HHSN268201300071C,
Quantitative Imaging Biomarkers Alliance (QIBA)

PROPOSED METHODOLOGY

QIBA will conduct its work under the NIBIB contract through frequent **conference calls**, **email** communications among the PI, Scientific Liaisons, RSNA Staff and various participants. **In-person meetings** are held at the RSNA Annual Meeting in late November, or early December, and in May of each year. Specific work on data collection projects funded with NIBIB contract money will be conducted by the sub-contractors, usually at academic sites.

The QIBA Steering Committee meets monthly by conference call. The Technical Committees and Task groups meet frequently as needed, often weekly.

We propose the following methodology to meet the objectives.

OBJECTIVE 1. DEVELOP AT LEAST 2 NEW PROTOCOLS AND QIBA PROFILES PER YEAR THAT ADDRESS DISEASES OF SIGNIFICANT BURDEN TO THE US POPULATION.

The work of the six QIBA Technical Committees follows a defined, coordinated process described below to develop solutions and promote their adoption. The QIBA approach entails the following:

I. *Identify Sources of Error and Variation in Quantitative Results from Imaging Methods*. Stakeholders work to identify problems leading to error or variability in quantitative results from imaging methods.

II. *Specify Potential Solutions*. Stakeholders identify potential strategies, infrastructure or guidelines for error mitigation and collaborate on development of hardware, software, and protocol solutions, documenting them in the form of QIBA Profiles.

III. *Test Solutions*. Vendors and researchers implement QIBA solutions (Profiles) to assess their feasibility and efficacy.

IV. *Promulgate Solutions*. Validated solutions (Profiles) are disseminated and implemented through vendor adoption, research integration and clinical education.

Academic imaging scientists and physicians, industry scientists, staff scientists from FDA and NIST, and RSNA staff members work together to apply the QIBA approach to a series of issues that need to be addressed to make diagnostic imaging quantitative. The approach is systematic, with the aim of producing a QIBA Profile (i.e., standardized specifications for image acquisition, collection, and post-processing) that includes one or more Claims and a process to specify what to achieve. QIBA Profiles take into consideration technical (product-specific) standards, user activities, and relationship to a clinically meaningful metric such as therapeutic response or other patient outcome measure. QIBA is also developing a compliance program to allow vendors and users to determine whether equipment and other actors are QIBA-Profile-compliant, using QIBA-branded or recommended phantoms (test objects), data sets, software and other tools. Examples of QIBA Profiles can be found at http://rsna.org/QIBA_Protocols_and_Profiles.aspx. The PI and Scientific Liaisons will ensure that at least two new Protocols and Profiles are developed each year.

OBJECTIVE 2. PERFORM INDIVIDUAL GROUNDWORK DATA COLLECTION AND ANALYSIS PROJECTS TO FILL GAPS IDENTIFIED DURING WORK DEVELOPING AT LEAST 6 QIBA PROFILES COVERING THE FOUR MAJOR IMAGING MODALITIES, CT, MRI, RADIONUCLIDES AND ULTRASOUND.

Steps II and III above stipulate scientific and technical project activity. Data relating to variability of the biomarker measurement are referred to as groundwork data. Groundwork data are extracted from the literature, and gaps in the data necessary to understand the sources of

variability are noted. These gaps lead to QIBA projects to obtain such data. The following are examples of groundwork tasks:

a. Technical Characteristics and Standards Groundwork:
    a. Systems engineering analysis of sources of variability, including consideration for co-variates
    b. Phantom development:
        i. Inventory of currently available phantoms
        ii. Assess applicability of existing phantoms
        iii. If new one is required, pursue development as defined by the Technical Committee
        iv. Create synthetic digital reference object (i.e., pseudo-data created to facilitate performance assessment for candidate implementations of the biomarker) to support algorithm performance testing and certification activities.
    c. Assessment of intrinsic scanner variability – same scanner, scanners from same manufacturer, scanners from different manufacturers
        i. Prospective Single- and multi-center phantom studies
    d. Assessment of intra- and inter-reader bias and variance of measurements on phantom and clinical images
        i. Phantom images from prospective single- and multi-center studies
        ii. Clinical images from no-change (“coffee break”) conditions on patients
        iii. Clinical images from retrospective clinical serial studies
    e. Candidate algorithm performance
        i. Begin with a single expert per software package (or method) working under ideal conditions, and use data obtained from clinical trials that used the QIBA Profile.
        ii. For each new imaging biomarker and its reference standard, determine the sensitivity and specificity for individual expert readers using appropriate outcome measure, such as prediction of survival at relevant established time-point (e.g., 6-month survival for advanced lung cancer).
        iii. Compare correlations between new and standard biomarkers with outcome measures.
        iv. Progress to multiple image analysts for each software package (or method).

Such projects comprise the mainstay of resource requirements to meet not only this objective but the others as well. We propose to consider candidate projects using a deliberative approach that entails an application, vetting by technical committees, and judgment by the Steering Committee on which projects to fund. The PI and Scientific Liaisons will ensure that the portfolio of funded projects apply to six different Profiles covering the four major modalities.

