QIBA Profile:
Ultrasound Volume Blood Flow (USVBF)

Edition: 2023
Stage: Stage 2 (Consensus)

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When referencing this document, please use the following format:

QIBA Ultrasound Biomarker Committee. Ultrasound Volume Blood Flow (2.1), Consensus Document. Quantitative Imaging Biomarkers Alliance, December 22, 2023. Available at: https://qibawiki.rsna.org/index.php/Profiles

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ABBREVIATIONS AND DEFINITIONS

AAPM – American Association of Physicists in Medicine

ACR – American College of Radiology

AIUM – American Institute of Ultrasound in Medicine

ARDMS - American Registry for Diagnostic Medical Sonography

ARRT - American Registry of Radiologic Technologists

AVF - Arteriovenous fistula

CCI - Cardiovascular Credentialing International

CSA – Cross-sectional area

CV – Coefficient of variation defined for a set of measurements as the standard deviation divided by the mean, often expressed as a percent.

EDV – End diastolic velocity

EFW – Estimated fetal weight

IAC – Intersocietal Accreditation Commission

IEC – International Electrotechnical Commission

KDOQI - Kidney Disease Outcomes Quality Initiative

MCA – Middle cerebral artery

MRI – Magnetic Resonance Imaging

PSV – Peak systolic velocity

QA – Quality Assurance

QC - Quality Control

QIBA – Quantitative Imaging Biomarker Alliance

RI – Resistive index

UVBF – Umbilical venous blood flow

VBF – Volumetric blood flow – blood volume that passes through a cross-sectional area of a vessel per unit time (mL/min). This is often referred to as flux (Q) in fluid dynamics.

V_{mean} – Spatial mean blood flow velocity, especially of that in a blood vessel, used in the computation of volumetric blood flow.

wCV – within subject coefficient of variation defined as coefficient of variation found in an inter-observer study of measurement error.

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** (Manufacturers/Vendors/Field Service Engineers, Sonographers/Technologists, Physicians, Physicist/Clinical Engineer/QA manager, and Image Analysis Tools) must meet the Checklist **Requirements** (Section 3) covering Product Validation, Staff Qualification, Pre-delivery, Installation, Periodic QA, Subject Handling, Image Data Acquisition, Image QA, and Image Analysis.

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

- The requirements are believed to be practical by the committee. Simplifications will be considered for future versions of the profile.
- 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.

This QIBA Profile (US Volume Blood Flow) addresses volumetric blood flow (volume of blood passing through a given vessel per unit time), which can be used as a biomarker of normal/abnormal physiologic conditions, disease progression or response to therapy. The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of volume blood flow measurements. In addition, traditional methods for volume flow using 2D imaging and spectral Doppler ultrasound measurements have not been widely used due to high variability, implicit assumptions, and high user interaction requirements.

1.1 Clinical Context

Ultrasound Volume Blood Flow (VBF) is used as a biomarker currently associated with the assessment of dialysis arteriovenous fistulas (AVFs). It has also been shown to be one of the most effective measures related to fetal growth when measuring volume blood flow in the umbilical vein. However, due to complications with the current, traditional methods, the accuracy and ease of use for making ultrasound VBF measurements have limited its clinical utility. The use of VBF in many clinical examinations and human trials could be extensive, particularly if the biomarker is validated. See Appendix B for a discussion of usage of this biomarker in practice.

In the claims presented below, the general methodology involves the use of 3D color flow imaging data (velocity and power) in the calculation of volume blood flow. The term “imaging system” refers to both the ultrasound scanner (machine) and the operator using the machine to perform VBF measurements. Changing either the operator or ultrasound scanner therefore results in a different imaging system. The working definition of “pulsatile” for the purposes of this profile is provided in the explanatory text found in Appendix B as footnotes to the claims.

1.2 Claims

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

- **Claim 1a: (cross-sectional, phantom)* For a measured constant volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.033Y) +/- 0.069Y * 1.96 mL/min.**

- **Claim 1b: (cross-sectional, clinical)† For a measured constant volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.033Y) +/- 0.2Y * 1.96 mL/min.**

- **Claim 1c: (cross-sectional, phantom)* For a measured pulsatile volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.149Y) +/- 0.143Y * 1.96 mL/min.**

- **Claim 1d: (cross-sectional, clinical)† For a measured pulsatile volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.149Y) +/- 0.2Y * 1.96 mL/min.**

- **Claim 2a: (technical performance claim)** For clinical subjects, the volume flow measurement in constant flow has a within-subject coefficient of variation (wCV) ≤ 20%.**

- **Claim 2b: (technical performance claim)†† For clinical subjects, the volume flow measurement in pulsatile flow has a within-subject coefficient of variation (wCV) ≤ 20%.**

See Appendix B for associated footnotes

The above claims were developed based on phantom studies conducted by the Ultrasound Volume Blood Flow Biomarker Committee and published studies in the peer-reviewed literature except as noted in Appendix B. These claims may not accurately reflect performance in patients under all imaging circumstances. The expectation is that during the Technical Confirmation and Clinical Confirmation phases, data on the actual field performance will be collected and changes made to the claims or the details, accordingly. At that point, this caveat may be removed or re-stated.

1.2.1 CURRENT PERFORMANCE

Based on the groundwork studies and literature review carried out by the QIBA USVBF Biomarker Committee, consider the following clinical scenario: Given initial and subsequent mean flow estimates, each with a confidence of +/- 20% of the mean value (coefficient of variation), the subsequent mean will be considered different from the initial mean based on 95% confidence limits if it lies outside of the repeatability range (i.e. if subsequent mean < (initial mean ± (0.20*initial mean)*2.77) < subsequent mean). Either pulsatile or constant flow can be used for the assessment of whether each type of flow measurement meets QIBA claims.

Clinical interpretation of findings is based on an estimate of volume blood flow through vessels of interest. The consequences of absolute flows will depend on the clinical circumstances for which the measurement is being made and are outlined in more detail in Appendix B. Flow will be defined in standard units, e.g., mL/min. Although flow estimates can be made in vessels with pulsatile or constant flows, measurements will initially reflect an estimate of mean flow.

1.3 Disclaimers

Standard of Care: The requirements are defined to achieve the Claim 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: QIBA Claims describe the technical performance of quantitative measurements. The clinical significance and interpretation of those measurements is left to the clinician. Some considerations for two specific example applications are presented in the following text.

Blood volume flow in the umbilical cord is considered analogous to cardiac output in adults, and blood flow measurements have proven useful for the diagnosis of prenatal conditions such as intrauterine growth restriction (IUGR) and pre-eclampsia[1-11]. Yet, despite the obvious benefits, umbilical cord blood flow measurements are hardly ever used clinically due to the fact that standard Doppler-based flow quantification methods produce highly variable results, are challenging to perform, and, in many cases, will generate incorrect flow estimates because of multiple faulty assumptions[12-15]. Nevertheless, the value of these measurements suggests that a simple, accurate, and reproducible method for measuring umbilical cord blood flow would be a valuable addition to ultrasound-based fetal assessments.

Hemodialysis is another clinical application that relies heavily on the evaluation of flow parameters. Once a fistula is created, there is a high failure rate prior to availability for use. Many of the fistulas fail to mature (not useable for dialysis) and some subsequently fail due to stenosis or occlusion. Volume blood flow in the draining vein of an arteriovenous fistula is important to evaluate whether a fistula can initially handle the flow needed for hemodialysis. It is currently one of three criteria that are predictive of a fistula that is mature. Volume flow is a key component since the draining vein must have enough flow to allow maintenance flow without collapse during hemodialysis. Based on study data and national guidelines[16], a minimum volume flow of 500 mL/min is needed in the draining vein. A separate study showed increased failure to mature rate if the volume flow was less than 413 mL/min[17]. The implied variation in the 2D method as well as the differential flow of ~100 mL/min in these two references would suggest that Claim 2b at <20% is appropriate. The vein should have a straight segment to allow for the cannulas. The other two criteria include vein diameter and vein depth. A depth of less than 5 mm and a vein diameter greater than 4 mm suggest that successful hemodialysis can be performed[18].

Once a fistula has matured and is being used for hemodialysis, ultrasound is used when there are signs or symptoms worrisome for dysfunction, most commonly due to stenosis. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines[16], the minimum ultrasound criteria for AVF maturity at 4 weeks are a vessel diameter of 4-5 mm and volume blood flow of 400-500 mL/min). Low flows suggest the development/presence of a stenosis, which may lead to occlusion. Stenosis characterization relies on b-mode and spectral Doppler values. It should be noted that a stenosis can be present, but the volume flows may be adequately maintained.

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.

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 described in section 3.1.

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

3. Profile Requirement Checklists

The following Checklists are the basis for conforming to this Profile (See Section 2). Appendix A provides this checklist ordered by Activity and includes additional information that may be helpful in understanding such activities and their basis.

Conforms (Y/N) indicates whether conformance to the requirement has been confirmed by the assessor. When responding **N**, it is helpful to include notes explaining why.

Feedback on all aspects of the Profile and associated processes is welcomed. Contact: qiba@rsna.org

3.1 Manufacturer/Vendor/Field Service Engineer Checklist

Note: This role includes all parties responsible for the delivery and maintenance of the scanner and associated components (transducers, system software, etc.) related to this profile. Parameters are associated with scanners and transducers to be used conformant to the claims. See note below concerning "Secondary Vendors".

Make/Model/Version: Assessment Date:

Parameter/Actor	Conforms (Y/N)	Requirement
Product Validation (see Section A.1)		
Acquisition Protocol		Shall be capable of storing protocols and performing scans with all the parameters as necessary based on the manufacturer implementation conformant with this profile.
Volume Blood Flow Bias and Variance		Shall validate that the performance of the scanner meets or exceeds those indicated in Claim 1 in Section 1.2. (See Assessment Procedure 4.1.1)
Volume Blood Flow Precision		Shall validate that the performance of the scanner meets or exceeds those indicated in Claim 2 in Section 1.2. (See Assessment Procedure 4.1.2)
Depth Range		Shall validate and provide the operating ranges and limitations for achieving claims in Section 1.2.
Blood Vessel Diameter		Shall validate and provide the operating ranges and limitations for achieving claims in Section 1.2.
Analysis Tools		Shall provide tools enabling quantitative measurements from the volumetric images that are necessary to reliably meet the profile claims (Assumes the use of volumetric methods for volume flow).
Staff Qualification (see Section A.2)		
Field Service Engineer Qualifications		If a Field Service Engineer is performing QA service as specified in this profile, then they shall be capable of performing the necessary phantom testing for VBF (See Assessment Procedure 4.2).
Pre-delivery (see Section A.3)		
VBF Variance and Bias		Shall provide volume flow performance statement that meets or exceeds those indicated in Claim 1 in Section 1.2.
VBF Precision		Shall provide statement that indicates the system meets or exceeds specs as indicated in Claim 2 in Section 1.2.

