PULSE-ECHO QUANTITATIVE ULTRASOUND BIOMARKER COMMITTEE

GUIDELINES FOR BIOMARKER WORK GROUPS

Thank you for contributing to the Pulse-Echo Quantitative Ultrasound Biomarker Committee (BC). This document's intent is to guide the work done by each biomarker working group (BWG) in order to achieve the goal of drafting claims, ideally by December 1, 2020.

I. Introduction

The following conceptual framework may be helpful to simplify the work of the various PEQUS work groups.

We presently have three biomarkers under consideration:

1. Attenuation
2. Sound speed
3. Backscatter

We have one disease process under consideration: non-alcoholic fatty liver disease (NAFLD), and within that disease, we have one biological concept that is the measurement focus: hepatic steatosis.

The work of relating the three biomarkers to the biological concept can be conceptualized as taking place on three levels:

- **Level 1: The measurement level**
  - At this level, we work to establish a reference standard and work to reduce variability and bias between measurements.
- **Level 2: The single biomarker predictor level**
  - At this level the relationship between the individual biomarker measurements and the biological concept is established.
- **Level 3: The multiple biomarker predictor level**
  - At this level the relationship between multiple simultaneous biomarker measurements and the biological concept is established.

The initial work of PEQUS focuses on Level 1. As part of this, we will agree on a measuring protocol for each biomarker and develop a phantom to test that protocol. The role of the phantom work group (PWG) is to develop the best possible measurement platform for the three candidate biomarkers. This phantom should, to the extent possible, be representative of the biophysical measurement environment expected in NAFLD with biomarker changes representative of those expected across the clinical hepatic steatosis range. This process is necessarily imperfect – making optimal compromises is part of the phantom task group's output.

In parallel, each BWG will focus on standardizing the measurement of each biomarker and reporting outputs, and ultimately on comparing technology alternatives in the phantom with the goal of developing methods to minimize bias and variability and, when these cannot be eliminated, to quantify these. Initial claims regarding bias and variability will be incorporated into the first draft of the **PEQUS Hepatic Steatosis** profile.

II. General Duties

The first goal of each BWG is to define a standard protocol for measuring and reporting the PEQUS biomarker of interest (attenuation/backscatter/sound speed). It is anticipated that these protocols will be based on the pre-existing literature and knowledge of the experts in the BWG. This protocol will contain draft claims regarding the anticipated accuracy and precision of the protocol. These draft claims will ultimately be tested in the PEQUS phantom.

III. Specific Tasks

1. Perform a literature review of the different methods used to measure each biomarker, focusing on methods that have been extensively validated in phantoms and applied pre-clinically and/or clinically. Novel methods will be incorporated in future versions of the profile. The information obtained from the survey shall include:
    a. Expected levels of accuracy and precision achieved with each method.
    b. Discussion on technical sources of error that can affect the accuracy and precision of the biomarker, some of which may include:
        i. Power spectrum estimation method
        ii. Data acquisition (sum-and-delay, plane wave imaging)
        iii. Parameter estimation and image reconstruction methods
        iv. Size and depth of region of interest
    c. Different biomarker reporting methods (e.g., attenuation at center frequency vs. attenuation slope; integrated backscatter coefficient vs. backscatter coefficient at center frequency)
2. Define a standard protocol for measuring and reporting the biomarker.
3. Draft claims regarding accuracy and precision with the standard protocol.
4. Work with the Phantom Work Group to define the phantom specifications needed to validate the draft claims.
5. Identify possible biological confounders, specify their commonality, magnitude, and clinical relevance and determine whether these should be managed within the profile and/or included in 2nd generation phantoms. These confounders might include:
    a. Fasting and hydration status
    b. Inflammation
    c. Fibrosis
    d. Thickness of subcutaneous tissue

IV. BWG leadership

Each BWG will select two work group co-chairs, who will be responsible for coordinating BWG activities:

- Set up regular BWG meetings (supported by AIUM staff)
- Produce BWG call summaries and document action items (supported by AIUM staff)
- Maintain shared committee working documents, presentations, etc. on the QIBA Wiki (supported by AIUM staff)
- When provided, distribute working materials to the BWG.
- Provide 10-minute progress reports on BC conference calls.
- Actively communicate with the Phantom Work Group to coordinate phantom specifications.

