not be achievable due to hardware limitations. The true PDFF spanned the relevant liver PDFF range (0-50%). The simulated R2* was 80 s^{-1}. Note that, even though these methods are generally known as "in-phase and opposed-phase", in practice not all the fat peaks will have these relative phases with respect to the water signal.

1.3 Disclaimers

Standard of Care: The requirements are defined to achieve the Claims and do not supersede proper patient management considerations. Requirements that disqualify an exam or lesion mean the performance in the Claims cannot be presumed but does not preclude clinical use of the measurement at the discretion of the clinician.

Confirmation of Claims: The claims are informed by groundwork studies, extensive literature review and expert consensus; they have not yet been fully substantiated by studies that strictly conform to the requirements given here. The QIBA Consensus, Claim Confirmation and Clinical Confirmation Stages will collect data on the actual field performance and appropriate revisions will be made to the Claims and/or the details of the Profile. At that point, this caveat may be removed or re-stated. (https://qibawiki.rsna.org/index.php/QIBA_Profile_Stages)

Scope of Claims: The quantitative performance values in the claims were obtained as described below.

Innovation: Profile requirements are intended to establish a baseline level of performance. Exceeding the requirements and providing higher performance or advanced capabilities is allowed and encouraged. The Profile does not limit the methods institutions and equipment suppliers use to meet the requirements.

Claim 1: Origin and Interpretation

The Cross-Sectional Claim is based on consideration of two components from prior studies (*PMID*: 33464181, *PMID*: 28892458). First is the evaluation of PDFF bias in phantom studies (within ±5% absolute PDFF), and the second is the evaluation of PDFF reproducibility in vivo (reproducibility coefficient RDC=4.1%, i.e., wSD = 4.1%/2.77 = 1.5%). Based on these components, the cross-sectional performance of liver PDFF quantification enables reliable measurement with absolute difference (with respect to the true PDFF) within the following range: bias ± 1.96 x wSD = ± 5% ± 1.96 x 1.5%, i.e., within ± 8%.

The evaluation of bias in phantoms is based on a 2021 multi-center, multi-vendor, and multi-platform study using a commercially available spherical phantom containing cylindrical vials with chemically calibrated PDFF values (nominally 0, 2.5, 5.0, 7.5, 10, 15, 20, 25, 30, 40, 50, and 100%). The study included a balanced number of 1.5T and 3T platforms from three vendors (GE Healthcare, Siemens, and Philips), and utilized each vendor's respective regulatory-cleared product PDFF pulse sequences and online data reconstruction pipelines (*PMID*: 33464181). Across a wide range of MRI scanners between the three vendors, the platform-specific bias did not exceed 1.00 ± 0.10 in slope (1.00 is the ideal slope), and ±1.5% (in absolute PDFF) in intercept (0 is the ideal intercept) when comparing measured MRI-PDFF versus the known true PDFF values. The 95% confidence interval **(CI)** for the true PDFF on the tested systems in the 2021 study also did not exceed ±5% (in absolute PDFF) from the measured PDFF value, across all clinically relevant liver PDFF values in the range of 0% to 50%. Specifically, in each of the MR vendors tested, at least one of the two acquisition protocols evaluated in the study provided measurements within ±5% of the true PDFF, across the range of liver PDFF between 0% and 50%. These confidence intervals represent the upper bounds of the error across all tested scanners. Some vendor systems with lower bias profiles have narrower CIs of less than ±5% from the true PDFF value.

The evaluation of reproducibility in vivo is described in detail below. In summary, a within-subject

standard deviation (wSD) of 1.5% has been observed for PDFF measurements obtained from different systems and/or acquisition parameters, using approximately co-localized regions-of-interest (*PMID*: 28892458).

Note that the Cross-Sectional Claim refers to the technical performance of PDFF measurements with respect to the true PDFF value. For example, a PDFF measurement of 30% reflects a true PDFF between 22% and 38% with 95% confidence. However, this claim does not refer to the clinical prognostic or predictive value of this measurement. In addition, this claim does not refer to the performance of PDFF measurements to predict histological grading of steatosis (see **Appendix B** for histology and clinical value of PDFF measurements).

Claim 2: Origin and Interpretation

According to the Longitudinal Claim, a change in absolute PDFF value by ±5% or more, if measured in the same location(s) within the liver, indicates a true change in PDFF has occurred with 95% confidence. This claim is based on rounding up the PDFF reproducibility coefficient (4.1%) established in a meta-analysis of PDFF mapping studies, when measuring co-localized regions-of-interest **(ROIs)**. Specifically, this claim arises from a meta-analysis of studies that evaluated the technical performance of PDFF mapping methods on various vendors, field strengths, and platforms (*PMID*: 28892458). This meta-analysis included 11 studies (425 participants, 9,103 measurements) that evaluated precision (repeatability and/or reproducibility) of PDFF mapping. Reproducibility was assessed with respect to different magnetic field strength, MRI vendor, and/or reconstruction method, as typically defined in the literature (*PMID*: 35878725). Liver PDFF ROI measurements had repeatability coefficient of 3.0%, and reproducibility coefficient of 4.1%. Subject-level liver PDFF measurements (i.e., not co-localized regions of interest) had higher repeatability **(RC)** and reproducibility **(RDC)** coefficients of 4.7%, and 5.5%, respectively (**Table 1**). For participant-level measurements, ROI location was an important source of variability, possibly reflecting biological heterogeneity of PDFF throughout the liver. Magnetic field strength, MRI device/scanner manufacturer, and reconstruction method each had minimal effects on reproducibility. In addition, this meta-analysis evaluated the linearity and bias of MRI-based PDFF using MR spectroscopy as the reference. However, linearity and bias results of MR spectroscopy are not included in this claim since the MR spectroscopy based PDFF itself may have measurement biases and variabilities. For this reason, MR spectroscopy is less preferable as a reference standard compared to highly controlled PDFF phantoms.

Table 1. Expected precision for alternate scenarios.

Subject-Level Precision		**Region of Interest (ROI)-Level Precision**	
Different Scanner & Parameters	**Same Scanner & Parameters**	**Different Scanner & Parameters**	**Same Scanner & Parameters**
RDC = 5.5% CI = [-5.5%, +5.5%]	RC = 4.7% CI = [-4.7%, +4.7%]	RDC = 4.1% CI = [-4.1%, +4.1%]	RC = 3.0% CI = [-3.0%, +3.0%]

- Precision is expressed by both the RC and RDC.
- RC refers to 95% limits of agreement between two measurements taken with the same scanner, same scan parameters and protocol, same data acquisition, reconstruction, and post-processing analysis workflow.
- RDC refers to 95% limits of agreement between two measurements taken with different scanners, or different scan parameters, or different data acquisition, reconstruction, and post-processing analysis workflow (*PMID*: 26267831).
- Subject-level precision refers to situations where ROIs are placed at different locations around the liver, incorporating expected biological variability of PDFF across the liver.
- ROI-level precision refers to situations where ROIs are placed at the same location in the liver, representative of true technical precision.

The confidence interval PDFF boundaries in **Table 1** can be interpreted as "error bars'' or "variability" around the measured PDFF value. If the measured change between two time points is within this confidence interval, one cannot be certain that there has been a real change in the hepatic fat content. However, if the measured PDFF difference between two time points is beyond the limits of the confidence interval, then one can conclude with 95% confidence that there has been a true change in PDFF, and that the perceived PDFF change is not due to measurement variability.

Impact of Iron in the Liver on PDFF

The technical performance described in this Profile may not be achievable in the presence of severe liver iron overload. The high R2* values (short T2* values) induced by the presence of iron deposition leads to rapid MR signal decay with increasing echo times **(TEs)** and causes severe noise propagation in PDFF mapping. With conventional PDFF acquisition protocols, PDFF quantification can become unreliable in the presence of high R2* (for example: beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T (*PMID*: 33783066). These thresholds can be extended through the acquisition of optimized (shorter) echo times. However, in the presence of extreme iron overload, the signal decays away before sufficient water-fat phase can be accumulated, precluding reliable PDFF quantification even if very short TEs are acquired. In the presence of some iron content in the liver (*PMID*: 36809220), reliable PDFF quantification can still be achieved.

2. Conformance

To conform to this Profile, participating Actors (staff and equipment) shall meet each requirement on their checklist in Section 3.

- Some requirements reference a specific **assessment procedure** in Section 4 that shall be used to assess conformance to that requirement. For the rest, any reasonable assessment procedure is acceptable.
- Staff must ensure requirements assigned to them are met; however, for the purpose of conforming to the profile, they may delegate a task rather than physically doing it themselves.
- Staff names represent roles in the profile, not formal job titles or certifications. E.g., Site equipment performance requirements are assigned to the Physicist role. The role may be filled by any appropriate person: a staff physicist, a managed contractor, or a vendor provided service.
- If a QIBA Conformance Statement is available for equipment (e.g., published by a scanner vendor), a copy of that statement may be used in lieu of confirming each requirement in that equipment checklist yourself by running the necessary tests.

To make a formal claim of conformance, the organization responsible for equipment or staff shall publish a QIBA Conformance Statement.

QIBA Conformance Statements:

- shall follow the current template: (https://qibawiki.rsna.org/index.php/QIBA_Conformance_Statement_Template)
- shall include an Appendix containing details recorded by the assessor as stated in requirements or assessment procedures (e.g., acquisition parameters)
- shall describe the test data used for conformance testing or alternatively provide access to it.

2.1 Discussion

The following section summarizes Actors and Activities (**Table 2**) needed to establish conformance of an MRI manufacturer, vendor, or third-party developer that provides PDFF methodology, hardware, and software, to this Profile. The section also summarizes Activities of an "end-user" that will utilize commercial PDFF products sourced from MRI manufacturers and third-party developers. Activities include, for example, ensuring that the Acquisition Device (i.e., MRI scanner, referred henceforth as scanner), Data Acquisition, Data Reconstruction, and Image Analysis Tool are conformant with the Profile, as well as Quality Assurance. Actors include staff such as MRI technologists and radiographers, medical physicists, and radiologists. It may be possible that not all Actors are on staff and present for a site. For example, a medical / MRI physicist may not always be available. In these instances, other available staff, if qualified, may perform Activities of the Profile. As outlined in **Table 2**, for example, "Scanner Operator" can include both the medical / MRI physicist and the MRI technologist / radiographer. Similarly, "Image Analyst" Activities can be fulfilled by the physicist, the technologist, or the radiologist. Specifically, the Actors should be involved in the following Activities.