Parameter/Actor	Conforms (Y/N)	Requirement
System, Transducer, and Software		Shall ensure the equipment intended for use is a compliant combination of system, software revision, and transducer.
US Imaging Performance		Any vendor shall ensure that the system performs consistently with manufacturer's published levels of performance (B-mode, Color Flow Mode, Power Mode and Volume Blood Flow).
Installation (see Section A.4)		
Hardware Damage		Field Service Engineer shall verify that there is no physical damage to hardware, including transducers.
Software Version		Shall verify to the site that the software version equals the version specified in the product's QIBA conformance statement.

NOTE: To ensure proper condition of systems and transducers, secondary vendors shall demonstrate volume flow equivalence to original systems and transducers using the performance and evaluation tests in Assessment Procedure 4.1 in a stable, calibrated volume flow phantom. In addition, it is expected that standard image quality equivalence tests would be part of quality assessment for sale, such as image uniformity and high-contrast-low-echo sphere visibility (IEC TS62736 Ed. 2). (See AIUM Statement on Transducer Testing and Repair - **https://www.aium.org/officialStatements/73**)

3.2 Image Analysis Tool Checklist

Make/Model/Version: Assessment Date: .

Parameter/Actor	Conforms (Y/N)	Requirement
Product Validation (see Section A.1)		
Depth Range Selection		Shall allow user to select the range of depths over which volume flow is computed.
Vessel Selection		Shall allow user to select the vessel of interest.
Multiple Vessels		Shall allow flow from multiple vessels to be measured in sequence.
Volume Flow Rate		Shall display volume flow rate(s) estimated from the 3D volume acquisition based on the user specified ROI. The volume flow rate may be provided for single or multiple volume acquisitions, or as the average of values computed across such acquisitions. Alternatives to these computation methodologies may exist that are manufacturer specific, but for all methodologies the performance shall match that of the claims.
Quality Index		Where needed to achieve profile performance, the system shall have the capability to display a data quality index that may be specific to a manufacturer's definition of the index.
Result Recording		Shall have the capability to record the resulting volume flow measurement, the quality index as defined by the manufacturer, and the version of the analysis tool used.

3.3 Physicist/Clinical Engineer/QA Manager Checklist

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

Physicist/Clinical Engineer/QA Manager Name(s): Assessment Date: .

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Parameter/Actor	Conforms (Y/N)	Requirement
Staff Qualification (see Section A.2)		
Physicist/Clinical Engineer Qualification		If performing acceptance testing and/or QA service for systems, then they shall be capable of performing the necessary phantom testing for VBF (See Assessment Procedure 4.2). Training to validate capabilities can follow that of section 4.3 as needed.
QA Manager Qualification		If performing acceptance testing and/or QA service for systems, then they shall be capable of performing the necessary phantom testing for VBF (See Assessment Procedure 4.2). Training to validate capabilities can follow that of section 4.3 as needed.
Installation (see Section A.4)		
System Conformance and Acceptance		If a profile conformance statement is provided by the system supplier, testing shall be performed to provide a baseline for future periodic QA testing. (See Assessment Procedure 4.2.1). In the absence of a conformance statement from the system supplier, conformance testing is required to confirm that VBF Measurements obtained with the ultrasound system and applicable transducers meet or exceed specifications as indicated in Claim 1 found in Section 1.2 and when operated as specified by the manufacturer. (See Assessment Procedure 4.1). Results shall be recorded and available for comparison to future QA results.
Periodic QA (see Section A.5)		
US Imaging QA		Shall perform standard ultrasound pulse echo imaging QA on the Ultrasound Scanner as specified by applicable guidelines of accrediting organizations (e.g., AAPM, ACR, AIUM, IAC, IEC).
Periodic Tests of Volume Flow Rate Performance		Shall confirm at least every 12 months that VBF measurement bias and variance obtained with the Ultrasound System are consistent with results obtained after installation when operated as specified by the manufacturer. (See Assessment Procedure 4.2.2). After a three-year period, a site may instead follow the manufacturer's instructions for periodic VBF quality testing.
US Imaging and VBF Phantom Characterization and Stability Testing		If the phantom is the property of the practice or the QA Physicist, confirmation of the flow phantom specifications shall be done as recommended by the phantom manufacturer or if deterioration is suspected. If a significant change (as defined in Section 4.2.2 Periodic QA) is seen in results with a given US system, it is necessary to obtain independent verification of whether the phantom or the system has changed.

Parameter/Actor	Conforms (Y/N)	Requirement
		Common problems with flow phantoms include fluid loss from the tissue mimicking (TM) material, partial loss of coupling of the scan window to the TM material, bubble or particle accumulation in the blood mimicking fluid, and failure of VBF calibration.

3.4 Sonographer/Technologist Checklist

Sonographer/Technologist Name: Assessment Date: .

Note: The role of the Sonographer/Technologist may also be taken by the Physician or other qualified medical personnel, such as PA, NP or other delegated physician extender, if performing the scanning.

General guidance on how to perform the VBF measurement envisioned by this Profile is provided in A.9, A.11, A.12, and A.13. Protocols used should be those provided by the manufacturer for a given system that have been validated for this Profile.

Parameter/Actor	Conforms (Y/N)	Specification
Staff Qualification (see Section A.2)		
Sonographer training specific to this VBF Profile		Following training in profile measurement techniques, each operator shall demonstrate ability to derive results, either in a calibrated flow phantom or in a combination of representative subjects and in an uncalibrated flow phantom, that agree with those obtained by a clinical trainer (See Assessment Procedure 4.3.2) for each model of US system used for QIBA VBF measurements at the site. A clinical trainer's skill shall be consistently demonstrated using a calibrated flow phantom, such as specified in Section A.1, or other phantom used for annual QA assessments. (See Assessment Procedure 4.3.1) If the trainer has performed at least two volume flow clinical measurements a month over the year, that year's phantom measurements are not required.
Subject Handling (see Section A.8)		
Patient Instructions		For umbilical vein flow and hemodialysis AVF/grafts, no prior instructions are necessary.
Image Data Acquisition (see Section A.9)		
Acquisition Protocol		Shall select a protocol that has been previously prepared and validated for this purpose where the ultrasound system, probe, and imaging preset are specified by the manufacturer.
Artifacts		Shall confirm the absence of color flow artifacts (e.g. motion artifacts such as flash or smear) that could affect the volume acquisitions. Shall monitor or review the acquired images to ensure that velocities in the target vessel remain(ed) within the color flow scale range (no aliasing) during the 3D sweep, unless otherwise instructed by manufacturer guidelines.
Target Vessel Identification and Position		Shall position the target vessel as directed by manufacturer guidelines including its position within the imaging volume such that the full extent of the target vessel cross section is covered and with a proper angle with respect to the transducer.
Image Acquisition		Shall verify for the selected system and probe that the target vessel lumen diameter,

Parameter/Actor	Conforms (Y/N)	Specification
Operating Ranges		depth, flow rate (expected), and signal-to-noise ratio (SNR) are all within the operating ranges provided in the manufacturer guidelines.
Image QA (see Section A.11)		
Target Vessel Position, Motion, and Artifacts		Shall confirm the target vessel remains within the appropriate imaging boundaries and is not cropped at any point throughout the entire image acquisition process. Shall confirm the absence of flow velocity aliasing, or that the aliasing is within the manufacturer-specified level of acceptable aliasing for the volume flow application. Shall confirm minimal vessel and tissue motion, including throughout the cardiac cycle as applicable, and that the image acquisition process is free from color flow artifacts.
Target Vessel Signal-to-Noise Ratio (SNR)		Shall confirm adequate color flow SNR in the target vessel if instructed by the manufacturer.
Image Analysis (see Section A.13)		
Target Vessel Mask and Unwanted Vessels		Shall employ an appropriate target vessel mask (manual, directional velocity, or manufacturer specific) during image analysis when adjacent vessels need to be excluded from contributing to the volume flow measurement.
ROI Selection		Shall select an ROI for flow measurement that avoids color flow artifacts.
Quality Feedback		Shall understand that volume flow measurement confidence may be supported by a quality feedback indicator, e.g., a quality index, and shall refer to manufacturer guidance on the proper use of such metrics.

3.5 Physician Checklist

Note: The Physician is responsible for the protocol parameters. They may choose to use a protocol provided by the scanner vendor. Working collaboratively with application specialists from the manufacturer and site sonographers and physicists is recommended as some parameters are system dependent and may require special attention.

Physician Name: Assessment Date:

Parameter/Actor	Conforms (Y/N)	Specification
Staff Qualification (see Section A.2)		
Training Specific to this VBF Profile		Shall understand and be knowledgeable in reporting volume blood flow results as being carried out according to this profile.
Subject Selection (see Section A.7)		
Clinical Indication		Measurement of blood volume flow in any selected vessel or group of vessels.

4. Assessment Procedures

Most requirements in the 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. When procedures are established, such methods may be submitted to QIBA with evidence that the results produced are equivalent to those here. Upon review by QIBA, the proposed method may be approved as an accepted assessment procedure in this Profile.

4.0. General guidance on image acquisition for 3DVBF

The following guidance is provided to all those collecting data for 3DVBF for the purposes of the assessment procedures here. Many of the general imaging principles should be followed when imaging and making 3DVBF measurements in any context. The guidance is divided into that for phantom and clinical studies.

4.0.1 Phantom Studies

The following are common considerations for measurements made in phantoms studies.

- Each ultrasound scanner will have different specific instructions provided by the manufacturer that should be followed.
- The transducer should remain relatively motionless during each measurement. Tolerance of motion will depend on the implementation of the method by a manufacturer and the operator should follow the recommendations provided. If transducer movement exceeds this recommendation during measurement, that value shall be discarded, and another measurement taken.
- Depth is defined as the distance from the transducer face to the center of the vessel of interest used for acquisition of the VBF value (not the region defined for color flow imaging display).
- For assessment testing, the transducer will be removed from contact with the phantom between each measurement and the image of the vessel reacquired. No effort to reposition the transducer in the same exact spot as the previous measurement shall be made or should be needed as the VBF is the same along the length of the vessel if such vessel is continuous.
- For these tests, a measurement is defined as completed when the scanner outputs a VBF to the screen or to a data collection table within the machine, e.g., DICOM file save completed such as for offline processing. A system may acquire multiple VBF values and then report an overall VBF value (e.g., mean or median). The number of VBF values (volumes used to compute the overall VBF value) would be that recommended by the manufacturer. The overall VBF value will be considered one measurement.
- The operators shall be blinded with respect to the actual volume flow setting for the phantom. The operator will however see many VBF measurements since the phantom will be used repeatedly. Therefore, the operator must NOT discard a VBF

measurement solely because it appears different from the others or from the assumed “true” value for the flow in the phantom.