V. Meeting arrangements

Schedule monthly BWG conference calls to discuss progress, preferentially two weeks after the BC conference calls. BC conference calls will occur, if possible, the first Friday of each month.

VI. Staff support

Therese Cooper (tcooper@aium.org) and Kelly Phillips (kphillips@aium.org) will assist BWG co-chairs to coordinate BWG activities.

VII. Additional comments

It is important that members of the BC use the same terminology when referring to quantitative imaging biomarkers. To this end, we encourage members of each BWG to review QIBA literature on biomarker terminology, for example:

a. Sullivan DC, Obuchowski NA, Kessler LG, Raunig DL, Gatsonis C, Huang EP, Kondratovich M, McShane LM, Reeves AP, Barboriak DP, Guimaraes AR. Metrology standards for quantitative imaging biomarkers. Radiology. 2015 Dec;277(3):813-25.
b. Kessler LG, Barnhart HX, Buckler AJ, Choudhury KR, Kondratovich MV, Toledano A, Guimaraes AR, Filice R, Zhang Z, Sullivan DC, QIBA Terminology Working Group. The emerging science of quantitative imaging biomarkers terminology and definitions for scientific studies and regulatory submissions. Statistical methods in medical research. 2015 Feb;24(1):9-26.
c. Obuchowski NA, Buckler A, Kinahan P, Chen-Mayer H, Petrick N, Barboriak DP, Bullen J, Barnhart H, Sullivan DC. Statistical issues in testing conformance with the quantitative imaging biomarker alliance (QIBA) profile claims. Academic radiology. 2016 Apr 1;23(4):496-506.

Appendix A provides an example of the structure of the claims that shall be produced by each BWG. This structure was modified from the shear wave speed profile and should only be used as a guide for the type of information that will be required.

Appendix A – Claim Structure

Compliance with the activities of this Profile by relevant staff and equipment supports the following claim(s):

CLAIM 1 – BIOMARKER ACCURACY AND PRECISION

Measured (attenuation/backscatter/sound speed): The biomarker is (attenuation, backscatter, sound speed) in the liver of a patient computed by (measuring technique). The biomarker is used for a single measurement and also for monitoring changes over time.

Clinical Application: (attenuation/backscatter/sound speed) is measured in the liver of patients with suspected diffuse liver disease, with or without fibrosis and/or inflammation of the liver and with suspected steatosis.

Bias: When measured in the right lobe of the liver in the manner specified in the profile and with equipment compliant with the specifications of the profile, the measured biomarker will be within ± 5% of the true biomarker value. This is based on numerous measurements of phantoms with physical properties very similar to human liver.

Precision: When measured in the right lobe of the liver in the manner specified in the profile with profile compliant equipment:

The measured (attenuation, backscatter, sound speed) is Y, the 95% CI is (Y_1-Y_2), and the coefficient of variation is Y_{CV}

- **Reliable measurements are made at a single location of the liver at the depth and approach specified and relationship to vessels as specified in the profile.**
- **The ranges of (attenuation, backscatter, sound speed) values over which the profile applies are X to X**
- **Patients are included as defined in the profile below.**

The same values hold for longitudinal studies when the same or different operators measure liver under the standard profile protocol.

Tests have shown that the possible confounders can affect the accuracy and precision of the biomarkers: (list confounders and how they affect the biomarker)

While the claim was developed by extensive review of the literature, it is currently a consensus claim that has not yet been fully substantiated by studies that strictly conform to the specifications given here. 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 claim or the details accordingly. At that point, the caveats associated to the confounders listed above may be removed or re-stated.

CLAIM 2 – BIOMARKER CHANGE

For a measured change in (attenuation/backscatter/sound speed) of X (Y2-Y1), a 95% confidence interval for the change is (Y2-Y1) ± 1.96 X [(Y1 X 0.05)2 + (Y2 x 0.05)2]1/2

This claim holds when:

- Reliable measurements are made at each time-point in exactly the same location of the liver documented by relationship of ROI compared to hepatic vessels at the depth and approach specified in the profile.
- Measurements at each time point are acquired using manufacturer specified protocol.
- Specify range of liver (steatosis/attenuation/backscatter/sound speed) over which this profile applies
- Patients are included as defined in the profile.