- Establish local policies, procedures, and training such that Actors can generate Profile-conformant data.
- Confirm that the scanner can acquire data necessary for PDFF quantification using acquisition

parameters recommended in this Profile.

- Confirm that a data reconstruction pathway is present for generating PDFF results on a 0-100% range (for liver applications, however, the physiological range of interest for PDFF is typically from 0-50%), and that DICOM header information for scaling slope and intercept are retained.
- Confirm that users can perform representative ROI measurements on the PDFF results and generate descriptive statistics, such as the mean and ROI area. Other possible descriptive statistics include median, and the range (minimum, maximum) PDFF values observed within the ROI.
- Confirm the availability of appropriate PDFF phantoms and establish QA procedures to assess PDFF bias, and as an option, linearity.
- Ensure continued Profile conformance after major scanner software and hardware changes (i.e., upgrades and updates), or complete replacement of MRI systems.

The Activities facilitate certification of an MRI manufacturer, vendor, third-party developer, and end-user site to Profile conformance. Profile conformance can be a requirement for acceptance of a site into a multi-site clinical trial utilizing PDFF, or to establish baseline performance across multiple sites and harmonize protocols across scanners. As noted from the two Profile claims, performance metrics include liver PDFF linearity and bias, repeatability, and reproducibility. To conform to this Profile, benchmarks for these metrics are suggested to ensure negligible contribution of technical errors to subsequent PDFF measurements and reflect anticipated baseline performance.

Table 2. Summary of Profile Actors and their typical Activities. Scanner Operator and Image Analyst are group terms suggesting common roles. The former may involve either a physicist or technologist; the latter may involve a physicist, technologist, or radiologist, depending on availability.

<table>
<tr><th colspan="3">Actors and Roles</th><th>Commonly Involved Activities</th></tr>
<tr><td>Physicist</td><td rowspan="2">Scanner operator</td><td rowspan="3">Image analyst</td><td>QA (Appendix A.3, A.8)</td></tr>
<tr><td>Technologist</td><td>Subject Handling and Positioning (Appendix A.5)
Data Acquisition and Reconstruction (Appendix A.6-A.7)</td></tr>
<tr><td>Radiologist</td><td></td><td>QA, Analysis, and Interpretation (Appendix A.3, A.8-A.10)</td></tr>
</table>

2.2 Specification

Parameter(s)	Actor(s)	Requirement(s)
Data acquisition	Scanner operator	Shall perform MRI protocols for PDFF quantification using parameters within this Profile's recommended ranges.
		Shall ensure there is availability of an appropriate PDFF phantom for QA procedures.
Data reconstruction	Scanner operator	Shall confirm that data reconstruction and post-processing steps have capabilities to generate PDFF maps on a scale of 0-100%, although 0-50% is the relevant physiological range for liver.
		Shall confirm that DICOM header tags for scaling slope and intercept are retained for proper display of PDFF maps. DICOM file format is the preferred output for PDFF maps, but other file formats may be used to convert PDFF DICOMs if they are equivalent to their DICOM counterparts in representing PDFF values.
Data post-processing and image analysis	Image analyst	Shall confirm that image analysis tools can facilitate users to perform ROI measurements and generate PDFF statistics, such as mean, median, and ROI area.
		Shall establish an image review process to identify artifacts that may hamper PDFF quantification.
		Shall assess PDFF bias during QA procedures and document results and performance.

3. Profile Requirement Checklists

The following "Checklists" are the basis for conforming to this Profile. Conforms (Yes/No) indicates whether conformance to the requirement has been confirmed by the assessor.

3.1 Scanner and Reconstruction Software Checklist

Make/Model/Version: _____ ***Assessment Date:*** _____
Comments: _____
_____

Parameter(s)	Conforms (Yes/No)		Requirement(s)
Acquisition device			✓ Shall have documentation of preventive maintenance and major hardware and software changes, updates, and upgrades of the scanner that may impact Profile conformance. ✓ Shall have documentation of a CSE MRI PDFF pulse sequence and protocol that can implement data acquisition using Profile conformant parameter settings and reconstruct PDFF maps.

3.2 Image Analysis Tool Checklist

Make/Model/Version: _____ ***Assessment Date:*** _____
Comments: _____
_____

Parameter(s)	Conforms (Yes/No)		Requirement(s)
Image display			✓ Shall correctly display PDFF images on a scale of 0-100%, although 0-50% is the relevant physiological PDFF range for liver. The display scale need not be linearly represented from 0-100%. Industry standard DICOM format is preferred.
Regions-of-interest			✓ Shall allow the user to place ROIs and summarize values within the ROIs, such as mean PDFF and area.

3.3 Physicist Checklist

The medical physicist may be an in-house staff or an external consultant with the appropriate qualifications and experience to perform the recommended activities in this Profile. A qualified technologist or vendor engineer may also perform these activities.

Physicist Name: _____ ***Assessment Date:*** _____
Comments: _____
_____

Parameter(s)	Conforms (Yes/No)		Requirement(s)
Installation			✓ Shall perform installation of CSE MRI PDFF software in accordance with manufacturer instructions. ✓ Shall validate and troubleshoot the functionality of PDFF protocols and workflow, including data acquisition, data reconstruction, and image analysis.
PDFF-specific QA			✓ Shall perform PDFF QA scans to assess bias to maintain Profile conformance. ✓ Shall visually evaluate images for adequate signal-to-noise ratio and presence of artifacts. ✓ Shall troubleshoot issues if PDFF bias results are not Profile-conformant.

3.4 Technologist Checklist

The Technologist is directly responsible for the data acquisition of the Profile, including subject positioning and subject handling. A medical / MRI physicist may also perform some of these activities.

Technologist Name: _____ ***Assessment Date:*** _____
Comments: _____
_____

Parameter(s)	Conforms (Yes/No)		Requirement(s)
Data acquisition			✓ Shall confirm that an appropriate scanner, protocols, and related software are used for PDFF-MRI. ✓ Shall confirm that in longitudinal studies, subjects are scanned preferably on the same scanner and software as previous exam(s), using similar imaging parameters.
Subject positioning and handling			✓ Shall scan the subject in a comfortable position (supine is common) and utilize coil receiver arrays secured around the subject to cover the liver. ✓ Shall prepare the subject for data acquisition during breath holds.
Data reconstruction and image analysis			✓ Shall review PDFF maps to confirm technical success of exams and re-acquire if visible artifacts, such as water-fat swaps and image artifacts are identified. ✓ Shall perform QA of PDFF results using internal (in vivo, i.e., adipose

			tissue, muscle, and spleen) and/or external (ex vivo, i.e., known PDFF phantom vials) references within the same imaging volume as the subject to confirm technical success. ✓ Shall confirm that, if available, other images are generated correctly. These include, for example, water, fat, in-phase, opposed-phase, and R2* map. ✓ Shall place ROIs on individual slices of the liver and avoid vascular and biliary structures and regions of high R2* (beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T). The size of ROIs is recommended to be greater than the area of a 1 cm diameter circle.

3.5 Radiologist Checklist

The Radiologist is responsible for the protocol parameters. They may choose to use a protocol provided by the scanner vendor or an altered one based on recommendations by the medical physicist. Working collaboratively with a medical physicist is recommended as some parameters are system dependent and may require special attention.

Radiologist Name_____Assessment Date: _____
Comments: _____
_____

Parameter(s)	Conforms (Yes/No)		Requirement(s)
Data acquisition			✓ Shall ensure CSE MRI PDFF protocols are Profile conformant and that suitable acquisition parameters are utilized. ✓ Shall ensure that technologists are appropriately trained to acquire Profile-conformant data.
Data reconstruction and image analysis			✓ Shall review PDFF maps to confirm technical success of exam. ✓ Shall confirm that, if available, other images are generated correctly (i.e., water, fat, in-phase, opposed-phase, R2* map). ✓ Shall place ROIs on individual slices of the liver and avoid vascular and biliary structures and regions of high R2* beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T. The area of the ROIs is suggested to be greater than that of a 1 cm diameter circle. ✓ Shall perform QA of PDFF results using internal and/or external references to confirm technical success of exam.

4. Assessment Procedures

Most requirements in Section 3 checklists can be assessed for conformance by direct observation and checked off. Some requirements (e.g., performance metrics) depend on a formalized assessment procedure, in which case that requirement references an Assessment Procedure here in Section 4.

The QIBA-defined procedures that follow are not intended to preclude reasonable alternative methods. Such methods may be submitted for review with evidence that the results produced by their implementations are equivalent to those here. Upon review by QIBA or similar agencies and committees, the proposed method may be approved as an accepted assessment procedure in this Profile.

To conform to this Profile, participating staff, and equipment ("Actors") shall support each activity assigned to them. To support an activity, the actor shall conform to the requirements (indicated by "shall language") listed in the specifications table of the activity subsections. 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 recommended imaging parameters for a liver PDFF protocol, describing how their product was configured to achieve conformance. Vendors shall also provide access to or describe the characteristics of the test set used for conformance testing.

4.1 PDFF bias in phantoms

This procedure can be used to assess the PDFF bias in water-fat emulsion phantoms. The assessor shall:

- Obtain or manufacture a PDFF phantom that includes multiple compartments (vials) with known PDFF values between 0-50% (see **A.3** for details).
- Set the phantom in the scanner room prior to scanning to stabilize temperature. One hour or longer is highly recommended.
- Scan the phantom on the desired 1.5T or 3T scanner, using a CSE MRI PDFF protocol relevant to liver imaging (possibly adjusting the field of view and/or spatial resolution). Ensure that the obtained echo times are appropriate for PDFF quantification.
- Repeat scans of the phantom as needed (see sample size discussion below).
- Measure PDFF values in each vial using ROI analysis after data reconstruction.
  Evaluate the bias (difference between measured and true PDFF values) for each vial. In addition to bias, linearity can also be evaluated between the measured and true PDFF. Although conformance assessment for PDFF does not establish thresholds for linearity, it is expected that the measured and true PDFF will have a linear relationship with slope close to 1.0 and intercept close to 0.0% (see *PMID*: 33464181 for representative analysis details). The assessment of linearity is an option recommended by the QIBA PDFF committee.