4.0.1 Clinical Studies

The following are common considerations for measurements made in clinical studies.

- The measurements will be made according to the instructions provided by the scanner Manufacturer to achieve the claims of this profile.
- As for the phantom data collection, a VBF measurement is defined as whenever a VBF value appears on the scanner screen upon completion of a given acquisition. However, some systems may acquire multiple volume scans before reporting a given measurement. In this case, this will be considered a single measurement.
- As for phantom VBF measurement, values obtained during visible patient or transducer movement exceeding manufacturer recommendations shall be discarded and repeated.
- Between each measurement, the transducer shall be removed from contact with the volunteer.
- VBF values that appear different from the others are never be discarded unless there was movement during the measurement, or another error occurred. Errors in measurement are defined as measurements where the Manufacturer instructions were not followed. If a VBF is discarded, a repeat VBF measurement shall be collected.
- Depth is defined as the distance from the transducer surface to the center of the vessel from which the VBF is acquired. For applications where anatomic scans are only over a limited depth range, such as dialysis access, the range of depths should span the nominal minimum and maximum expected clinically. However, the operating range considered as conforming to this profile will be defined by the depth range tested so selection of applications should span the desired range.
- Volume flow rate range should span those expected for the clinical application. It is preferred that these include the range of normal flows and flows associated with those anticipated for commonly performed diagnoses.
- Vessel diameter range should span those expected for the clinical application. It is preferred that these include the range of normal diameters and diameters associated with those anticipated for commonly performed diagnoses.

4.1. Product Validation (including Secondary Vendors, see NOTE in 3.1)

4.1.1. For Claim 1

For assessment of VBF performance and conformance in phantoms, a calibrated flow phantom with the specifications given in section A.1 shall be used. These phantoms can be obtained from phantom manufacturers and consist of a tissue mimicking material through which a blood equivalent fluid is pumped at a known volumetric flow rate. The phantom of section A.1, commonly referred to as the QIBA phantom, is designed to provide an appropriate challenge to both the ultrasound scanner and

operator in the performance of this measurement. Other flow phantoms of similar specifications can be used for routine QA testing and site assessment, but this QIBA phantom design is preferred as a teaching tool and required for Product Validation.

The assessment phantom data will consist of volume flow acquisitions obtained by operators who have been qualified by training and testing. It is understood that these operators may not have been trained as described in this profile since this assessment may be performed at the time a system/model is initially released and validated. Data shall be acquired according to the guidance of 4.0.1 with the additional following considerations:

- The measurements shall be performed for each transducer model to be considered as conforming to the profile.
- The room temperature at which the testing was performed should be recorded. It is strongly recommended that the measurements be performed at the temperature at which the phantom was calibrated by the phantom manufacturer or using the calibration methods specified by the manufacturer.

The suggested data for Claim 1 assessment is as follows. For each transducer on a system/model to be qualified, the measurements should be made for at least 4 depths (minimum, 25% of maximum, 75% of maximum and maximum). At each depth, volume flow rates of at least the minimum, 25% of maximum, 75% of maximum and maximum should be tested. This would be for one vessel diameter as described for the calibrated flow phantom with the specifications given in section A.1. For each of these measurement conditions, three repeats should be performed as described in 4.0.1. If the system/model is being tested for conformance for pulsatile flow, these measurements would be repeated for constant and pulsatile flow. Data would be analyzed to provide evidence of conformance.

4.1.2. For Claim 2

For assessment of conformance to Claim 2, an initial clinical investigation as described below must be performed at the time a system/model is initially released and validated. A peer-reviewed publication of an equivalent study is acceptable. Subsequent testing, e.g., following software updates, can be performed as for Claim 1 and require no additional clinical testing. Data shall be acquired according to the guidance of 4.0.2 with the additional following considerations:

- The measurements shall be performed for each transducer model to be considered as conforming to the profile.
- Data shall be based on the intended application (e.g., umbilical flow or dialysis access flow)

The suggested data for Claim 2 assessment is as follows. For each transducer on a system/model to be qualified, measurements should be made in 6 representative subjects for the clinical application. The measurements should span the depth range as minimum and maximum expected for clinical application for the given subject. Flow rates and vessel sizes in a given subject may vary depending on intended clinical application but the repeatability within subjects is the target of this testing. For each of these measurement conditions, three repeats should be performed as described in 4.0.2. If the system/model is being tested for conformance for pulsatile flow, these measurements would be repeated for constant and pulsatile flow. These measurements shall be made by at least two operators across these subjects. It is recommended that these measurements be performed by two operators on each subject to establish the intraoperator and interoperator repeatability of these measurements. Data would be

analyzed to provide evidence of conformance as described in section 4.5.

4.2. QA testing

4.2.1. Acceptance (Installation and Baseline Measurements)

If a conformance statement is not available from the vendor for a given scanner/transducer, testing would be required for a delivered system. In this case, volume flow rates should be measured in a calibrated phantom using manufacturer specified presets, following the procedures of 4.1.1 and for each applicable transducer. Data shall be acquired according to the guidance of 4.0.1 and the assessment of Section 4.1.1.

If a conformance statement is provided, testing shall be performed in a calibrated phantom to confirm system performance and provide a baseline for future periodic QA testing. Sites shall perform these measurements shortly after conducting conformance tests or accepting assurance of conformance of the ultrasound VBF system and software. Data shall be acquired according to the guidance of 4.0.1 with the additional following considerations:

- Tests can be performed using a conventional (straight-tube) flow phantom with calibrated flow rates and imaging depth spanning that required to properly assess the scanner and transducer.
- Results shall be recorded and available for comparison to future periodic QA results.

The suggested data for acceptance assessment is as follows. For each transducer on a system/model to be qualified, the measurements should include depths of 25% and 75% of maximum depth indicated as the conformance specification by the manufacturer. At each depth, volume flow rates of 25% and 75% of maximum conformance specification by the manufacturer should be tested. This would be for one vessel diameter in the flow phantom. For each of these measurement conditions, one measurement is made. If the system/model being tested for acceptance is conformant for pulsatile flow, these measurements would be repeated for constant and pulsatile flow. Each measurement would be compared to Claim 1 that specifies the 95% confidence limit for profile conformance. It is expected that all measurements would meet the claim but if this is not the case, additional measurements may be necessary to increase confidence in meeting the claim. Data would be retained for comparison to future periodic QA assessments.

4.2.2. Periodic QA

The suggested annual QA testing paradigm would be one that follows from the acceptance testing. Data shall be acquired according to the guidance of 4.0.1 with the additional following considerations:

- Tests would be performed on all scanners at the site and for every transducer. There is no requirement to test every combination, only that all systems and transducers are tested at least once.
- Tests shall be performed annually for at least three years.
- After this three-year period, a site may instead follow the manufacturer's instructions for periodic VBF quality testing.

The suggested data for periodic QA assessment would be the same as that used for acceptance testing (4.2.1) but the number of depths and flows rates can be reduced if necessary. Each measurement would be compared to Claim 1 that specifies the 95% confidence limit for profile conformance. Additional testing may be required if expected performance does not match Claim 1 and would be considered a significant change in system performance.

4.3. Training

4.3.1. Clinical Trainer

Assessment of Clinical Trainer skill will provide a means of assuring a level of performance for volume flow measurements that should then allow consistent training of other sonographers. The volume flow measurements are quantitative and therefore achieving a level of accuracy, i.e., in a calibrated phantom, provides confidence in reliable clinical results and achievement of performance consistent with profile claims. This is an initial method that will be revised as additional data are obtained on the level of training required to achieve the profile performance.

Measurements shall be performed according to the guidance of 4.0.1 in a calibrated phantom and 4.0.2 in human subjects with the additional following considerations:

- A phantom may be available to a site for this purpose through a loan or rental program or as part of a QC contract if resources are limited.
- Note that these data are suitable for establishing site conformance as seen in Section 4.4.
- If a site has ultrasound systems from more than one Manufacturer, the clinical trainer must be proficient on each. Therefore, the test measurements must be performed for each Manufacturer's system (only one set of test measurements per Manufacturer model).
- Selection of subjects for clinical tests should be those expected for the common clinical applications.

The suggested phantom data for assessment of clinical trainer skill is as follows. For a representative of each type of transducer capable of 3D volume flow on a given system/model used in the clinic, the measurements should include depths of 25% and75% of maximum depth indicated in the conformance specification of the manufacturer. At each depth, volume flow rates of 25% and 75% of maximum conformance specification of the manufacturer should be tested. This would be for one vessel diameter in the flow phantom. For each of these measurement conditions, three repeats should be performed as described in 4.0.1. Data would be analyzed to provide evidence of operator performance sufficient to match profile Claim 1.

The suggested data for clinical assessment is as follows. For a representative of each type of transducer on a system/model used in the clinic, measurements should be made in 6 representative subjects for the representative clinical application. The measurements should span the depth range as minimum and maximum expected for clinical application for the given subject. Flow rates and vessel sizes in a given subject may vary depending on intended clinical application but the repeatability within subjects is the target of this testing. For each of these measurement conditions, three repeats should be performed as described in 4.0.2. If the system/model is being tested for conformance for pulsatile flow, these measurements would be repeated for constant and pulsatile flow. Data would be analyzed as in section 4.5 to provide evidence of operator performance sufficient to match profile Claim 2.

4.3.2. Sonographers

To fully demonstrate that sonographers/technologists are capable of performing VBF measurements meeting the claims, they would fulfill the requirements of the clinical trainer. For practicality, the clinical trainer may take the responsibility of allowing a subset of such tests based on their accumulated experience with the sonographer/technologist in question and other sonographers/technologists. This

subset might well exclude testing on phantoms unless otherwise necessary for training or retraining.

4.4. Site Assessment for QIBA Conformance

To establish a site as meeting this profile, both phantom and clinical studies are required.

4.4.1. Phantom Studies

Measurements shall be performed according to the guidance of 4.0.1 in a calibrated phantom with the additional following considerations:

- A phantom may be available to a site for this purpose through a loan or rental program or as part of a QC contract if resources are limited.
- Tests are performed for each Manufacturer's system (only one set of test measurements per Manufacturer model) with associated transducers.

