PULSE-ECHO QUANTITATIVE ULTRASOUND BIOMARKER COMMITTEE

GUIDELINES FOR PHANTOM WORK GROUP

Thank you for contributing to the Pulse-Echo Quantitative Ultrasound Biomarker Committee (BC). This document's intent is to guide the work done by the phantom work group (PWG) in order to achieve the goal of defining phantom specification and manufacturing for the multisite study, 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 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 to the PWG, each biomarker work group (BWG) will focus on standardizing the measurement of each biomarker and how they are reported, 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 goal of this PWG is to define the structure and composition of phantoms needed to assess the performance of standardized measurement protocols defined by the BWGs for each of the PEQUS biomarkers (attenuation/backscatter/sound speed) for the estimation of liver steatosis, and to carry out their procurement.

III. Specific Tasks

With input from the three PEQUS BWGs (attenuation/backscatter/sound speed), the PWG is expected to complete the following:

1) Determine clinically relevant ranges for the three PEQUS biomarkers in different stages of liver steatosis (from stage 0 to 3).

2) Determine appropriate reference standard measurement methods for phantom material properties for attenuation, backscatter, and sound speed.

3) Define specifications for a set of phantoms which meet the following criteria:
    a) Each phantom will exhibit acoustic properties representative of a different liver steatosis stage. Together, the entire set will exhibit the spectrum of acoustic properties determined in 1).
    b) If possible, phantoms will be compatible with fat-quantification using MR PDFF.
    c) If possible, phantom structure will mimic steatotic liver morphology with similar size and distribution of lipid droplets.
    d) Phantom acoustic properties must be stable for at least the duration of the multisite study (1 year) and robust to transportation between sites.

4) Coordinate the procurement or manufacture of phantoms.

IV. PWG leadership

The PWG will select two work group co-chairs, who will be responsible of coordinating the activities of the PWG. This includes the following tasks:

- Set up regular PWG meetings (supported by AIUM staff)

- Produce PWG 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 PWG.
- Provide 10-minute progress reports on BC conference calls.
- Actively communicate with each BWG to coordinate phantom specifications

V. Meeting Arrangements

Schedule monthly WG 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 work group co-chairs coordinate the activities of the BWG.

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.