Sample Size Considerations and Independence of Measurements in Multi-Vial Phantoms

In multi-vial phantom scans, the main source of variability in measurement errors will be noise (i.e., the measurement errors in two consecutive measurements of the same multi-vial phantom will be very similar aside from the effects of image noise). The image noise should be spatially independent across vials in the absence of parallel imaging acceleration and undersampled data acquisitions. However, in practice, the use of multiple coil channels even in the absence of parallel imaging acceleration and

undersampled data acquisitions can lead to spatially varying noise characteristics in the images and resultant PDFF maps. Here, we model measurement errors on different vials within the same image as approximately independent. This approach facilitates the use of multi-vial phantoms with vials that include different PDFF values spanning the range 0-50%. For example, a phantom containing 10 vials with PDFF between 0-50%, when scanned once will lead to a sample size of 10 (N=10) as defined below. The same phantom scanned twice will lead to N=20.

To demonstrate conformance with this Profile, several conditions shall be met.

- The 95% CI for the true PDFF should not exceed ±8% (in absolute PDFF) from the measured PDFF value, across all clinically relevant liver PDFF values in the range of 0% to 50%. The bias component of this cross-sectional claim is within ± 5%, as determined from phantoms, as discussed next. The remainder, up to ±8%, is due to precision as discussed below in Section 4.2.

- The CI for mean bias across PDFF measurements (including all vials in the phantom, and all scan repetitions if any) shall be within ±5.0%. The rationale for this requirement is as a non-inferiority test with respect to the mean bias observed across PDFF values in (*PMID*: 33464181), which was on the order of 2-3%.

- The worst-case bias across a particular PDFF value (i.e., the bias observed at a particular phantom vial showing the worst bias) should be within ±7%. Note that this condition is based on the point estimate (single measurement if a single repetition, or average of multiple repetitions) in a specific vial showing the largest absolute deviation from the true PDFF value. The rationale for this requirement is as a comparison to the worst-case bias observed across multiple PDFF values in (*PMID*: 33464181), which was on the order of 5%.

The steps below outline procedures for estimating the mean bias. The table below, and the accompanying **Figure 3** illustrate the half-width of the 95% CIs for the mean bias as a function of sample size. Note that four estimates of the estimated variance are considered based on the data in (*PMID*: 33464181). The CIs for mean bias were computed with the following steps: for each case, bias is defined as $b\_i = [(Y\_i - X\_i)]$, where X_i is the true value of the measurand. Over N cases estimate the mean bias as $\hat{b} = \sum_{i=1}^{N} b_i / N$. The estimate of variance of the bias is defined $\widehat{Var}_b = \sum_{i=1}^{N} (b_i - \hat{b})^2 / N(N-1)$. The 95% CI for the bias is defined as $\hat{b} \pm t_{\alpha=0.025,(N-1)df} \times \sqrt{\widehat{Var}_b}$, where $t_{\alpha=0.025,(N-1)df}$ is from the Student's t-distribution with α=0.025 and (N-1) degrees of freedom.

Variance of PDFF measurements	Variance estimate
Pooled for 1.5T data for true PDFF between 0%-50%	6.1
Pooled for 3T data for true PDFF between 0%-50%	3.7
Worst-case at 1.5T (true PDFF = 47.5%)	19.4
Worst-case at 3T (true PDFF = 47.5%)	15.5

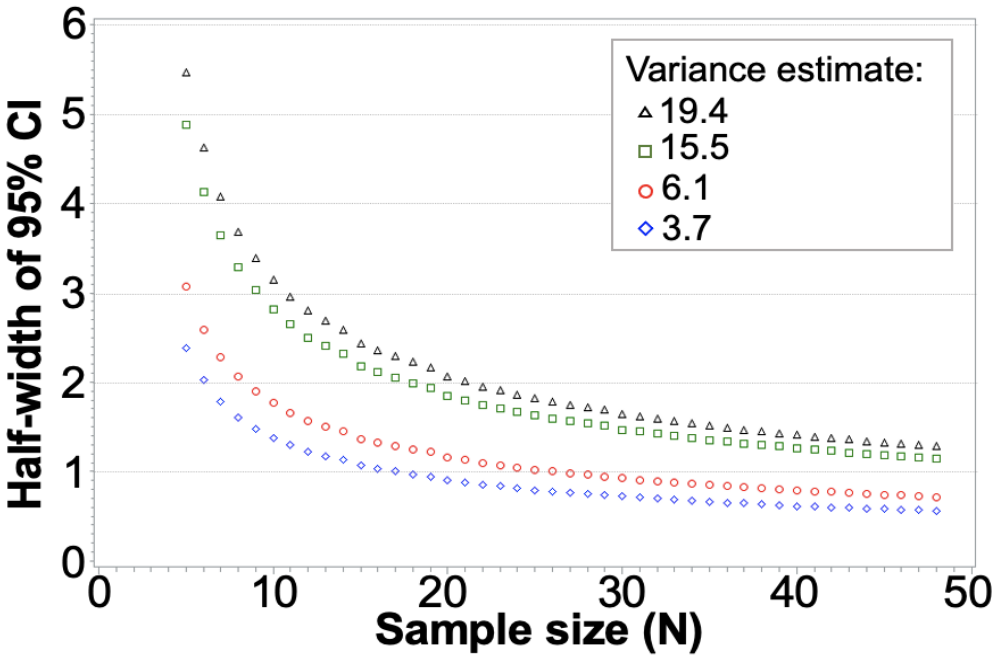


Figure 3. Sample size requirements vs. half-width of 95% CI for several variance estimates for mean bias, based on data from *PMID*: 33464181. For example, a sample size of N=17 with a variance estimate of 3.7 will lead to a half-width of the 95% CI of approximately 1.0% (absolute PDFF units). Therefore, if the measured mean bias is 2.0%, the CI will span 2.0±1.0%. One measurement in one PDFF vial represents a sample size of 1.

4.2. PDFF Repeatability

This procedure can be used to assess PDFF repeatability (variability under the same conditions - same scanner, same parameters, etc.) (*PMID*: 26267831). Repeatability is assessed in terms of a Repeatability Coefficient (RC), expressed in units of PDFF (%). The repeatability study should be performed in vivo in human subjects, and not in phantoms. The subject should be removed from the scanner and the scanner should see them as a new patient when the repeated scan data are collected.

Importantly, this Profile requires evaluation of repeatability (instead of reproducibility) for conformance assessment, for the following reasons**.** In the meta-analysis publication (*PMID*: 28892458), a repeatability coefficient of 3.0% and a reproducibility coefficient of 4.1% were determined. Although Claim 2 is focused on reproducibility, direct evaluation of reproducibility as part of conformance assessment is challenging for many reasons. A central challenge of standardizing such assessment is that reproducibility can be defined over multiple dimensions (acquisition parameters, field strength, MRI platform, MRI vendor, etc.). Therefore, stipulation of the conformance assessment procedures would need to define which dimensions shall be evaluated for reproducibility, and to what extent (i.e., it is more difficult to obtain reproducible measurements across multiple vendors and platforms than across slightly different acquisition parameters). Further, scanning human subjects across multiple systems at different geographical locations within a short period of time is logistically challenging. Instead, evaluation of repeatability in a test-retest experiment is better defined and feasible and is therefore the focus of this Profile. Note that excellent reproducibility does not preclude severe bias. For this reason, conformance to this Profile will only be satisfied if a user demonstrates successfully both Claim 1 (low bias in PDFF

phantoms measurements) and Claim 2 (a low repeatability coefficient for in vivo liver PDFF measurements).

To evaluate repeatability, the assessor shall:

- Scan each subject at least twice on the same day, following guidelines outlined in this Profile.
- Use the same scanner, protocol, data reconstruction, and post-processing workflow for each scan.
- Reposition each subject between scans.
- Ensure that scanned subjects represent a broad range of clinically relevant liver PDFF values.

Users should construct 95% CIs for their RC and are encouraged to demonstrate non-inferiority with respect to values reported in **Table 1** in Section 1.3. In other words, the RC should be comparable to the values in **Table 1** in Section 1.3 and a non-inferiority tolerance of ±2% for the CIs is recommended by the QIBA PDFF committee.

Sample Size Considerations for estimates of Repeatability Coefficient

Sample Size	N=10	N=15	N=20	N=25
95% CI for wSD	[2.10, 5.26]	[2.22, 4.64]	[2.30, 4.33]	[2.35, 4.14]

The table above summarizes the width of 95% CIs for the estimates of within-subject standard deviation **(wSD)** as a function of the sample size, assuming the true wSD is 3%. For example, if the goal is to test that a site's wSD is less than 5%, and if the site's estimated wSD is 3%, then a sample size of N=15 (i.e., 15 human subjects) would suffice. It is highly recommended that the cohort of scanned subjects have PDFF values spanning a relatively wide range of clinically relevant values, representing healthy status and mild, moderate, and possibly severe fatty liver disease. The CIs were computed with the following steps: for each case, calculate the mean and within-subject SD as: $\bar{Y}_i = (Y_{i1} + Y_{i2})/2$ and $wSD_i^2 = (Y_{i1} - Y_{i2})^2/2$, where Y_{i1} and Y_{i2} are repeat measures of subject *i*. From a sample size of N, estimate wSD as: $wSD = \sqrt{\sum_{i=1}^{N} wSD_i^2 / N}$. The 95% CI for the wSD is the defined as: $\left[\sqrt{\frac{(N)wSD^2}{\chi^2_{\frac{\alpha}{2},(N)}}}, \sqrt{\frac{(N)wSD^2}{\chi^2_{\left(1-\frac{\alpha}{2}\right),(N)}}}\right]$, where $\chi^2_{\alpha,N}$ is from a chi-square distribution with $\alpha/2$=0.025 and N degrees of freedom.

Appendix A: Activity Requirements

This Appendix organizes Profile requirements according to the sequence of activities involved in generating the biomarker. The requirements here are the same as those in the requirement checklists in Section 3. The step-by-step activity organization can be more conducive to ferreting out sources of variance by the Biomarker Committee and may be helpful for users of the Profile to understand the big picture. The requirement checklist organization in Section 3 is more convenient for the individuals, systems, and organizations checking their conformance to the Profile.

A.1. Product Validation

This activity evaluates equipment (Scanner, Reconstruction Software, and Image Analysis Tool) prior to their use in the Profile (e.g., at the factory). Product validation includes validations and performance assessments necessary to reliably meet the Profile Claim.

A.1.1 DISCUSSION

The following details were considered safe to reasonably assume, rather than increase the Profile conformance effort by including them as formal requirements. If these assumptions are not met, the staff or equipment are not conformant to the Profile.

- The MRI scanner meets performance requirements set forth by the manufacturer and local regulatory and accreditation agencies.
- The installation and initial validation of the CSE MRI PDFF pulse sequence and related software has been performed by a service engineer or medical physicist.