The suggested phantom data for site assessment is as follows. For each transducer capable of 3D volume flow on a given system/model used in the clinic, the measurements should include depths of 25% and75% of maximum depth indicated in the conformance specification of the manufacturer. At each depth, volume flow rates of 25% and 75% of maximum conformance specification of the manufacturer should be tested. This would be for one vessel diameter in the flow phantom. For each of these measurement conditions, three repeats should be performed as described in 4.0.1. Data would be analyzed to provide evidence of site performance sufficient to match profile Claim 1. Results should include at least two sonographers representative of the staff.

4.4.2. Clinical Studies

Measurements shall be performed according to the guidance of 4.0.2 in human subjects with the additional following considerations:

- For sites where anatomic scans are only over a limited depth range, such as dialysis access, the two selected depths should be at nominal minimum and maximum expected clinically.

The suggested data for clinical assessment is as follows. For each transducer on a system/model used in the clinic, measurements should be made in 6 representative subjects for the clinical application. The measurements should span the depth range as minimum and maximum expected for clinical application for the given subject. Flow rates and vessel sizes in a given subject may vary depending on intended clinical application but the repeatability within subjects is the target of this testing. For each of these measurement conditions, three repeats shall be performed as described in 4.0.2. If the system/model is being tested for conformance for pulsatile flow, these measurements would be repeated for constant and pulsatile flow. These measurements shall be made by at least two operators across these subjects. It is recommended that these measurements be performed by two operators on each subject to establish the intraoperator and interoperator repeatability of these measurements. Data would be analyzed as in section 4.5 to provide evidence of site performance sufficient to match profile Claim 2.

4.5. VBF Measurement Consistency

The above assessment procedures can be used by a scanner vendor or an imaging site to assess the imaging performance of an ultrasound system in combination with sonographers. The data obtained in the above assessment procedures can be evaluated using the processes described in the following paragraphs. These are the suggested analysis approaches that would allow assessment to establish

profile conformance.

4.5.1. Within Subject Measurement Variation

VBF claims use within-subject coefficient of variation (wCV) as an important quality metric, wCV computation from the test dataset (e.g., datasets as described under 4.1 and 4.4 above) is as follows (next paragraph):

For each case (corresponding to the anatomic site of a single patient where the variable i denotes the case number or a given flow rate and location within a phantom), the first measured VBF represents the first replicate measurement (denoted Y_{i1}) and the second measured VBF represents the second replicate measurement (Y_{i2}) for that case. For phantoms, i takes on the single value i =1. For patient data, there are six volunteer subjects so the variable i ranges from 1 to 6. For each case and for each combination of depth and volume flow values, the assessor shall first calculate the mean and variance of the measurements (three per operator per machine). From these values, the variance divided by the square of the mean ($mean^2$) will be calculated for each case and the results for each case will be summed and the total divided by the number of cases (one for the phantom and 6 for the human data). The square root of this value is the wCV. The equations for these computations are:

$$\widehat{wCV} = \sqrt{\sum_{i=1}^{N}\left\{\frac{Variance_i}{Mean_i^2}\right\}/N}$$

where N=6 for the patient data and N = 1 for phantom data.

As noted in the preceding paragraph, if data were acquired from more than one brand of machine and more than one operator, the measurements from all machines and all operators should also be pooled for the computation to accurately reflect these sources of variability.

4.5.2. Maximum Allowable Variance

To assure site conformance to the profile claims, the upper 95% confidence bound of the wCV computed above must be less than the wCV reported in the claim +5% to ensure that the calculated wCV for a site meets the claim with 95% confidence for non-inferiority. Suppose the sites estimate CV is 15% and the upper 95% confidence bound reaches 21%. The 21% would be compared to the 20% in claim 2 plus non-inferiority margin of 5%. Thus since 21% < 25%, conformance is achieved. For practical purposes, the non-inferiority criterion is based on a upper bound wCV = $((0.2)^2*46.979/30)^{1/2}$ = 0.2503 or 25% where 0.2 is the claim wCV and 46.979 is the Chi Squared value for 30 degrees of freedom given as (number of subjects)*(number of measurements each -1) or 6*(6-1). The six subjects correspond to the clinical testing for site assessment (see 4.4.2) and the six measurements are three measurements at each of two sites (minimum and maximum depth for a given subject). The resulting upper bound is 25%. Therefore, with a claim wCV of 20%, we will set the non-inferiority criterion at 5%.

4.5.3. Percentage Bias Estimation (Claim 1)

At the present time, bias claims for phantoms only are expected as there is concern about the available clinical methods for estimation of true VBF in patients. Currently the values obtained using a standard

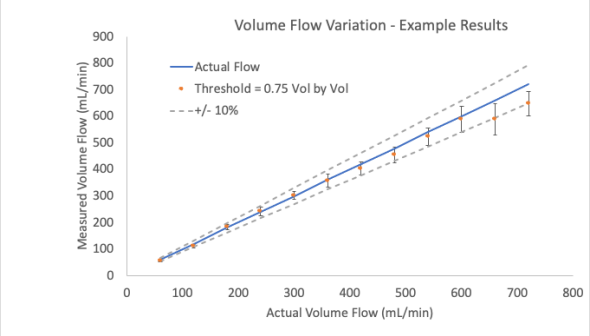
acquisition procedure (metered pump) in phantoms are considered the reference standard for bias and linearity estimation.

For each of the 4 measurement situations (two volume flow rates and two depths) with 3 measurements at each, the data available are 2*2*3 x N where N is the number of operators.

For each measurement (denoted Y_i) the assessor shall calculate the % bias: $b_i = [(Y_i - X_i)/X_i] \times 100$, where X_i is the true value of the measurand. Over N acquisitions estimate the population bias: $\hat{b} = \sum_{i=1}^{N} b_i \,/N$. The estimate of variance of the bias is $\widehat{Var}_b = \sum_{i=1}^{N}(b_i - \hat{b})^2 \,/N(N-1)$. The assessor shall calculate the 95% CI for the bias 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. The lower bound of the 95% CI must be > -2% + claim bias and the upper bound of the 95% CI must be < 2% + claim bias. For example, in Claim 1a, the bias is 0.033 (3.3%) such that the lower bound must be > 1.3% and the upper bound < -5.3%.

4.5.4. Scanner Linearity Estimation and Slope Estimation. (Claim 1 - Manufacturer)

The phantom data set can be used again for this evaluation where linearity assessment is possible given data is collected in the Product Validation (section 4.1) at four different depths and four different volume rates. These data and their analysis would allow for the development of a future claim related to linearity. Although we have no indication of operator dependence, it is suggested that the initial assessment use data for the same operator and ultrasound system such that each operator and US system can be analyzed separately. The test data for each operator and machine consists of 48 measurements (3 measurements for each of four different measurement depths and for four different volume flow values). Previous tests in phantoms have indicated a high level of linearity as evidenced in the example results below for one system and operator.



For each operator and ultrasound system/transducer combination one can calculate linearity as follows:

Using the same nomenclature for Y_i and X_i as above, the assessor shall fit an ordinary least squares (OLS) regression of the Y_i's on X_i's.

A quadratic term is first included in the model to rule out non-linear relationships: $Y = \beta_o + \beta_1 X + \beta_2 X^2$. If $|\beta_2| > 0.5$ and R-squared (R^2) >0.90 then the quadratic term should be retained; if not, the assessor shall fit a linear model: $Y = \beta_o + \beta_1 X$, and estimate R^2.

For the linear model fit, let $\widehat{\beta_1}$ denote the estimated slope. The assessor shall calculate its variance as $\widehat{Var}_{\beta_1} = \{\sum_{i=1}^{N}(Y_i - \hat{Y}_i)^2 \,/(N-2)\} \,/ \sum_{i=1}^{N}(X_i - \bar{X})^2$, where $\hat{Y}_i$ is the fitted value of Y_i from the regression line and $\bar{X}$ is the mean of the true values. The assessor shall calculate the 95% CI for the slope as $\widehat{\beta_1} \pm t_{\alpha=0.025,(N-2)df} \sqrt{\widehat{Var}_{\beta_1}}$.

Allowable Slope Range: For most Profiles it is assumed that the regression slope equals one. Then the 95% CI for the slope should be completely contained in the interval 0.95 to 1.05. A future claim related to linearity can be made based on the analysis of such data across manufacturers and their systems.

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

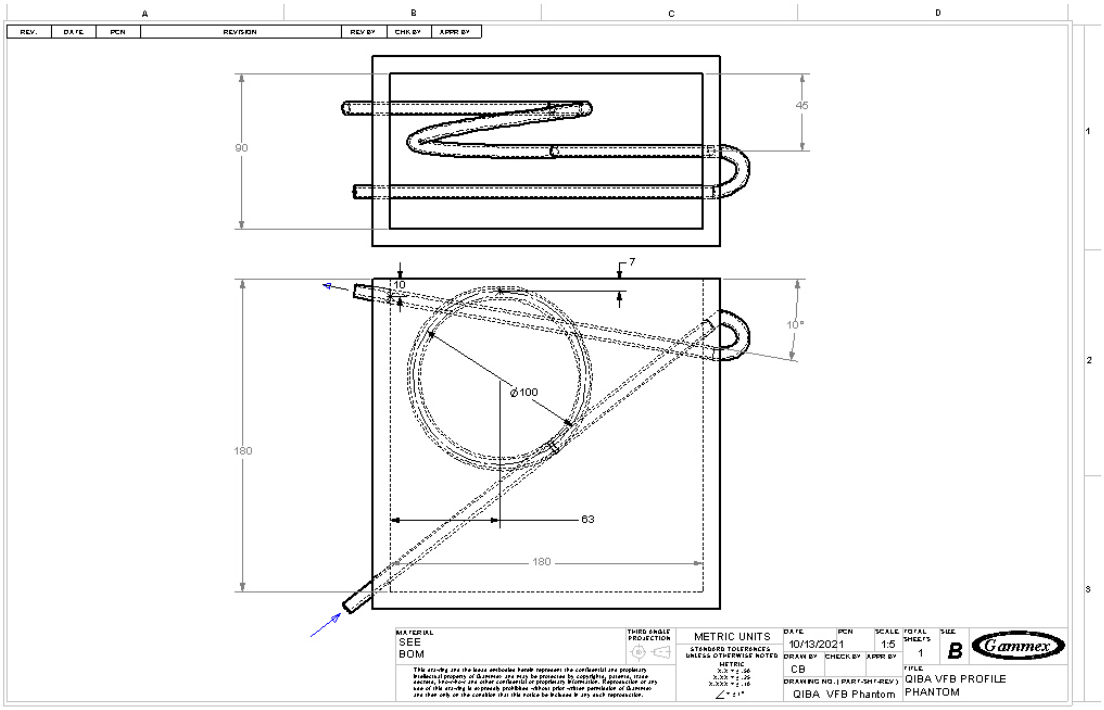
This activity evaluates equipment (Scanner, Reconstruction Software, and Image Analysis Tool) prior to their use in the Profile (e.g., at the factory). Product validation includes validations and performance assessments necessary to reliably meet the Profile Claim.