OBJECTIVE 3. DEVELOP PROCEDURES AND PROCESSES FOR HARDWARE AND SOFTWARE MANUFACTURERS AND USERS TO DEMONSTRATE COMPLIANCE WITH QIBA PROFILES.

Through conference calls and face-to-face meetings, the QIBA Technical and Steering Committees will jointly develop a general set of procedures and processes to demonstrate compliance with QIBA Profiles as well as to conduct groundwork projects for specific biomarkers to actualize this. This general approach will then be tailored to specific compliance programs for the mature QIBA Profiles. The process will include development of predictive metrics for use in calibration and quality control programs and development of evaluation procedures to verify compliance by vendors and providers of service with QIBA profiles.

OBJECTIVE 4. DETERMINE FROM EXPERT CONSENSUS THE DESIGN REQUIREMENTS FOR PHYSICAL AND VIRTUAL (DIGITAL) REFERENCE OBJECTS NEEDED FOR DETERMINATION OF IMAGING BIOMARKER VARIABILITY OR TO DEMONSTRATE COMPLIANCE WITH QIBA PROFILES, AND COMMISSION THE CONSTRUCTION OF SUCH REFERENCE OBJECTS THROUGH SUBCONTRACTS FOR AT LEAST 4 PROFILES.

We will formalize reference standards and objects (aka physical or virtual phantoms) for verification of QIB measurements including formal process description, publication of broad-spectrum testing results in peer-reviewed scientific journal(s), distributing announcements through presentations and/or other advertising, providing user manuals and expected results and tolerance ranges. We will ddeposit such digital reference data sets (empirical and synthetic) into the QIBA data warehouse to aid in vendor testing and biomarker compliance. Doing so will provide to manufacturers, users, and testing organizations,a process for using freely available simulation software platform and available, referenced phantoms to facilitate demonstration of compliant measurements under equivalent conditions while allowing protection of proprietary and confidential information. The PI and Scientific Liaisons will ensure that the phantom development projects relate to at least four Profiles.

OBJECTIVE 5. COLLECT IMAGES AND ASSOCIATED CLINICAL DATA FOR THE RSNA-QIBA IMAGE WAREHOUSE OR OTHER LOCATIONS, AND PERFORM ANALYSES ON THE DATA TO SERVE QIBA COMMITTEES AND THE BROADER IMAGING COMMUNITY.

All data created by QIBA are to be made available to the public, either for secondary analyses by other investigators, or to allow others to check and validate the conclusions drawn by QIBA participants. To facilitate such data availability, we created an Ad Hoc Committee on Open Image Archives (Task Force) to generate a report containing recommendations re: repositories of quantitative imaging biomarker data.

The task force delivered several ‘use cases’ as well as other documents supportive of defining proposals for implementation. Four classes of QIBA use cases were defined:

A. Comparative Evaluation of Imaging Biomarker Performance versus Gold Standard;
B. Public Resource Shared Data (*e.g.*, Image Processing Algorithm Development);
C. FDA Approval of Clearance of Imaging Tests; and
D. Pharma Clinical Trials with Imaging Biomarkers as Endpoints

The QIBA Steering Committee subsequently decided to form a joint QIBA/Radiology Informatics Committee to draft a plan for potential RSNA involvement re: imaging data warehouses going forward. Imaging data warehouse needs for each of the QIBA Technical Committee Working Groups were summarized and common features noted. These included the requirement to accommodate different image and non-image data formats (including, in addition

to DICOM image files, a variety of other file formats such as XML, TIFF, NiFTI, etc.) and a wide variety of relevant clinical metadata. In addition, the following needs were identified: data input and search and query-retrieve capabilities; image de-identification, data security and user authentication with group sharing; and data output statistics and analytics functions, though not necessarily image display applications. Also noted were the need for a "trusted third party", the need to promote a culture of sharing perhaps with a reward system for participation, a business model for long-term sustainability

Based on approval from the RSNA Board, we have created an initial implementation of the image warehouse with the associated capability described above. The “Quantitative Imaging Data Warehouse” (QIDW) is currently in pilot phase. As images are collected from clinical trials, groundwork projects funded by this NIBIB contract and other sources, the technical committees will perform analyses to inform or test details in QIBA Profiles or compliance specifications.

OBJECTIVE 6. PROVIDE SUPPORT FOR QIBA STAFF, SCIENCE ADVISER, SCIENTIFIC DIRECTOR, PROGRAM DIRECTOR, PROJECT MANAGEMENT, MEETINGS, TRAVEL, AND CONFERENCE CALLS.

We will conduct the activity necessary to meet the various objectives through support provided by RSNA staff assigned to QIBA as well as key industry leaders who will assist the frequent QIBA Technical Committee and other (e.g., ad hoc) committee conference calls, and occasional workshops or other in-person meetings of the key individuals, as needed. With this new contract cycle we will be appointing four Scientific Liaisons with responsibilities to the Technical Committees and projects in each of the four QIBA modalities
They are:

- Andrew Buckler – CT
- Paul Carson – US
- Edward Jackson – MR
- Paul Kinahan – PET/NM

The PI, RSNA staff, and Scientific Liaisons will meet by weekly or bi weekly conference calls to monitor and facilitate all QIBA activities, including project management, meetings, travel and committee conference calls.