A.1.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Acquisition device	Scanner operator	Shall confirm that a 2D or 3D CSE MRI PDFF spoiled gradient-recalled-echo pulse sequence is available on the scanner and that a Profile-conformant protocol can be implemented.
Data reconstruction	Scanner operator	Shall generate PDFF maps that are appropriately scaled from 0-100%, although 0-50% is the relevant physiological PDFF range for liver applications. Industry standard DICOM file format is preferred to facilitate further post-processing and image analysis.
Image analysis	Image analyst	Shall confirm that users can place multiple ROIs on PDFF maps and return descriptive statistics for each ROI.

A.2. Staff Qualification

This activity evaluates staff (Radiologist, Physicist, and Technologist) prior to participation in the Profile. Staff Qualification includes training, qualification, or performance assessments necessary to reliably meet the Profile Claim.

A.2.1 DISCUSSION

This activity involves evaluation of the Profile's participating Actors. Documented training by a qualified radiologist, senior technologist, or medical physicist, and demonstration of proficiency in PDFF workflow should be considered for all participating Actors. Evaluating the professional qualifications of

the Actors is beyond the scope of this Profile. It is presumed that everyone has the proper educational background, professional degree, and licensure to perform their respective roles. There may be an overlap of roles, as suggested in **Table 2**. All Actors involved in this Profile should:

- understanding principles of CSE and spoiled gradient-recalled-echo imaging, including the terminology, concepts, and conventions defined in **Appendix D**.
- understanding CSE MRI PDFF workflow, including data acquisition, data reconstruction, post-processing, and image analysis, and handling QA phantoms.

A.2.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Proficiency	All	Shall undergo training by a qualified radiologist, senior technologist, or medical physicist in understanding PDFF principles, concepts, conventions, terminology, and workflow.

A.3. Periodic Quality Assurance

This activity involves quality assurance of the scanners that are periodic, not directly associated with a specific subject. Periodic QA includes calibrations, phantom imaging, performance assessments or validations to ensure the scanner is aligned, calibrated, and functioning as needed to reliably meet the Profile Claim. Performance measurements of specific protocols are addressed in Section 4.

A.3.1 DISCUSSION

The following details were considered safe to reasonably assume, rather than increase the Profile conformance effort by including them as formal requirements. If these assumptions are not met, the staff or equipment are not conformant to the Profile.

Periodic QA procedures should be followed for the scanner and related equipment, as required by manufacturers and regulatory and accreditation bodies. It is assumed that a qualified medical physicist will document and perform these QA procedures. If a physicist is not available, a trained radiographer / MRI technologist can also perform these QA procedures.

Additional PDFF-specific QA procedures to assess Profile conformance are described below. These procedures are especially recommended, for example, when pulse sequences are updated on the scanner due to software and hardware changes, when determination of site eligibility and qualification in a trial or study is needed, and any time protocol parameters are changed in a way that could impact PDFF performance. These include, for example, changes to echo times and echo spacings, changes to matrix size, field-of-view, and spatial resolution. PDFF-specific QA scans should be performed across the relevant PDFF range to primarily determine the bias (ideal bias: 0) and secondarily the linearity (ideal slope: 1) of PDFF measurements against known reference PDFF values in a phantom. A threshold of +/-5% absolute PDFF bias is suggested for this PDFF-specific QA test to pass and conform to Claim 1 of the Profile.

In general, the same or similar PDFF acquisition protocol as used in humans should be used. Any performance concerns and errors should be documented and reported. It is recommended that the PDFF-specific QA phantom includes multiple PDFF values between 0% and 50%, mimicking physiologically relevant hepatic fat content to appropriately evaluate bias. Although there is currently no consensus regarding the minimum number of vials to be used in a typical PDFF-specific QA phantom, the use of more vials that are broadly distributed across PDFF values of physiological relevance in the liver from 0-50% will

improve assessments. An example series of PDFF vials can be (0%, 5%, 10%, 15%, 20%, 30%, 40%, 50%). Additionally, there's no consensus on the type of fat or oil to be used in phantom construction, although previous data does not suggest to be a critical factor (*PMID*: 25845713).

At the time of this Profile writing, PDFF phantoms from third-party manufacturers are available commercially (*PMID*: 33464181). "Home-made" phantoms of water-fat emulsions constructed by individual centers may also be acceptable (*PMID*: 30430684, 30913055, 33768291), if processes are established to determine their stability and the validity of their reference PDFF values. When performing PDFF-specific QA phantom scans, the phantom used should be kept in the scanner room for a sufficient period to ensure that the phantom's temperature has equilibrated with the ambient room temperature prior to scanning. The room temperature should be recorded and the use of an MRI-safe thermometer in the scan room is recommended. Temperature is a known confounder in PDFF quantification and it may be necessary to include temperature corrections into the reconstruction algorithm when scanning phantoms instead of human subjects (*PMID*: 27080068).

There are several options for PDFF-specific QA phantoms, listed below in order of increasing complexity. Some references on these phantoms include: (*PMID*: 19856457, 27080068, 32783200, 36515810). While commercial PDFF-specific QA phantoms are available for purchase from third-party manufacturers (*PMID*: 33464181), there are also options for manufacturing "home-made" (*PMID*: 30430684, 30913055, 33768291).

- **0% PDFF (no fat) Phantom:** A large tub of water or agar gel can be used to confirm spatial uniformity of 0% PDFF across a nominal field of view. As some examples, a bottle of water, or a large bag of hospital intravenous saline, can be used.

- **Multi-Vial Phantoms:** These gradually varying PDFF phantoms include multiple vials with emulsions of known PDFF values, for example, in the range 0% to 50%. The content of these vials can be manufactured in different ways, such as:
  a. Serial dilution of water-fat emulsions of known PDFF%. Dilutions can be made from commercially available emulsions of known fat content, such as Intralipid® or Microlipid®. This approach will confirm bias (and linearity) of PDFF measurements from 0% PDFF to the maximum fat content of the original commercial emulsion.
  b. Like above, but with water-fat emulsions of known concentrations fabricated in the laboratory to mimic any nominal PDFF value.
  c. Like (b), with additional solutions and ingredients added to adjust and match the T1, T2, and/or T2* relaxation properties of the liver. These formulations may also include agarose, $CuSO_4$, $MnCl_2$, $NiCl_2$, Gadolinium-based contrast agents, or iron oxide particles, among others (*PMID*: 32783200).

For the options listed above, the individual PDFF vials can be standalone or enclosed in a larger container, such as a housing containing doped water or agar gel. The purpose of this water bath housing is to protect the vials, facilitate repeatable positioning during longitudinal QA procedures, improve B0 homogeneity, remove signal voids caused by air in the space between the vials, and relatedly minimize the potential for water-fat signal swaps.

A.3.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
PDFF-specific QA	Scanner operator	Shall perform PDFF-specific QA procedures by testing for bias and linearity on a periodic basis using a PDFF-specific phantom with 0-50% PDFF range.
		Shall assess any deviations and identify sources of error in PDFF measurements in the QA procedure. A threshold of +/-5% absolute PDFF bias is suggested for this PDFF-specific QA test to pass and conform to Claim 1 of the Profile.

A.4. Protocol Design

This activity involves designing and validating image acquisition protocols. Protocol design includes constraints on acquisition and reconstruction parameters necessary to reliably meet the Profile Claim.

A.4.1 DISCUSSION

Protocol Design is considered to take place at the imaging site; however, sites may choose to make use of protocols developed elsewhere. It is not intended that design and validation be repeated for each subject. The goal of the PDFF protocol is to obtain data that enables the estimation of proton density-weighted signals for water and fat, using multi-echo CSE pulse sequences. The data acquisition and reconstruction should therefore address all relevant confounding factors in the acquired signal, including T1 bias, T2* bias, multi-peak fat spectral bias, B0 field inhomogeneity, noise bias, and inter-echo phase errors (see **Appendix D**). Some of these confounding factors can be minimized through judicious selection of acquisition parameters, whereas others require correction at the data reconstruction stage. Common pulse sequence characteristics of liver PDFF protocols using multi-echo spoiled gradient-recalled-echo approach (*PMID*: 21769986, 28842937, 28936896, 33464181) are summarized in **Table 3**.

- Acquisitions can be 2D multi-slice with or without inter-slice gaps, or 3D volumetric.
- To minimize T1 bias between water and fat proton signals, it is common to use a low flip angle. For 2D acquisitions with longer TRs (i.e., 150-200 msec), flip angles around 10° are common. For 3D acquisitions with short TRs (i.e., 7-15 msec), flip angles between 3°-5° are common.
- Alternative approaches to address T1 bias include (*PMID*: 32754942, 31724776, 32243665, 35307745):
  a. Performing T1 correction with different flip angles (i.e., dual or variable flip angle) data. This approach enables explicit estimation of the T1 relaxation times of water and fat signals. The T1 values are then used to correct PDFF estimation.
  b. Using centric phase encoding with flip angle modulation.
- Although separation of water and fat signals is feasible in principle from only two echoes (*PMID*: 31286208), additional estimation and correction for R2* (1/T2*) effects requires at least three echoes (*PMID*: 18306404). Currently, the use of more than three echoes (often four or six), with uniform echo time spacing (ΔTE) is common. Typical ΔTE are less than half the water-methylene fat proton phase cycle (i.e., ~2.3 msec at 1.5T and ~1.15 msec at 3 Tesla). Multiple echoes can be acquired in a single echo train using monopolar (i.e., fly-back) readout schemes. Additionally,

multiple interleaved echo trains and/or bipolar readout schemes can be employed. This Profile does not restrict the method with which multiple echoes are acquired by the pulse sequence (i.e., in a single TR train, in multiple interleaved TR trains, and whether in monopolar (fly-back) or bipolar (non-fly-back) manner). Potential phase inconsistencies that arise between the echoes should be addressed subsequently by appropriate reconstruction software.

Table 3. Representative parameters for PDFF acquisitions using a steady-state spoiled gradient-recalled-echo sequence. Range of values are listed as suggestions.