A.1.1 DISCUSSION

Commercially available Doppler ultrasound flow phantoms or Doppler string phantoms may be used by manufacturers to confirm sensitivity and velocity accuracy of conventional Doppler modes and settings.

For testing and verification of volume flow performance, and for confirming Clinical Trainer skills, a customized phantom is suggested that takes into account several considerations such as vessel geometry, orientation, depth, size (5 mm diameter in current QIBA phantom), volume flow rates and flow profile that address applications discussed in section Appendix B. The suggested phantom design also includes a simple inclined vessel for Doppler and conventional volume flow QA purposes.

QIBA Phantom Properties:
The phantoms selected for instrument verification and pre-delivery testing by the manufacturer should meet the following specifications:



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Background Specifications (applies as well for b-mode phantoms used in testing)

a. Specific Attenuation Coefficient: 0.5 ± 0.05 dB/cm/MHz at 1-9 MHz

680 b. Backscatter Coefficient: 3 X 10^{-4} $cm^{-1}Str^{-1}$ ± 3 dB at 3 MHz[21].

c. Background Material Speed of Sound: 1540 ± 30 m/sec

Fluid Specifications

a. Fluid Speed of Sound: 1550 ± 20 m/sec

685 b. Fluid Attenuation Coefficient: < 0.1 dB/cm-MHz

c. Fluid Viscosity: 4.5 centi-Poise $\pm$ 0.5 centi-Poise

d. Fluid Backscatter Level: At least 30dB lower than that of the background material

e. Fluid density and that of the particle should be matched as closely as possible to create neutral buoyancy for the particles.

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Other Specifications

a. Vessel Inside Diameter: 5 mm $\pm$ 0.05 mm

b. Volume Flow Rate: 60mL/min – 1000 mL/min (constant flow), accurate to $\pm$3% & phantom manufacturer provided conversion for a mean flow rate in pulsatile flow mode.

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Testing of phantom acoustic properties should be as specified by the AIUM guidelines[19].

Volume and Shape: See drawing. The phantom contains one continuous tube, with two distinct sections. There is a straight section inclined at 10 degrees with respect to the horizontal. In regions where parabolic flow profiles exist, this would also serve the purposes of testing velocity detection accuracy for

700 conventional Doppler QA, with no alteration in the flow profile. A second section contains a single loop providing opportunities for volume flow evaluation in vessel sections at various depths, orientations,

and flow profiles. This section would be useful to demonstrate the utility of the 3D volume technique vs 2D spectral Doppler based volume flow measurement. Parabolic flow may exist in straight portions of this section depending on the flow velocity.

Volume Flow Phantom Temporal Stability testing:

- Inspect scanning surface for any depression
- Evaluate whether there is any increase in echogenicity of the blood mimicking fluid (evidence of bubbles or clumping of scatterers)
- Inspect pulse wave spectrum to assess changes in blood mimicking fluid
  - The phantom should be run for at least 10 minutes prior to use (following the manufacturer instructions)
  - Monitoring in pulse wave, watch for spikes in the spectrum, running initially at a low flow rate and then increasing.
  - Future considerations should be given to methods to further quantifying the signal power (either in pulse wave or power mode imaging) to monitor changes over time.

If the phantom manufacturer has other criteria for stability testing prior to acoustic property testing, those shall be used instead.

The following specifications are all to be verified by the manufacturers responsible for the corresponding Actor when referring to a device or other such entity. All of these lie outside the site responsibility.

Assumptions: 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 <u>not conformant</u> to the Profile.

- Phantom is maintained in good condition following manufacturer recommendations and is properly calibrated.

<u>A.1.2 SPECIFICATION</u>

Parameter	Actor	Requirement
Acquisition Protocol	Scanner Manufacturer	Shall be capable of storing protocols and performing scans with all the parameters as necessary based on the manufacturer implementation conformant with this profile.
Volume Blood Flow Bias and Variance	Scanner Manufacturer	Shall validate the performance of the scanner meets or exceeds those indicated in Claim 1 in Section 1.2. (See Assessment Procedure 4.1.1)
Volume Blood Flow Precision	Scanner Manufacturer	Shall validate the performance of the meets or exceeds those indicated in Claim 2 in Section 1.2. (See Assessment Procedure 4.1.2)
Depth Range	Scanner Manufacturer	Shall validate and provide the operating ranges and limitations for achieving claims in Section 1.2.
Blood Vessel Diameter	Scanner Manufacturer	Shall validate and provide the operating ranges and limitations for achieving claims in Section 1.2.
Analysis Tools	Scanner Manufacturer	Shall provide tools enabling quantitative measurements from the volumetric images that are necessary to reliably meet the profile claims. (Assumes the use

Parameter	Actor	Requirement
		of volumetric methods for volume flow)
Depth Range Selection	Image Analysis Tool	Shall allow the user to select the range of depths over which the volume flow is computed.
Vessel Selection	Image Analysis Tool	Shall allow user to select the vessel of interest.
Multiple Vessels	Image Analysis Tool	Shall allow flow from multiple vessels to be measured in sequence.
Volume Flow Rate	Image Analysis Tool	Shall display volume flow rate(s) estimated from the 3D volume acquisition based on the user specified ROI. The volume flow rate may be provided for single or multiple volume acquisitions, or as the average of values computed across such acquisitions. Alternatives to these computation methodologies may exist that are manufacturer specific, but for all methodologies the performance shall match that of the claims.
Quality Index	Image Analysis Tool	Where needed to achieve profile performance, the system shall have the capability to display a data quality index that may be specific to a manufacturer's definition of the index.
Result Recording	Image Analysis Tool	Shall have the capability to record the resulting volume flow measurement, the quality index as defined by the manufacturer, and the version of the analysis tool used.

A.2. Staff Qualification

This activity involves evaluating the human Actors (Physician, Physicist/Clinical Engineer/QA manager, and Sonographer/Technologist) prior to their participation in the Profile. Staff Qualification includes training, qualification, or performance assessments necessary to reliably meet the Profile Claim.

A.2.1 DISCUSSION

These requirements, as with any QIBA Profile requirements, are focused on achieving the Profile Claim. Evaluating the medical or professional qualifications of participating actors is beyond the scope of this profile. It is recognized, however, that specialized operator/sonographer/technologist training is needed to properly conduct the activities of this profile. This is detailed in Table A.2.2.

A.2.2 Specification

Parameter	Actor	Specification
Qualifications Specific to this VBF Profile	Physicists/Clinical Engineers	If performing acceptance testing and/or QA service for systems, then they shall be capable of performing the necessary phantom testing for VBF (See Assessment Procedure 4.2). Training to validate capabilities can follow that of section 4.3 as needed.
Qualifications Specific to this VBF Profile	Field Service Engineers	If a Field Service Engineer is performing QA service as specified in this profile, then they shall be capable of performing the necessary phantom testing for VBF (See Assessment Procedure 4.2).
Qualifications Specific to this	QA Managers	If performing acceptance testing and/or QA service for systems, then they shall be capable of performing the

Parameter	Actor	Specification
VBF Profile		necessary phantom testing for VBF (See Assessment Procedure 4.2). Training to validate capabilities can follow that of section 4.3 as needed.
Qualifications Specific to this VBF Profile	Physicians	Shall understand and be knowledgeable in reporting volume blood flow results as being carried out according to this profile.
	Sonographers/Technologists	Following training in profile measurement techniques, each operator shall demonstrate ability to derive results, either in a calibrated flow phantom or in a combination of representative subjects and in an uncalibrated flow phantom, that agree with those obtained by a clinical trainer (See Assessment Procedure 4.3.2) for each model of US system used for QIBA VBF measurements at the site. A clinical trainer's skill shall be consistently demonstrated using a calibrated flow phantom, such as specified in Section A.1, or other phantom used for annual QA assessments. (See Assessment Procedure 4.3.1) If the trainer has performed at least two volume flow clinical measurements a month over the year, that year's phantom measurements are not required.

A.3. Pre-delivery

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

A.3.1 DISCUSSION

The performance statement by the manufacturer can be based on testing performed on a phantom with the specifications as given in A.1.

A.3.2 SPECIFICATION

Parameter	Actor	Requirement
VBF Variance and Bias	Scanner Manufacturer	Shall provide volume flow performance statement that meets or exceeds those indicated in Claim 1 in Section 1.2.
VBF Precision	Scanner Manufacturer	Shall provide statement that indicates the system meets or exceeds specs as indicated in Claim 2 in Section 1.2.
System, Transducer, and Software	Scanner Manufacturer	Shall ensure the equipment intended for use is a compliant combination of system, software revision, and transducer.
US Imaging Performance	Scanner Manufacturer or any Scanner Vendor	Any vendor shall ensure that the system performs consistently with manufacturer's published levels of performance (B-mode, Color Flow, Power Mode and Volume Blood Flow).

NOTE: To ensure proper condition of systems and transducers, secondary vendors shall demonstrate volume flow equivalence to original systems and transducers using the performance and evaluation tests of A.5.2 in a stable, calibrated volume flow phantom. In addition, it is expected that standard image quality equivalence tests would be part of quality assessment for sale, such as image uniformity and high-contrast-low-echo sphere visibility (IEC TS62736 Ed. 2). (See AIUM Statement on Transducer Testing and Repair - **https://www.aium.org/officialStatements/73**)

A.4. Installation

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

A.4.1 DISCUSSION

Following installation of an ultrasound system with VBF software, or installation of new VBF software versions on an existing in-house system, it is important for users to verify that the system meets the specifications in Claim 1 of Section 1.2 of this profile. These tests also provide initial data for comparison of future tests and assessments of the system as done during routine quality assurance sessions.

A.4.2 SPECIFICATION

Parameter	Actor	Requirement
Hardware Damage	Manufacturer/Vendor/ Field Service Engineer	Shall verify that there is no physical damage to hardware, including transducers.
Software Version	Manufacturer/Vendor/ Field Service Engineer	Shall verify to the site that the software version equals the version specified in the product's QIBA conformance statement.
System Conformance and Acceptance	Medical Physicist, Clinical Engineer, and/or QA Manager	If a profile conformance statement is provided by the system supplier, testing shall be performed to provide a baseline for future periodic QA testing. (See Assessment Procedure 4.2.1). In the absence of a conformance statement from the system supplier, conformance testing is required to confirm that VBF Measurements obtained with the ultrasound system and applicable transducers meet or exceed specifications as indicated in Claim 1 found in Section 1.2 and when operated as specified by the manufacturer. (See Assessment Procedure 4.1). Results shall be recorded and available for comparison to future QA results.

A.5. Periodic QA

This activity involves quality assurance of the scanners that is periodic, not directly associated with a specific subject. Periodic QA includes calibrations, phantom imaging, performance assessments or validations to ensure the scanner is functioning as needed to reliably meet the Profile Claim.

A.5.1 DISCUSSION

Most ultrasound practices conduct routine quality control tests of scanning equipment to verify that transducers are free of flaws, to evaluate the adequacy and effectiveness of system displays, to assure consistency of system sensitivity with each transducer, and to assess geometric accuracy in grayscale (B-mode) imaging. Such testing is generally done at least annually and serves as one component in the laboratory accreditation process followed by ultrasound clinics.

Quantitative volume blood flow measurement results derived following this profile represent a new paradigm in diagnostic information obtained with ultrasound scanners. The measurement method provides accurate volume flow data, even in physiological situations where conventional Doppler methods would fail. The conceptual framework for this success relies on systems being properly set up and accounting for signal acquisition and processing parameters, including those outlined in Section A.9 of this profile. As experience is being gained in the use and stability of these color flow-based techniques, it is essential that clinical sites also include periodic testing to verify the ongoing accuracy of volume flow data. These tests should be done under conditions that challenge the imaging system similarly to challenges that are encountered during clinical procedures. These challenges include imaging depths and orientation of vessels, transmission through attenuating media, weak echo signals due to ultrasound waves scattered from blood and giving rise to Doppler and color flow signals and accommodating the range of flow velocities and volume flow rates that must be accurately measured to continue to meet the claims of this profile.

A phantom that strives to incorporate these characteristics and challenges is described in Section A.1. Ideally, this phantom design would be employed by sites for periodic testing. However, in the absence of this phantom, routine, commercially available flow phantoms with constant and pulsatile flow at variable depths may be substituted by sites. Initial, baseline tests should be carried out as part of the acceptance test process done by site personnel, as specified in Section A.4. Then, at least annually, sites should verify that volume flow results are consistently obtained with the same accuracy specifications that were met during the initial testing. Initial requirements for this profile include continuing this process for at least a 3-year period.

Operator skill in generating volume flow measurements using ultrasound also must be maintained in order to meet the expected bias and variance limits defined in this profile. Routine phantom tests, where volume flow rates are known and do not change from those generated during initial tests present an important opportunity for clinical trainers and sonographers/technologists to help maintain their skill level. Therefore, it is recommended that these clinical personnel also contribute to conduction of measurements during periodic QA tests.

Assumptions: 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 Physicist, Clinical Engineer or QA Manager performs relevant quality control procedures as recommended by the manufacturer or otherwise required such as for accreditation and records the date/time of QC procedures for auditing.

A.5.2 SPECIFICATION

Parameter	Actor	Requirement
US Imaging QA	Physicist, Clinical Engineer or QA Manager	Shall perform standard ultrasound pulse echo imaging QA on the Ultrasound Scanner as specified by applicable guidelines of accrediting organizations (e.g., AAPM, ACR, AIUM, IAC, IEC)..
Periodic Tests of Volume Flow Rate Performance	Physicist/Clinical Engineer or QA Manager	Shall confirm at least every 12 months that VBF measurement bias and variance obtained with the Ultrasound System are consistent with results obtained after installation when operated as specified by the manufacturer. (See Assessment Procedure 4.2.2). After a three-year period, a site may instead follow the manufacturer's instructions for periodic VBF quality testing.
US Imaging and VBF Phantom Characterization and Stability Testing	Physicist/Clinical Engineer or QA Manager	If the phantom is the property of the practice or the QA Physicist, confirmation of the flow phantom specifications shall be done as recommended by the phantom manufacturer or if possible deterioration has occurred. If a significant change (as defined in Section 4.2.2 Periodic QA) is seen in results with a given US system, it is necessary to obtain independent verification of whether the phantom or the system has changed. Common problems with flow phantoms include fluid loss from the tissue mimicking (TM) material, partial loss of coupling of the scan window to the TM material, bubble or particle accumulation in the blood mimicking fluid, and failure of VBF calibration.

A.6. 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.6.1 DISCUSSION

Any and all content related to this section is integrated within Sections A.9 Image Data Acquisition through A.13 Image Analysis where guidance is provided on acquisition and reconstruction procedures and parameters that are necessary to reliably meet the Profile Claims.

A.7. Subject Selection

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

A.7.1 DISCUSSION

Two different classes of subjects who could undergo ultrasound volume flow measurements are described in this Profile. These include pregnant women who are being screened for fetal abnormalities during the typical 20-week ultrasound examination or any pregnancy in which umbilical cord blood flow could be considered a measure of fetal wellbeing over time or assessment of therapeutic maneuvers. The second class of subjects are those in whom blood flow measurements in dialysis AVFs/grafts are performed to assess the initial viability or functionality soon after surgery, i.e., is the blood flow in a AVF or graft sufficient to support the dialysis process. It is also applied when there is clinical concern for

impending failure of a functional AVF or other clinical signs of fistula dysfunction.

A.7.2 SPECIFICATION

Parameter	Actor	Requirement
Clinical Indication	Physician	Measurement of VBF in any selected vessel or group of vessels.

A.8. Subject Handling

This activity involves handling each imaging subject at each timepoint. It includes subject handling details that are necessary to reliably meet the Profile Claim.

A.8.1 DISCUSSION

Again, there are a myriad of potential applications for ultrasound volume flow assessment. For the two applications discussed herein, no special issues related to subject handling exist that are known to uniquely affect VBF as defined in this profile. However, there are clearly physiologic conditions and other factors that affect blood flow and interpretation of a measurement of any parameter depends on the circumstances under which the measurement is made.

For VBF, one can expect changes in blood flow for different physiological and pathological states such as resting and active, medication or other factors affecting heart rate and blood pressure, dehydration, Valsalva maneuver, patient's position (upright vs prone). For dialysis patients, the VBF measurement may be affected by the timing with respect to their dialysis schedule although no specific examination of this has been made. In all cases, a standard protocol may help to minimize the variation in data acquisition for estimating volume blood flow.

Assumptions: 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.

NONE

A.8.2 SPECIFICATION

Parameter	Actor	Requirement
Patient Instructions	Sonographer/Technologist	For umbilical vein flow and hemodialysis AVF/grafts, no prior instructions are necessary.

A.9. 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.6) 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.9.1 DISCUSSION

This section provides guidance on the 3D volume flow measurement image data acquisition process for a general, non-specific blood vessel and the envisioned implementation. Based on these image data acquisition guidelines, an operator will be able to successfully perform an acquisition that is specific to a target blood vessel, or blood vessels, in their application. These guidelines are intended to be broadly applicable across a wide range of ultrasound systems and probes and may need to be further adapted to a specific system and probe based on manufacturer guidelines provided. Alternative volume flow methods may have different requirements and manufacturer guidance.

Ultrasound system, probe, and imaging preset – Select the ultrasound system, probe, and imaging preset required for 3D volume flow measurement as specified by the manufacturer. The manufacturer shall provide sufficient imaging feedback for guidance. The selected imaging preset must be specified by the system manufacturer as the preset intended for 3D volume flow measurement.

Imaging mode – Three-dimensional volume flow image acquisition should be performed in the imaging mode specified by the system manufacturer. Color flow mode, or color Doppler mode, is the most common imaging mode used for 3D volume flow quantification. However, the required imaging mode is manufacturer specific and could include color power mode, or power Doppler mode, and other manufacturer-specific variants. At a minimum, the manufacturer-specific imaging mode must provide mean velocity information.

Image acquisition parameters –Guidelines to achieve the appropriate acquisition processing are detailed in the manufacturer-specific instructions for a given scanner.

Probe frequency and line/plane density – Probe frequency and color flow beam spacing (lateral (line), elevational (plane) density) determine the total number of color flow beams that can be positioned fully inside the target vessel lumen. Implementations of 3D volume flow might consider using a specification based on the total number of color flow beams that can be positioned fully inside the lumen as a metric for performance. Any scanner-specific guidance will be provided by the manufacturer.

Target vessel identification and position – Manufacturers will provide guidance on vessel visualization for their scanners and methods for selection of the vessel for measurement.

Image acquisition operating ranges – Several factors associated with the target vessel can affect the ability to accurately measure volume flow. As a consequence, volume flow measurement accuracy, repeatability, and reproducibility may be specified by the manufacturer for specific systems and probes, along with corresponding operating ranges for target vessel lumen diameter, depth, flow rate, and signal-to-noise ratio (SNR). Some general guidance is provided below, and manufacturer-specific guidance would be provided with their scanners.

- **Lumen diameter** – The smaller the lumen relative to the ultrasound beamwidth, the more challenging it is to achieve accurate volume flow measurements.
- **Depth** – The depth of the vessel also increases measurement difficulty due to the tendency for beamwidths to increase and signal-to-noise ratio to decline (due to attenuation).
- **Flow rate (expected)** – Although flow rate should have a relatively small influence on the accuracy of volume flow measurements, the PRF and wall filter need to be set appropriately (see more below).
- **Color Flow Signal-to-noise ratio (SNR)** – Many factors can affect the signal-to-noise ratio, but where possible transducer operating frequency and gain should follow the manufacturer guidance.

- **Gray scale imaging** – Gray scale should be such that the target vessel is well seen and centered in the longitudinal and transverse planes, with the focal zone at the mid vessel. Gray scale should be that typically used clinically (intermediate between a dark and bright image).

Pulse repetition frequency (PRF) –Recommendations for the setting of PRF should follow those provided by the manufacturer likely including considerations to avoid aliasing while maximizing dynamic range in flow velocities.

Color flow gain – Accurate volume flow measurement requires the acquisition of accurate and reliable velocity estimates with good signal-to-noise throughout the vessel and cardiac cycle. Manufacturers may choose to apply additional gain internally for the purposes of volume flow quantification. Consult each manufacturer's instructions for specific guidance on setting the gain.

Wall filter (WF) – The wall filter, or wall motion filter, should typically be set to the lowest possible value in order to maximize signal detection throughout the entire lumen of the target vessel, and in particular near the lumen boundary. Manufacturers may provide additional guidance for their respective scanners.

Lateral transmit and elevational focus positions –Lateral and elevational focusing is manufacturer specific and any guidance should be provided.

Doppler angle and steering angle – Although the 3D volume flow measurement is relatively independent of Doppler angle (beam-to-flow angle), the recommendation is still to acquire with as small a Doppler angle as possible to avoid reduced sensitivity in both velocity and power, and any wall filter effects on low velocity flow. This applies to steered and non-steered beams. Further guidance on Doppler and steering angles may be provided by the manufacturer.