Parameter	1.5T	3T	Considerations
Field of view	as needed	as needed	Avoid aliasing.
Number of slices	as needed	as needed	Cover pertinent portions of the liver.
Matrix size	≥ 128 × 128	≥ 128 × 128	Suggested in-plane resolution ~1-2 mm.
Slice thickness (mm)	5-10	5-10	Patient-dependent parameter: may adjust slice thickness within the 5- to 10-mm range to accommodate patient's breath-hold capacity and liver size, while maintaining adequate SNR.
Inter-slice spacing (mm)	2D only: 0-5	2D only: 0-5	Patient-dependent parameter applying to 2D acquisitions only: may adjust inter-slice spacing within the 0- to 5-mm range to accommodate patient's breath-hold capacity and liver size.
TR (msec)	2D: 150-250 3D: 10-15	2D: 100-200 3D: 6-10	Minimize T1 bias.
First TE (msec)	0.8-2.4	0.7-1.2	As short as possible.
Number of Echoes	>3	>3	More than 3 recommended; 6 preferred.
TE spacing (msec) ΔTE	1.2-2.4	0.7-1.2	Provide sufficient sampling of the relative water-fat phase given hardware capability.
Flip angle (degrees)	2D: 10-12 3D: 3-5	2D: 8-10 3D: 2-4	Minimize T1 bias.

Note: The Radiologist is responsible for the protocol parameters and for ensuring that the protocol has been validated, which may be done by an in-house medical physicist, a physics consultant, or other staff (such as vendor service or specialists) qualified to perform the validations described. Protocol design should be done collaboratively between the medical physicist and the radiologist with the ultimate responsibility to the radiologist. Some parameters are system dependent and may require attention from

a medical physicist. They may choose to use a protocol provided by the vendor of the scanner.

A.4.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Pulse sequence	Acquisition device MRI scanner	The scanner shall acquire CSE MRI PDFF data using a multi-echo 2D or 3D spoiled gradient-recalled-echo pulse sequence.
Anatomical coverage		The pulse sequence shall image a slice or slices of the liver. It is acceptable to image the liver in multiple concatenated slabs.
T1 bias		The acquisition shall minimize T1 signal bias, using appropriate TR and flip angle settings.
Number of echoes, TEs		The acquisition shall acquire multiple equally spaced echoes, or "points", to address water-fat separation and T2* correction. Four to six echoes are recommended.
Other considerations		The acquisition shall acquire the data with minimal respiratory artifacts with a scan time that is conducive to breath holds.

A.5. Subject Selection and Handling

This activity describes criteria and procedures related to the selection of appropriate imaging subjects that are necessary to reliably meet the Profile Claim. It also involves handling each imaging subject at each timepoint. It includes subject handling details that are necessary to reliably meet the Profile Claims.

A.5.1 DISCUSSION

Liver PDFF does not require any additional subject selection procedures beyond conventional practices concerning MRI Safety and contraindications. Listed below are some additional considerations:

- Local policies for patient and research subject eligibility for MRI exams should be followed. Contraindications to an MRI exam and considerations for MRI safety should be followed. Actors should be aware that MRI conditional medical implants and devices near the liver may introduce image artifacts that can hinder PDFF quantification.
- Subjects may be scanned in a variety of positions based on patient comfort considerations. For longitudinal studies, subjects should be scanned in a consistent position to facilitate co-localization of ROI measurements. The supine position with head-first entry into the scanner bore is the most common.
- A set of receiver coil arrays should be used. In larger subjects, the integrated body receive coil may be used, at the expense of reduced signal-to-noise ratio. Utilizing the integrated body receive coil will also remove the capability of employing parallel imaging.
- Currently, PDFF scans are performed with breath holds to minimize respiratory motion and related image artifacts. Practicing breath hold instructions prior to the exam is also recommended for the Scanner Operator and the participant. This familiarizes the subject with the procedure and allows the Scanner Operator to gauge the subject's breath hold capacity.
- Existing data suggest that meals and the timing of meals prior to an MRI exam do not affect PDFF measurements (*PMID*: 31168893). Therefore, fasting prior to PDFF exams is not required. However, fasting may be helpful to avoid peristalsis (*PMID*: 31168893). Large amounts of

intestinal gas and food in the gastrointestinal tract may also result in image artifacts.

- PDFF acquisition may be performed prior to or following the administration of MRI contrast media (*PMID*: 25305414, 27052456).

A.5.2 SPECIFICATION

Parameter	Actor	Requirement
Subject selection	Scanner Operator	Shall determine subject eligibility for MRI exam using local guidelines with regards to safety and MRI contraindications.
Subject handling and positioning	Scanner Operator	Shall position the subject in the scanner comfortably, with supine, head-first entry being the most common approach.
		Shall ensure receive coil arrays are positioned appropriately to cover the liver region, with a landmark laser crosshair placement near the xiphoid process of the sternum.
		Shall familiarize the subject with breath holds.
Device selection	Scanner Operator	Shall confirm in a longitudinal follow-up exam, a subject is scanned in the same position as the baseline exam, using preferably the same scanner and the same PDFF protocol.

A.6. Image Data Acquisition

This activity involves acquisition of image data for a subject. It includes details necessary to reliably meet the Profile Claim. This activity applies to every subject. Protocol Design (Section A.4) touches on similar parameters but addresses details that are not done for each subject, such as designing standard protocols and validating protocol performance with phantoms.

A.6.1 DISCUSSION

Figure 4 below summarizes the PDFF data acquisition process. A 3-plane localizer or scout image set is acquired first, upon which axial slices using a 2D or 3D CSE spoiled gradient-recalled-echo pulse sequence are prescribed (red boxes) about the liver. A PDFF map, scaled typically from 0-100%, is then generated after data acquisition. In most implementations currently available from commercial packages, a co-registered series of water and fat images are also generated. The current Profile does not dictate the k-space trajectory with which PDFF data are acquired. Although Cartesian methods are common, non-Cartesian radial k-space trajectories, for example, can also be used, which can facilitate free-breathing exams (*PMID*: 34662702). Scan acceleration techniques such as parallel imaging and compressed sensing may also be used (*PMID*: 31730658, 33893853).

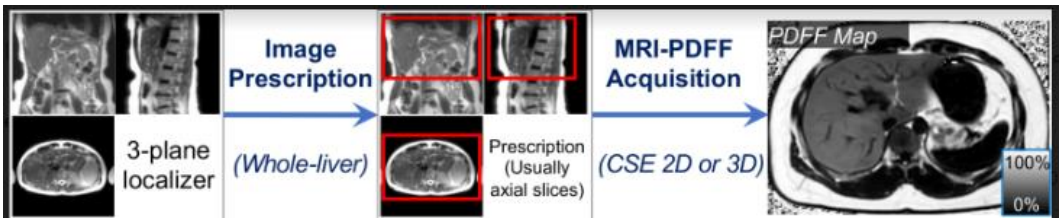
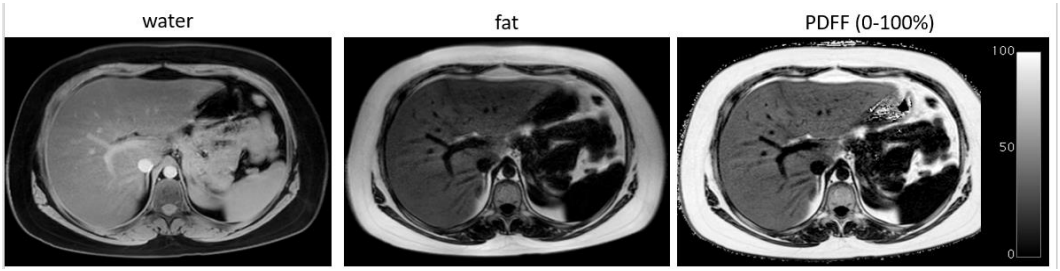


Figure 4. Schematic of PDFF data acquisition workflow process.



A.6.2 SPECIFICATION

Parameter	Actor	Requirement
Data acquisition	Scanner operator	Shall be performed on a Profile-conformant scanner and utilize a Profile-conformant CSE MRI PDFF protocol.
Technical success	Scanner operator	Shall review the reconstructed images and PDFF maps to confirm technical success of the exam and re-acquire the data if visible artifacts and errors are identified.

A.7. Image Data Reconstruction

This activity involves the reconstruction of image data for a subject. It includes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim. This activity applies to every subject. Protocol Design (Section A.4) touches on similar parameters but addresses details that are not done for each subject, such as designing standard protocols and validating protocol performance with phantoms.

A.7.1 DISCUSSION

Reconstruction of the acquired data is performed to create quantitative PDFF maps of the liver and primarily involves separating the water and fat signals on a voxel-wise basis whilst addressing confounding factors (see **Appendix D**). At the time of this Profile writing, commercial vendors including the MRI manufacturers provide online algorithms to generate PDFF maps in industry standard DICOM format. Although not an explicit requirement for this Profile, it is common for the data reconstruction pipeline to also yield co-registered series of images representing the water signal, the fat signal, the in-phase signal (sum of water and fat), the opposed-phase signal (difference of water and fat), and a R2* map.

A.7.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Data reconstruction	Scanner operator	Shall confirm that the scanner generates PDFF maps and outputs them in industry standard DICOM format on a scale of 0-100%, although 0-50% is the relevant physiological PDFF range for liver applications. Other file formats may be used by third-party developers to convert PDFF DICOM files for post-processing and subsequent ROI measurements if evidence can be if they are equivalent to their DICOM counterparts in representing PDFF values.
		Shall confirm that, if available, other supporting images are generated (i.e., water, fat, in-phase, opposed-phase, R2*).

A.8. Image Quality Assurance

This activity involves evaluating the reconstructed images prior to image analysis. It includes image criteria that are necessary to reliably meet the Profile Claim. This activity applies to every subject. Prior activities, such as Subject Handling (Section A.5), include requirements that attempt to avoid issues mentioned here, but it can still be necessary to confirm during this QA step whether those prior activities were successful.

A.8.1 DISCUSSION

The quantitative PDFF maps of the liver generated from successful exams should demonstrate images that are free from artifacts. This QA is performed between image generation and analysis. Image content characteristics are checked for conformance with the Profile. It is expected that sites perform other QA as part of good imaging practices.

The Radiologist is identified here as ultimately responsible for this activity; however, sites may find it beneficial for MR technologists and radiographers, medical physicists, and image analysts to review these details at the time of imaging and identify cases which might require a repeat acquisition and/or reconstruction to address issues with patient motion or artifacts. Similarly, some or all these checks may be performed by the radiologist at reporting time to detect whether the technologist was unsuccessful in avoiding them at acquisition time and as a result some or all of the PDFF measurements may then be identified as not within the performance target of the Profile. Once PDFF maps are reconstructed for a subject, the quality of the results should be evaluated by checking for potential problems, errors, and artifacts. The following QA steps are recommended:

- PDFF maps should be displayed on a scale of 0-100%, although 0 to 50% is the physiologically relevant range in the liver.
- QA using internal (in vivo) and/or external (ex vivo) references within the same imaging volume as the subject should be employed. Two emerging and mutually compatible approaches involve:
    - Checking the PDFFs value within non-fat regions and structures such as lean muscle and the spleen should be ~0-5% and checking the PDFF values within areas of high-fat-content such as healthy adipose tissue should approximately be between 75%-100%. A range is given here for PDFF of healthy adipose tissue as it can vary from subject to subject. Note that adipose tissue will only measure in this range for hybrid- and complex-based methods that can resolve PDFF across the full 0-100% range and should not be used as a reference for magnitude based PDFF mapping methods that have approximately 0-50% range (*PMID*: 32318847)
    - In addition to using muscle, spleen, and adipose tissue as reference PDFF measurement points, separate phantom vials containing water-fat emulsions with known PDFF values in the range of 0-50% PDFF can also be used as reference points during in vivo scanning. Checking these phantom vials with known PDFF values that are placed in the imaging volume (preferably under the patient to avoid respiratory motion artifacts) and comparing values measured in the vials to the known reference values can be beneficial. This approach is advantageous in that the true PDFF values are known,

whereas there is some uncertainty in the PDFF values of adipose tissue and other organs in vivo due to inter-individual variability. This approach may also be more applicable in subjects with little subcutaneous adipose tissue.

- Individual PDFF voxel values of <0% or >100% may be present and are not realistic. These non-physiological values are due to noise in the parameter estimation, and do not constitute a problem per se, since PDFF measurements are obtained over ROIs. However, excessive noise is a concern, and measurements should not be made in overly noisy regions within the liver where PDFF standard deviation is greater than 10% over a ROI located in homogeneous hepatic tissue (*PMID*: 33783066). A large ROI standard deviation may also suggest erroneous inclusion of artifacts and should be checked.
- If R2* (or T2*) maps are also available from the exam co-localized to the PDFF maps, they should be checked for areas of high-iron content in the liver as well as areas of severe B0 field inhomogeneity, field variation, and magnetic susceptibility (*PMID*: 24585403). These areas should be avoided during ROI placement.
- Areas of water-fat signal swaps due to reconstruction error should be avoided when placing ROIs. If signal swap occurs throughout most of the liver, the PDFF scan should be rejected.
- If parallel imaging was used during the PDFF acquisition, reconstruction artifacts such as residual signal aliasing should be checked. If parallel imaging artifacts occur within the liver, the PDFF scan should be rejected.
- Visible ghosting artifacts from severe patient motion should be checked. Visible artifacts from inadequate field-of-view and signal aliasing should be checked. If found and they confound ROI placement, the PDFF scan should be rejected.

A.8.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Image quality, validity of PDFF values	Image analyst	Shall confirm that images contain the liver within the imaging field-of-view and that there is visually adequate signal-to-noise ratio.
		Shall confirm that images are free of visible artifacts, such as patient motion, parallel imaging, and water-fat swaps.
		Shall identify areas of the liver parenchyma where large ROIs can be used and PDFF can be reliably measured. These areas shall exclude visible image artifacts, blood vessels, bile ducts, etc., and shall not contain high R2* values suggestive of high iron overload (beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T).
		Shall reference, if available, water, fat, in-phase, opposed-phase, and R2* maps to place appropriate ROIs in the liver.
		Shall check lean and adipose tissue, as well as reference phantom vials, for appropriate PDFF measurements.

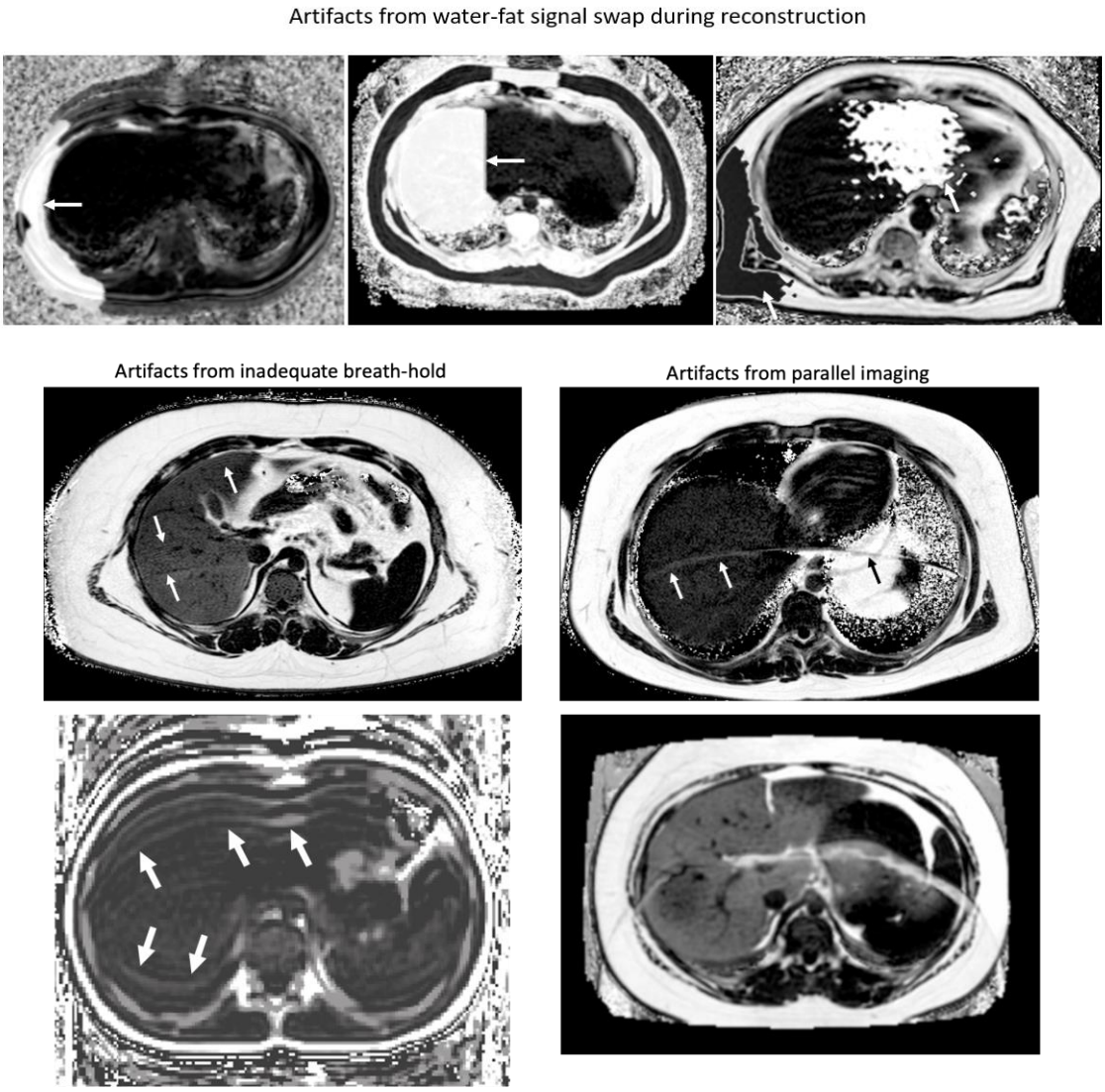


Figure 5. (top) Examples of water-fat swaps as observed on resultant PDFF maps (white arrows). (Bottom left) Examples of respiratory motion artifacts, or ghosts, due to inadequate subject breath hold. (Bottom right) Examples of residual parallel imaging artifacts, which largely arise from incomplete unaliasing of the subcutaneous adipose tissue.

A.9. Image Distribution

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

A.9.1 DISCUSSION

Industry standard DICOM file formats should be used to distribute the reconstructed PDFF maps. Post-processing workstations and image analysis tools should correctly display the DICOM PDFF maps on a meaningful scale representative of 0-100% PDFF. To ensure correct pixel value transformation, the DICOM header information "rescale slope" and "rescale intercept" or "real world value mapping sequence" should be retained. Other file formats may be used by third-party developers to convert PDFF DICOM files for post-processing and subsequent ROI measurements if evidence can be if they are

equivalent to their DICOM counterparts in representing PDFF values.

A.9.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
PDFF maps	Scanner operator	Shall ensure that PDFF maps are generated as its own image series and initially transmitted, preferably, in DICOM format. Shall ensure that PDFF values are scaled and displayed correctly on a range of 0-100%.

A.10. Image Analysis and Interpretation

This activity involves producing the quantitative measurements described in the Profile Claim. It also describes criteria and procedures related to clinically interpreting the measurements and images that are necessary to reliably meet the Profile Claim. This activity applies to every subject. Requirements related to the assessment of the general performance of the tool or operator go in sections A.1 (Product Validation) and A.2 (Staff Qualification) respectively.

A.10.1 DISCUSSION

PDFF of the liver is commonly measured by placing ROIs on the PDFF maps (*PMID*: 28842937 26536609 28705058 30736759). Multiple ROIs are often used across the liver to reflect overall hepatic steatosis burden. At the time of this Profile writing, there is no consensus on the methods of ROI sampling, including the choice of ROI locations and sizes. In general, more than one ROI is placed within homogeneous regions of the liver, avoiding large blood vessels, lesions, bile ducts, areas of high iron content (i.e., beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T), and visible image artifacts.

As hepatic steatosis can be heterogeneous, it is generally accepted that interrogation of multiple, larger ROIs of the liver that involve both lobes and/or multiple segments is preferred, in order to minimize bias and/or variability of the summary PDFF values related to heterogeneity of steatosis (*PMID*: 28705058). A commonly used strategy is applying multiple ROIs across the liver (*PMID*: 26536609). As an alternative, whole-liver segmentation can also be used to summarize the PDFF of the liver. Summary PDFF values from the measured regions should be reported. Summary values often include the mean over the ROI, although other statistics, such as the median, can also be used (*PMID*: 29322549). When multiple ROIs are used, the average or weighted average (for example, weighted by area of each ROI) can be used to summarize the PDFF of the liver. If available, the observed range of PDFF values across the ROIs can be reported to reflect possible liver fat heterogeneity.

When longitudinal measurements of PDFF are made in the same subject, it is important to use similar ROI approaches across all time points, to avoid additional variability and/or bias. If possible, it may be helpful to align PDFF maps and colocalize ROIs across different time points in the same patient. The Image Analyst should be aware that the liver may change with some interventions, especially surgery. Such interventions may lead to marked changes in the anatomical configuration of the liver and organ size and alter the fat content of the liver regionally.