Constant versus pulsatile flow – In constant flow, since there is no significant variability in flow throughout the cardiac cycle, there is no need to acquire time-resolved or heart-rate synchronous volume flow image datasets. Total acquisition time will be determined by the amount of time needed to acquire a reliable and accurate temporal mean volume flow estimate. In pulsatile flow, the approach depends on whether time-average mean flow or time-resolved flow is required. In the latter case, systems must be able to acquire time-resolved 3D data. In the former case, time averaging may still be applied provided there is a means for asynchronous acquisition.

A.9.2 SPECIFICATION

Parameter	Actor	Requirement
Acquisition Protocol	Sonographer/Technologist/ Physician	Shall select a protocol that has been previously prepared and validated for this purpose where the ultrasound system, probe, and imaging preset are specified by the manufacturer.
Artifacts	Sonographer/Technologist/ Physician	Shall confirm the absence of color flow artifacts (e.g. motion artifacts such as flash or smear) that could affect the volume acquisitions. Shall monitor or review the acquired images to ensure that velocities in the target vessel remain(ed) within the color flow scale range (no aliasing) during the 3D sweep, unless otherwise instructed by manufacturer guidelines.
Target Vessel Identification	Sonographer/Technologist/ Physician	Shall position the target vessel as directed by manufacturer guidelines including its position within the

and Position		imaging volume such that the full extent of the target vessel cross section is covered and with a proper angle with respect to the transducer.

A.10. 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.6) 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.10.1 DISCUSSION

Any and all content related to this section is integrated within A.9 Image Data Acquisition and A.13 Image Analysis and any additional details would be provided manufacturer.

A.11. Image QA

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.8), include requirements that attempt to avoid issues mentioned here, but it can still be necessary to confirm during this QA step whether or not those prior activities were successful.

A.11.1 DISCUSSION

Target vessel position, motion, and artifacts – The target vessel must remain within the boundaries of 3D volume used for the volume flow measurement. Vessel and tissue motion during the image acquisition could affect measurement accuracy, and therefore the process should be completed in the absence of color flow artifacts. In any of the following scenarios, either discard the affected 3D acquisition or the affected volume in the 4D acquisition, or restart the 4D acquisition:

- **Target vessel moves outside volume used for measurement** – Occurs when any portion of the target vessel moves outside the selected imaging volume during the acquisition – this should absolutely be avoided.
- **Target vessel flow velocity aliases** – Flow velocity aliasing in the target vessel should be avoided as much as possible and throughout the entire cardiac cycle, particularly in systole. Some manufacturer algorithms may be able to correct aliasing artifacts (further details may be provided by the manufacturer).
- **Motion artifacts in C-plane** – Motion artifacts such as flash or smear may appear in the C-plane or target vessel during the acquisition if (1) the target vessel moves rapidly, (2) there is bulk patient movement, or (3) the operator moves the probe.

Target vessel signal-to-noise ratio (SNR) – The target vessel color flow (velocity, power) signal-to-noise ratio (SNR) is primarily impacted by imaging depth and color flow gain, and will affect 3D volume flow measurement accuracy. Manufacturers may provide guidance on target vessel SNR using a quality indicator that would help identify image acquisition scenarios that are expected to yield poor accuracy or repeatability. Such quality indicators may be provided as a single numeric value or a quality map.

Parameter readjustment – During the image acquisition setup process, the target vessel may move or change orientation and the probe may shift. Therefore, all scanner parameters should be re-assessed prior to starting the 3D volume flow acquisition. In particular, PRF or scale, and color flow gain should be checked and, if necessary, adjusted to comply with their corresponding guidelines. In addition, and if necessary, the A-plane ROI size and 3D elevational sweep angle should be adjusted to ensure that the target vessel is positioned to intersect the C-plane in cross section and near the elevational-lateral center.

A.11.2 SPECIFICATION

Parameter	Actor	Requirement
Target Vessel Position, Motion, and Artifacts	Sonographer/Technologist/ Physician	Shall confirm the target vessel remains within the appropriate imaging boundaries and is not cropped at any point throughout the entire image acquisition process. Shall confirm the absence of flow velocity aliasing, or that the aliasing is within the manufacturer-specified level of acceptable aliasing for the volume flow application. Shall confirm minimal vessel and tissue motion, including throughout the cardiac cycle as applicable, and that the image acquisition process is free from color flow artifacts.
Target Vessel Signal-to-Noise Ratio (SNR)	Sonographer/Technologist/ Physician/ Acquisition Device*	Shall confirm adequate color flow SNR in the target vessel if instructed by the manufacturer.

*It is possible that SNR assessment may be automated.

A.12. Image Distribution

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

A.12.1 DISCUSSION

Assumptions: There is no specific requirement for access to an archival system such as a standard Picture Archiving and Communication System (PACS) related to this profile. However, if available and offline processing is to be performed, it is assumed that the images will be archived in a format compatible with such processing.

A.13. Image Analysis

This activity involves producing the quantitative measurements described in 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.13.1 DISCUSSION

Data quality verification – The 3D/4D color flow data should be reviewed prior to making post-processing volume flow measurements to ensure the following:

a) target vessel is within scan volume

b) temporal flow profile covers an entire cardiac cycle(s) (synchronous acquisition)
c) color and grayscale portion of images are of good quality and depict lumen boundary
d) absence of velocity aliasing and color flow artifacts (see A.9.2) in target vessel and immediately surrounding background.

Target vessel mask and unwanted vessels – A target vessel mask may be needed during image analysis in order to exclude adjacent vessels from contributing to the volume flow measurement. If vessels that are not of interest are also visible, these vessels should be excluded by the operator. The manufacturer should provide a means for this selection. Two possible approaches might be manual masking and directional velocity masking, as described below. Any recommended masking procedure is manufacturer specific and would be provided in the Protocol.

- **Manual mask** – In manual tracing, the vessel lumen might be traced or the unwanted vessels might be excluded.
- **Velocity-based directional mask** – The removal of unwanted vessels can be facilitated by flow direction, i.e., velocity-based masking, where the contribution from either positive or negative velocities are omitted from the volume flow quantification. For example, in the umbilical cord, velocity-based masking could be used to remove arterial flow when only venous flow is desired, or vice versa.
  - For pulsatile flow lumens with reverse flow, directional masking might not be possible as positive and negative velocities might be present in the time resolved data, i.e., across a cardiac cycle(s).
  - The PRF should be set such that even adjacent vessels are not aliased. Aliased components of an adjacent vessel may compromise the ability of a velocity-based directional mask to isolate the target vessel.

In certain anatomies, the scanned flow geometry may be complex, e.g., umbilical cord. It may be that the flow enters and leaves the lateral/elevational field of view and thus would only be partially included in the scan volume. Turbulent flow, or other reasons for aliasing or temporally directional flow/velocity, could be present as well. The user should check for these and select an appropriate location for the flow measurement that avoids color flow artifacts. Depending on the implementation by the manufacturer, the operator may select location at a particular depth or a depth range to obtain the flow measurement.

Quality feedback – Depending on the implementation by different manufacturers, in addition to the flow measurement, the system may also provide a quality index to reflect the confidence of the result. This quality index would be used as a reference for the operator to decide whether to use the flow value for clinical diagnosis or to reacquire the flow measurement.

A.13.2 SPECIFICATION

Parameter	Actor	Requirement
Target Vessel Mask and Unwanted Vessels	Sonographer/Technologist/ Physician/ Image Analysis Tool*	Shall employ an appropriate target vessel mask (manual, directional velocity, or manufacturer specific) during image analysis when adjacent vessels need to be excluded from contributing to the volume flow measurement.
ROI Selection	Sonographer/Technologist/ Physician/ Image Analysis Tool*	Shall select an ROI for flow measurement that avoids color flow artifacts.
Quality Feedback	Sonographer/Technologist/	Shall understand that volume flow measurement confidence

Parameter	Actor	Requirement
	Physician/ Image Analysis Tool*	may be supported by a quality feedback indicator, e.g., a quality index, and shall refer to manufacturer guidance on the proper use of such metrics.

*It is possible that these assessments may be automated.

A.14. Image Interpretation

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

A.14.1 DISCUSSION

NA

A.14.2 SPECIFICATION

Parameter	Actor	Requirement

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.

Volumetric blood flow (VBF), typically in units of mL/min, defines a blood volume that passes a cross-sectional area of vessel per unit time (t) and is equal to the spatial mean flow velocity (V_{mean}) multiplied by vessel cross-sectional area (CSA): VBF(t) = V_{mean} (t) x CSA(t). Small errors in either component can cause large errors in calculated volume flow[22]. Estimates of VBF are made by a number of different methods some of which are invasive (Swan-Ganz catheter-based method and others using similar dye dilution approaches) and others noninvasive (ultrasound and MRI imaging). The context of the proposed biomarker needs to be understood in relation to the traditional ultrasound approach. In one common traditional approach, the user is required to place a spectral Doppler sample volume fully across the vessel to obtain a representative velocity distribution for the calculation of the V_{mean}. This includes correcting for the angle of the vessel with respect to the interrogating ultrasound beam. Small errors in the angle correction can result in significant inaccuracies. There is an implicit assumption that the power weighted Doppler velocities will provide the correct V_{mean} which can be influenced by the beam profile and other factors. In addition, the user is imaging the vessel to obtain a longitudinal view of the vessel to get the velocity vectors of flow to be along the direction of the angle correction. Any out of plane components are then not represented in such an assumption. With this longitudinal view, the operator is assuming that the vessel has a circular geometry as the operator then makes a measurement of the vessel diameter. These assumptions are limited by the degree that the longitudinal image is oblique to the vessel and because the vessel may not be circular. Volume flow calculations can produce large errors for small vessel diameters. For example, a 0.4 mm error in measuring a small vessel (4 mm)

was reported to have a 21% error in flow calculation[13]. Moreover, in high resistance flow, the retrograde component needs to be accounted for in the calculation. For example, normal flow in the brachial artery in the arm while mapping anatomy and assessing blood flow prior to dialysis placement has a triphasic waveform, with a retrograde component. A decision made to include the retrograde component may result in a blood flow to the forearm and hand that clinically seems quite low, and so this retrograde component is excluded from the brachial artery measurement of flow during planning for fistula placement.