A.10.2 SPECIFICATION

Parameter(s)	Actor(s)	Requirement(s)
Liver PDFF analysis and ROI reporting	Image analyst	Shall measure liver PDFF using image analysis software that facilitates the placement of multiple ROIs. If multiple ROIs are involved, a weighted measurement using the area of the ROIs as weights can be used.
		Shall use the largest possible ROIs in the liver and its lobes on the PDFF maps, whilst avoiding boundaries, vascular and biliary structures, etc. ROIs with areas larger than that of a 1 cm diameter circle are recommended. ROI size of at least 4 cm^2 is highly preferred.
		Shall exclude areas of image artifacts and high R2* values (beyond 300 s^{-1} at 1.5T and 450 s^{-1} at 3.0T), the latter representative of severe iron overload.
		Shall report descriptive statistics for each ROI used.

Appendix B: Biomarker Usage

This Appendix discusses concepts and considerations related to the meaning of the Claims and the application of this Biomarker in clinical contexts.

Clinical Value and Application

Non-alcoholic fatty liver disease (NAFLD), referred to as metabolic associated fatty liver disease (MAFLD) since 2022, is the most common chronic liver disease worldwide, with a global prevalence of approximately 25% (*PMID*: 26707365). The hallmark feature is accumulation of fat in hepatocytes (liver steatosis) (*PMID*: 34546125). Approximately 20% of patients with MAFLD will develop the more severe non-alcoholic steatohepatitis (NASH), characterized by hepatocyte injury and inflammation. Since 2022, the term "NASH" has been replaced by metabolic dysfunction-associated steatohepatitis, or MASH. For example, 20% of patients with MASH will develop advanced liver fibrosis and/or cirrhosis, and this percentage is expected to increase substantially over the next decade (*PMID*: 28802062). Multiple metabolic comorbidities are associated with MAFLD, including obesity (51%), type 2 diabetes (23%), hyperlipidemia (69%), hypertension (39%), and metabolic syndrome (41%). The association between MAFLD and cardiovascular disease has been the subject of increased research interest in recent years. For example, there is a high-risk of coronary plaque with MAFLD, independent of cardiovascular risk factors, body mass index, and extent and severity of coronary artery disease (*PMID*: 25369449). In patients with MAFLD, cardiovascular disease mortality far exceeds liver-specific mortality.

Various liver PDFF thresholds have been identified in different studies for children and adults. For example, the Dallas Heart Study identified a threshold of 5.6% as the 95% limit in a cohort with no risk factors for liver disease (*PMID*: 15339742). In pediatric studies, a threshold of PDFF of 3.5% was determined as diagnostic for MAFLD (*PMID*: 27818597), and a threshold of 3.0% was shown to be predictive for metabolic syndrome (*PMID*: 25916386). However, these thresholds have slightly varied from other reports (*PMID*: 25659155, 27351583). Recently, PDFF thresholds for mild, moderate, and severe steatosis have been proposed at 5%, 15%, and 25%, respectively (*PMID*: 34546125). Focused MRI protocols have been developed for evaluation of liver fat using PDFF (*PMID*: 30917020). These protocols are typically designed around a single breath-hold PDFF scan, and may enable rapid, cost-effective detection, staging, and treatment monitoring of MAFLD in the clinic.

Relationship to Histology

The claims in this Profile do not relate to the performance of PDFF measurements to predict histologically determined liver steatosis. This performance has been evaluated separately in multiple studies and is summarized in **Table 4**. The diagnostic accuracy of PDFF for histologically-confirmed hepatic steatosis was: diagnostic area under the receiver-operating characteristics curve **(AUROC)** 0.96-0.98, sensitivity 0.92-0.95, specificity 0.90-0.93, across multiple meta-analyses (*PMID*: 30899974, 30877459, 33128454, 35087774). The classification accuracy of steatosis grade 1, 2, and 3 (mild, moderate, severe) has also been evaluated in these studies. For classification of grade 0-1 vs. 2-3, the measured accuracy was: AUROC 0.90-0.92, sensitivity 0.79-0.94, specificity 0.74-0.88. For classification of grade 0-2 vs. 3, the measured accuracy was: AUROC 0.71-0.74, sensitivity 0.87-0.89, specificity 0.74-0.89. Several PDFF thresholds have been proposed for histological grading of steatosis, ranging 3.7-6.4% for ≥Grade 1, 12.0-17.5% for ≥Grade 2, and 16.4-23.3% for Grade 3. When grading steatosis severity by measured PDFF

values, it is recommended to standardize to a published PDFF-based grading system and make an appropriate reference to the used criteria.

Table 4. Hepatic Steatosis Detection and Grading Classification Accuracy by PDFF

	Grade 0 vs. 1-3	Grade 0-1 vs. 2-3	Grade 0-2 vs. 3	Reference
Summary AUROC	0.98	0.91	0.90	*PMID*: 30899974
	0.98	0.92	0.92	*PMID*: 30877459
	0.97	0.90	0.90	*PMID*: 33128454
	0.96	-	-	*PMID*: 35087774
Summary Sensitivity	0.93	0.94	0.74	*PMID*: 30899974
	-	0.83	0.79	*PMID*: 30877459
	0.92	0.79	0.71	*PMID*: 33128454
	0.95			*PMID*: 35087774
Summary Specificity	0.90	0.74	0.87	*PMID*: 30899974
	-	0.89	0.89	*PMID*: 30877459
	0.93	0.88	0.89	*PMID*: 33128454
	0.92	-	-	*PMID*: 35087774

Application in Clinical Trials

There is a need for non-invasive methods to replace biopsy for the diagnosis and treatment monitoring in clinical trials for MASH (*PMID*: 36523866). MRI-PDFF is a non-invasive, widely available, accurate, reproducible quantitative biomarker of triglyceride concentration in tissue, and has been used increasingly in clinical trials over the past decade. MRI-PDFF is particularly promising for clinical trials that evaluate therapeutic agents with a strong anti-steatosis effect. In these clinical trials, MRI-PDFF can be used as a threshold, for example, with a value of 8%, for subject entry criteria (*PMID*: 33179266). Importantly, MRI-PDFF has been shown to be more sensitive than liver biopsy to small longitudinal increases or decreases in liver fat (*PMID*: 23696515). In recent studies, the ability of changes in MRI-PDFF to predict histologic response has been demonstrated. Indeed, when a relative reduction of 30% in liver PDFF was achieved, the odds of MASH resolution improved by 5.5-fold, and the odds of improvement in liver fibrosis by at least one stage increased by 6.5-fold (*PMID*: 33883248).

Appendix C: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Proton Density Fat Fraction (PDFF) Biomarker Committee. The committee is composed of representatives from academia, professional societies, scanner manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, government research organizations and regulatory agencies, among others. All work is considered pre-competitive.

For a description of the committee and its work, see: https://qibawiki.rsna.org/index.php/Committees.

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Appendix D: Conventions, Definitions, Lexicon

Chemical-shift-encoded (CSE) MRI
A multi-echo MRI-based acquisition and reconstruction approach is used to estimate the fat fraction by encoding the chemical shift between protons in triglyceride or fat and protons in water.

CSE data reconstruction
Reconstruction methods that generate separated water and fat images, along with parametric maps of PDFF (and other variables) based CSE data. Methods can utilize source echo data in complex (magnitude and phase) form or magnitude-only form. Hybrid methods can use a weighted combination of magnitude-only and complex data from the source echoes.

Confounder-corrected CSE MRI
A CSE approach where acquisition and reconstruction practices have corrected or minimized all meaningful sources of signal bias through appropriate selection of acquisition parameters and appropriate modeling of the signal during data reconstruction.

In-phase echo times (nominal)
The echo times in a gradient-recalled-echo acquisition which the water peak at 4.7 ppm and the dominant triglyceride methylene (-CH2-) peak at 1.3 ppm are mathematically in phase. At 1.5T, the nominal in-phase echo times occur every 4.6 msec (i.e., 4.6, 9.2, 13.8 msec, …). At 3T, the nominal in-phase echo times occur every 2.3 msec (i.e., 2.3, 4.6, 6.9 msec, …). The modifier "nominal" is used because other minor fat peaks are not in-phase with the water peak at these echo times (see multi-frequency interference or multi-peak fat spectral complexity).

Multi-frequency interference or multi-peak fat spectral complexity
The systematic error introduced into fat fraction estimation by signal interference effects between different types of proton moieties in the triglyceride molecule. Depending on their position in the triglyceride molecule, these protons have different resonance frequency locations ranging from 0.9 ppm to 5.29 ppm. At current clinical magnet field strengths of 1.5 Tesla and 3 Tesla, some of these resonance frequencies are not resolvable. The removal of bias caused by multi-frequency interference or multi-peak fat spectral complexity can be accomplished by incorporating the relative amplitude of each proton triglyceride peak in the PDFF mathematical model. Generally, the relative amplitudes are assumed based on an accepted triglyceride model, such as the six-peak model proposed in this reference (*PMID*: 21834002).

Noise bias
The systematic error introduced into fat fraction estimation by image noise. For magnitude reconstruction, image noise causes underestimation of the true fat fraction because the noise adds baseline positive signal at each echo time, which reduces the observed relative signal oscillation; the degree of underestimation is greatest at fat fractions near 50%. For complex reconstruction, image noise causes overestimation of the fat fraction when the true fat fraction is low. The reason is that positive noise is added to the rectified fat and water signals. If the true amount of fat is low, adding positive noise to the fat signal can substantially increase its measured magnitude. By comparison, the noise has a

negligible effect on the measured magnitude of the dominant water signal. Minimization of noise bias can be achieved by selection of appropriate acquisition parameters. For magnitude reconstruction, using large voxels and the lowest receive bandwidth that achieves the appropriate echo spacing is recommended. For complex reconstruction, noise bias reduction depends on selection of optimal echo spacing.

Out-of-phase (or opposed-phase) echo times (nominal)
The echo times in a gradient-recalled-echo acquisition which the water peak and the dominant triglyceride methylene (-CH2-) peak are mathematically out of phase. At 1.5T, the nominal out-of-phase echo times occur at 2.3 msec and then every 4.6 msec thereafter (i.e., 2.3, 6.9, 11.5 msec, …). At 3T, the nominal out-of-phase echo times occur at 1.15 msec and then every 2.3 msec thereafter (i.e., 1.15, 3.45, 5.75 msec, …). The modifier "nominal" is used because other minor fat peaks are not out-of-phase with the water peak at these echo times (see multi-frequency interference or multi-peak fat spectral complexity).

Parametric map
A reconstructed image that shows the parameter of interest, such PDFF and R2*.

Phase errors
The systematic error introduced into fat fraction estimation by unexpected phase accumulation in the acquired signals. One source of phase error is due to residual eddy currents. Another possible source is from interleaved echo trains or bipolar "non-fly-back" readout schemes.

Proton density fat fraction (PDFF)
The ratio of the measured density of mobile protons from triglycerides (i.e., fat - *f*) to the total density of mobile protons from triglycerides and water (*w*):

$$PDFF = \frac{PD_f}{PD_f + PD_w}$$

The PDFF is expressed as a percentage (%) and ranges from 0-100%. The PDFF is equivalent to the SFF after all sources of meaningful bias have been reduced. It is considered a fundamental MR property of tissue and, when measured properly, a reliable indicator of true fat content. For liver applications, 0-50% PDFF is the physiologically relevant range. A parametric map that shows pixel by pixel the PDFF values across the image or ROI is referred to as a PDFF map.

PDFF Phantom
An inanimate object containing often single or multiple vials of water-fat emulsions of known PDFF values designed to mimic anatomical tissue, used frequently to ensure that MRI systems and imaging methods are operating properly within specifications.

Signal fat fraction (SFF)
The ratio of the signal intensity of mobile protons from triglycerides (fat-*f*) to the total signal intensity of mobile protons from triglycerides and water (*w*):

$$SFF = \frac{S_f}{S_f + S_w}$$

The SFF is expressed as a percentage (%) and ranges from 0-100%. The SFF is not an accurate indicator of true fat content and may be biased since its value may be modulated by numerous confounding factors (see below, such as T1 bias and T2* bias and multi-frequency interference or multi-peak fat spectral complexity).

T1 bias
The systematic error introduced into fat fraction estimation by the intrinsic differences in T1 relaxation times of mobile protons from triglycerides and water. The magnitude of the bias is greatest when the fat fraction is 50%. T1 bias can be removed or minimized by either explicitly incorporating T1 relaxometry values in the PDFF signal model, or by selecting selection of appropriate acquisition parameters in a spoiled gradient-recalled-echo CSE sequence. Small flip angles are often employed to reduce the impact of T1 bias. Centric phase encoding order and variable flip angle approaches can also be used but in these cases, care needs to be taken to ensure the magnetization is fully recovered before the acquisition is started.

T2* bias
The systematic error introduced into fat fraction estimation by T2* signal decay across the multiple echo data readouts. Since T2* decay reduces the observed signal oscillation caused by water-fat frequency interference, it tends to cause fat fraction underestimation. One exception is the two-point Dixon methods in which the nominally out-of-phase echo is collected with a longer echo time than the nominally in-phase echo: for such methods, T2* decay causes fat fraction overestimation. The magnitude of T2* bias depends on multiple factors, including but not limited to echo spacing, field strength, and iron content in the liver. In T2* bias correction methods, a single T2* value is often assumed for water and triglycerides in the signal model during CSE data reconstruction.

Region-of-interest
Abbreviated as ROI, a region on an image in which the values of a parameter are recorded. ROIs are typically drawn during analysis using post-processing software.

Repeatability
Agreement between repeated measures made under near-identical conditions. Examples: repeated measurements of PDFF without repositioning the subject (within exam repeatability) or with repositioning on the same day (between exam repeatability). The same acquisition/reconstruction software and analysis should be used.

Reproducibility
Agreement between measurements made under different conditions. Examples: repeated measurements of PDFF made at least several days apart; or made with scanners of different field strengths, vendors / manufacturers, or acquisition/reconstruction software, or analyzed by different post-processing procedures.

Water-fat signal swap

A water-fat signal swap is an image artifact in the derived water or fat images (and resultant PDFF parametric maps) where the data reconstruction algorithm mistakes the fat component of the signal as water and the water component as fat, leading to a signal swap. This may occur over the whole image or in a localized region. The PDFF in swapped regions can therefore be erroneous. These swaps can be evident to a trained observer but become more challenging to detect when the liver fat content is very high. For example, a PDFF of 54% in the liver could be an apparent water-fat swap of a true PDFF of 46%.

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Open Issues:

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

Q. The Profile's conformance testing Section (4.1) does not include steps to directly evaluate the cross-sectional claim. Instead, this section is focused on evaluation of mean bias. A. Explicit steps should be added to Section 4 to evaluate the 95% confidence interval of individual PDFF measurements, to support the cross-sectional Claim.
Q. Should the Profile include latest technical developments in data acquisition, such as compressed sensing and non-Cartesian k-space trajectories? A. Although there are some existing publications on liver PDFF quantification using advanced acquisition techniques such as compressed sensing and non-Cartesian trajectories, their availability from vendors as commercial products is not yet widespread. This Profile should consider these advancements in future iterations.
Q. Should the Profile recommend how PDFF should be reported in the literature? Does the reporting structure differ for research vs. clinical applications? A. There are relevant literature studies on PDFF reporting in the liver, including recommendations on how ROIs are used (*PMID*: 28705058, 26536609). Co-localized ROIs are recommended for longitudinal measurements. In general, when placing ROIs in the liver, multiple large ROIs are recommended, avoiding vessels bile ducts, lesions, areas of high iron content (high R2* values), and image artifacts. Mean PDFF values are acceptable for reporting. Additionally, in the future, median values within the ROI and the range observed within the ROI should be considered. Future versions of the Profile can also consider how to harmonize reporting of liver PDFF to reflect organ fat heterogeneity.
Q. Should the Profile recommend how temperature in phantom acquisitions be addressed? Should the Profile recommend temperature correction for PDFF quantification algorithms in phantom PDFF scans? A. The water-fat off-resonance is a function of temperature, so phantoms (or tissues) scanned at a temperature far from body temperature can lead to a water-fat off-resonance that is different from that observed in vivo (i.e., 3.5 ppm between the water peak and the main methylene peak in phantoms at room temperature, instead of the 3.4 ppm observed in vivo). This effect leads to PDFF errors in CSE-based quantification in phantoms, if not adjusting for this shift. These temperature dependent errors in PDFF phantoms are dependent on the acquired echo times, as well as on the reconstruction algorithm, such as magnitude versus complex fitting. Thus, the current Profile states that temperature correction may be necessary but does not impose it or recommend it as it may be infeasible or unnecessary in some cases. Future revisions of this Profile should revisit the issue of temperature correction.
Q. Should the Profile address emerging methods that involve Artificial Intelligence, Machine Learning, and Deep Learning at the level of data acquisition, data reconstruction, and image analysis? For example, emerging algorithms for automated liver PDFF measurement using AI-based detection/segmentation of the liver may soon reach widespread adoption. Should the Profile explicitly mention the possibility of automated measurement?

A. The Profile should consider in the future ROI measurements that are made automatically by software, in addition to being manually placed by a user, if the ROIs cover enough of the liver tissue and lead to precise measurements. Automated measurements on phantoms are similarly feasible and should be acceptable per the Profile. Future revisions to this Profile should consider advanced methods of data acquisition and reconstruction aimed for example at reducing the number of requisite echoes, data denoising, and automated liver segmentation. The current Profile has not addressed any advanced methods that are not commercially available at the time of the Profile writing.

Q. Should the Profile include recommendations for magnetic field strength other than 1.5T and 3T, for example in both the low-field and high-field regimes?

A. At the time of this Profile's writing, 1.5T and 3T scanners remain popular in clinical practice. While CSE acquisitions and PDFF quantification are certainly feasible at lower and higher magnetic fields, there has not been extensive phantom or in vivo studies to assess bias (and linearity) at these alternative field strengths. Future revisions to this Profile should consider other magnetic field strengths.

Q. The Profile recommends periodic QA for an end-user but does not specify the frequency with which QA should be performed. The Profile also does not recommend a time after the previous demonstration of Profile conformance before evidence of conformance needs to be redemonstrated.

A. Future revisions of this Profile should consider recommending and regulating the frequency of QA procedures. Future revisions to this Profile can also consider recommending and regulating a time frame for assessing and maintaining Profile conformance, possibly independent of software and hardware changes to the MRI scanner and PDFF technology.

Closed Issues:

These issues have been considered closed by the Biomarker Committee. They are here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

Q. What are the requirements for conformance tests (phantoms, volunteers, patients)?

A. Conformance testing is required for developers of a new commercial PDFF product. Developers may for example be from an MRI vendor or a third-party independent entity. For PDFF products that have been demonstrated by the developers to be Profile conformant, the end-user at an individual site need not to repeat the full extent conformance testing that was performed by the developer, if utilizing the PDFF products in accordance with developer specifications. However, quality assurance is strongly recommended for the end-user, which should include, at a minimum, routine scans of a PDFF phantom and QA checks on in vivo PDFF studies. See Figure 1, Section 4, and Section A.8 for additional guidance.

Conformance testing should include bias and repeatability assessments as outlined in **Section 4**. Procedures should be described in sufficient detail in a manner that is reproducible by others. Bias testing should be performed using a series of fat (triglyceride)-water mixture (emulsion) PDFF phantom, covering broadly a typical range of PDFF values for liver fat quantification (0-50%). The phantom emulsions should have known values based on proton-density, rather than volume or weight fat fractions. Validation by MR spectroscopy or an independent non-MR reference standard of (fat) triglyceride and water hydrogen (proton) concentration, such as biochemical triglyceride extraction analysis (*PMID*: 23204926), is also acceptable. Conformance testing also includes a repeatability study in human subjects. The subject cohort should be representative of the target patient population of intended use (*PMID*: 28892458), and should be adequate in size to compute meaningful repeatability coefficients (*PMID*: 29298603).

Q. Does the Profile include just original equipment manufacturer (OEM) MRI vendor implemented methods for PDFF or does it also include other PDFF approaches (i.e., Contract Research Organization, Academic Research Organization, third-party developers).

A. The current Profile is written to address all providers of PDFF products, whether OEM manufacturer or third-party developer.

Q. Should the Profile recommend fasting vs. non-fasting state before a CSE MRI PDFF exam?

A. There is currently no evidence to suggest that fasting is required for a PDFF exam. However, other concurrent imaging procedures such as MR elastography and MR enterography may require fasting, nonetheless.

Q. Should the Profile include all variations of PDFF implementations (T2* modeling, T1 bias, bi- vs. mono-polar echo readouts, interleaved echo trains, partial Fourier, k-space undersampling, magnitude vs. complex vs. hybrid data approaches, etc.)?

A. The Profile currently does not specify the details of technical implementation for both CSE data acquisition and reconstruction. The techniques employed should be appropriately validated by conformance testing.

=-=-=-= End of Profile =-=-=-=