Despite these limitations, there are clear clinical examples where carefully performed volumetric blood flow measurements using the traditional method will yield clinically significant results. Take the case of umbilical venous flow. Ferazzi et al. studied 37 growth restricted fetuses shortly before delivery to clearly establish that umbilical vein blood flow (UVBF) is reduced on a weight-specific basis (mL/min/kg)[6]. Parra-Saavedra and colleagues more recently compared UVBF with standard Doppler velocimetry for predicting adverse outcomes in small fetuses with EFW < 10^{th}%[15]. Umbilical venous flow was a better predictor of non-reassuring fetal status during labor and for metabolic acidosis when compared to Doppler velocimetry. In that cohort, 53 of 193 small fetuses (27%) had non-reassuring fetal status that required emergency delivery and 21 (11%) of newborns developed metabolic acidosis. When combined with middle cerebral artery (MCA) Doppler velocimetry, UVBF better identified small fetuses with perinatal morbidity. These observations suggest that UVBF may represent an important physiologic parameter linking placental function to fetal growth if technical refinements could bring it into clinical use[23].

Similarly, clinical evidence exists for the use of volume blood flow in the assessment of dialysis arteriovenous fistulas (AVFs). Six-week ultrasound measurements of AVF blood flow, diameter and depth moderately predicted unassisted and overall AVF clinical maturation with an area under the receiver operating characteristic curve of 0.79 and 0.76 respectively, in a large recent multicenter clinical trial. Multiple other factors considered did not further improve AVF maturation prediction[18].

So, the precedence for the clinical use of volume blood flow does exist but its use has been limited by the difficulty in making such measurements and consequently surrogate velocity measurements and indices of the same have been used. Therefore, the identification and verification of an accurate, reproducible and operator-independent ultrasound measurement method as a biomarker for volume blood flow could have a significant impact for numerous applications in clinical practice.

This profile does not specify the methodology that must be used but does examine an approach using 3D/4D Doppler power and velocity data to pursue this biomarker. Other approaches could be considered if they comply with the verification criteria defined in this document. The identified examples above of umbilical cord and dialysis AVFs are examples of potential clinical applications. Ultimately, volumetric flow in an identified vessel of sufficient size for the selected methodology would have broad application.

The clinical applications discussed in this Profile are admittedly chosen somewhat arbitrarily. However, they are ones in which there is a relatively large experience of volume blood flow measurements at least in the literature, i.e., umbilical vein/umbilical cord blood flow and dialysis AVF/graft blood flow and to which the authors of this profile have clinical experience. There is a myriad of other potential applications of volume flow. A possible metric that could be used to appreciate the range of potential

applications for volume flow would be to count the number of clinical instances where surrogate measurements of volume flow such as resistive indices, pulsatility indices, velocity, or mean velocity color flow or power mode pixel numbers per unit area or volume for "perfusion" assessments are employed. Each one of these methods, or variants thereof, has been used to assess tissue viability or disease states in virtually every human organ and body part. This is because all living tissue requires blood flow to survive, and assessment of that flow can reflect viability or disease states. Yet, none of these surrogate metrics measures true volumetric blood flow, which is really the desired quantity. If it were possible to convert these surrogate metrics into true blood flow, the number of applications for volume flow would be huge; the range of which being far beyond the scope of this or any single profile.

Footnotes associated with Profiles Claims

***Claims 1a and 1c:** These claims are based on phantom studies for flows of *X* = 60-720 mL/min performed at multiple sites for multiple scanners from different manufacturers[24]. It is therefore currently subject to the conditions described in that reference. This includes the corresponding resistive index (RI = (PSV - EDV) / PSV where PSV = peak systolic velocity and EDV = end-diastolic velocity) of 0.85 for the pulsatile flow in the phantom used for those studies. Additional studies would be required to determine the dependence of claims based on the degree of pulsatility. However, performance in comparably complex flows and similarly validated could be considered as conforming to this claim. Note that the original analysis included all of the systems tested. In the development of this profile, we considered results separately for constant and pulsatile flow and excluded some systems having identified outlying performance. Therefore, with respect to Claim 1a, results for Systems 1 and 2 were considered and for Claim 1c, only those for System 1 were included. In the latter case, there were three sites with three different operators using three different scanners of the same model so this still represents a level of reproducibility in this phantom testing.

†**Claims 1b and 1d:** The clinical performance target of 20% described in Section 1 is used to define these cross-sectional claims based corresponding results seen in the phantom studies.

****Claim 2a**: This claim is based on two clinical studies in umbilical venous flow published in the peer-reviewed literature (Detailed discussion provided in the following paragraph.) and relates to the repeatability of the measurement using the Gaussian surface integration method (see section 3.9) on 3D Doppler data. It is understood that 1) "constant flow" is assumed to have no more than a 0.25 resistive index value over the period of the data acquisition, 2) the accuracy is not being validated in the clinical setting due to a lack of appropriate reference standard and 3) there are additional applications for volume flow beyond those given as representative examples here. These latter two conditions may be addressed in future revisions of this profile. Note that the value of 0.25 for the resistive index (RI) was selected based on the lowest RI seen in normal umbilical arterial flow [25] (2.5^{th} percentile at 41 week gestational age was 0.36) and a value >0.15 for abnormal umbilical venous flow [26, 27]. Also "constant" in this context assumes that the overall variation in flow over the image acquisition period due to physiologic or other reasons is minimal. In any case, the measurement will be the average of the flow during the acquisition period.

For umbilical venous blood flow, evaluations have been performed on two different ultrasound systems. In one system using a mechanically swept array[9], the reproducibility of the volume flow measurements was assessed by making multiple measurements along the length of the umbilical cord. Note that volume flow in the umbilical vein should be the same at any point along the length of the

cord. Up to three locations were assessed in each of 35 subjects. Umbilical venous volume flow measurements were reproducible in the mean estimate, with a within-subject coefficient of variation of 20.3%±10.1%. Using a second ultrasound system from a different manufacturer[28], this with a 2D electronic array, volume flow measurements in the umbilical vein were made in 12 subjects, again for at least three locations along the cord. These measurements showed reproducibility with a mean coefficient of variation of 18%±14%. In some of the most careful studies in umbilical venous blood flow using 2D methods with spectral Doppler, Rizzo et al. found that the intra-observer and inter-observer agreements showed mean percentage differences (and 95% confidence limits of agreement) of 1.01% (-21.87 to 23.85%) and 1.12% (-20.70 to 22.95%), respectively[29]. This provides further impetus for the criteria indicated in Claim 2a. It should be noted that the authors also state that part of the inclusion criteria was "successful recording of umbilical vein (UV) diameter and Doppler flow velocity waveforms" such that more difficult cases may result in greater variability. The measurement of vessel diameter is known to be a significant source of measurement error in volume blood flow. So the ultrasound methodology also included semi-automated selection of the umbilical vein diameter using a technique previously shown to improve intra-observer and inter-observer variability[30]. These factors together likely make the reproducibility assessed here better than what might be expected more generally in the common clinical setting.

††**Claim 2b**: Reproducibility of volume blood flow in AVFs was evaluated. In the absence of measurements using the 3D Gaussian method, we examined volume flow measurements using the 2D spectral method taken from a series of 38 AVF studies conducted at the University of Alabama at Birmingham (UAB) between 1-November-2019 and 18-February-2020. For each study, three volume flow measurements were made. The average and standard deviation of these measurements for each case were computed along with the within subject coefficient of variation (wCV). Across these subjects, the average wCV was 8.87 ± 5.08% (Personal communication, Michelle Robbin 3/2020). This was considered an exceptionally good wCV from a group of sonographers well-trained in making such measurements. One recent study did examine the intra- and inter-observer variability in what the authors said was "in such a way that it was representative of the routine preoperative work-up at the study institution"[31]. While this publication only provided the Bland-Altman analysis for vessel diameter, the lead author reanalyzed the inter-observer data for the volume blood flow in the branchial artery after AVF and found mean percentage differences (and 95% confidence limits of agreement) of -11.87% (-26.5 to 2.7%). In a follow-up analysis of these data, the mean and standard deviation of the absolute values of the percent differences were found to be 16.9 ± 6.7%. It should be noted that similar to the UAB training level for sonography, the authors say, "Another limitation is that the present study was set in a tertiary referral centre with trained vascular technicians with ample experience in pre-AVF DUS examination, possibly hampering generalisability of the results." So, the results of both studies may underestimate the variability that might be seen in common clinical practice. With all these considerations, an initial technical performance Claim 2b was set as above.

Some dialysis therapy units have a built-in system to measure flow through the dialysis access. These measurement systems typically report flow ranging from 0-2000 mL/min (and ">2000 mL/min" when flow registers as such). Therefore, the potential exists for a comparison to a reference standard although more evaluation would be needed to validate the basis for such a standard before a claim could be developed based on this comparison. An additional claim could be with respect to changes in dialysis pump speed, e.g., we can measure a change of *X* mL/min to within ±15% with a 95% CI. We likely will not be able to consider this a measure of absolute flow. We would also need to know the

accuracy of the reference standard (dialysis pump).

The level of pulsatility associated with this claim is not fully determined at this point as the examination described above is based on the context of AVF assessment. This would be an ongoing effort as the technology is developed and utilized.

Appendix C: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Ultrasound Volume Blood Flow 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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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. In particular, comments on these issues are highly encouraged during the Public Comment stage.

Q. Line 683 – Is there need for additional specification on the fluid for the phantom, such as

scatter size (or equivalently, frequency dependence of backscatter coefficient)? Is there need to say something about avoiding aggregation of scatterers? A. There is likely need to provide additional specifications, particularly with regard to the backscatter level and its frequency dependence. This is currently being assessed. Regarding aggregation, this is addressed in Lines 709-710 as a part of the Volume Flow Phantom Temporal Stability testing.
Q. Lines 929-935 – For pulsatile flow, should the acquisition time correspond to an integer number of cycles? A. If the acquisition is asynchronous then the only requirement is that the acquisitions be distributed randomly in time with enough samples for a mean estimate. This was meant to imply over multiple cardiac cycles such that ensuring an integral number of cycles was not a requirement. However, if this is not the case then it is true that sampling should be such that there is no bias due to fractional cardiac cycles. Additional wording may be required to explain this point based on any further questions in this regard.
Q. Line 1124 - This is the resistive index as measured in the QIBA phantom SN940035-4581-2 on 25Jan2022. A. There is likely need to make additional measurements of the resistive index in the QIBA phantom used for the experiments of reference 24.
Q. Lines 1127-1133 - This text explains an additional analysis that was performed of the results in reference 24 related to pulsatile flow. A. May need to consider an additional appendix or other source to further explain the analysis that was performed where the number of systems considered from those in Reference 24 is reduced.
Q. Lines 1183-1187 – In communication with the authors of reference 31 an additional analysis of their results was performed. A. May need to consider an addition appendix or other source to further explain the analysis that was performed.
Q. Lines 1203-1205 – There may be sources of data that could be added in a future revision. These data include a carotid artery study conducted at the University of Michigan and brachial artery measurements made as a part of a study in arteriovenous fistula maturation. A. May need to consider an analysis of such data to further inform this profile in the future.