HHSN268201500021C,
Quantitative Imaging Biomarkers Alliance (QIBA)

PROPOSED METHODOLOGY

QIBA will conduct its work under the NIBIB contract through frequent **conference calls** and **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 April or 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 modality-specific Coordinating Committees meet quarterly, and the nine Biomarker Committees and eleven Task Forces meet as frequently as needed, often weekly. In addition, the Process Committee meets twice monthly, and the Quantitative Imaging Data Warehouse (QIDW) Oversight Committee meetings monthly.

We propose the following methodology to meet the objectives.

OBJECTIVE 1: CREATE AND DISSEMINATE NEW PROTOCOLS AND QIB PROFILES EACH YEAR THAT ADDRESS DISEASES OF SIGNIFICANT BURDEN TO THE US POPULATION.

The work of the nine QIBA Biomarker 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 issues 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 technical specifications for image acquisition, collection, and post-processing) that includes one or more Claims and a process to specify how to achieve the Claim(s). 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 conform to the requirements of the QIBA-Profiles 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 at least two new Protocols and Profiles are developed each year.

OBJECTIVE 2: PERFORM FIELD TESTS AND REVISE EXISTING QIB PROFILES AS NEEDED.

Once developed and vetted by the relevant parent Biomarker Committee and modality-specific Coordinating Committee, each Profile undergoes a public review, with comments and recommendations from such a review addressed point by point by the parent Biomarker

Committee. Such a publicly reviewed Profile must then be implemented in a field test to allow technical confirmation in the "real world" setting, e.g., clinical trial implementation. The first Profile to progress to a field test was the DCE-MRI v1.0 Profile. Based on a study design funded by a Round-2 NIBIB-funded project, a multi-center, multi-vendor DCE-MRI study in a prostate cancer population, ACRIN 6701, was initiated to test the implementation of key aspects of the DCE-MRI v1.0 Profile. This study is nearing completion and outcomes from the study will inform future revisions of the Profile. For the present contract, field tests and/or revisions of several existing Profiles are planned, and the details of the field tests and/or revisions will be submitted in the Preliminary Work Plan.

The Process Committee, which was formed during the most recent contract period due to the rapid growth in the number of Biomarker Committees and Task Forces, is reviewing all aspects of the development, maintenance, and retirement of QIBA Profiles. Recommendations of the committee, once approved by the Steering Committee, will be implemented during Year 1 of the NIBIB contract.

OBJECTIVE 3: PERFORM INDIVIDUAL GROUNDWORK DATA COLLECTION AND ANALYSIS PROJECTS TO FILL GAPS IDENTIFIED DURING WORK DEVELOPING QIB PROFILES COVERING THE FOUR MAJOR IMAGING MODALITIES, CT, MRI, NUCLEAR MEDICINE, AND ULTRASOUND.

Steps II and III, cited under Objective 1 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 of co-variates
    b. Phantom development:
        i. An inventory of currently available phantoms is prepared
        ii. The applicability of existing phantoms is assessed
        iii. If a new phantom is required, development of such a phantom, as defined by the relevant Biomarker Committee, is pursued
        iv. If needed for algorithm performance assessment and/or conformance testing, the Biomarker Committee develops a digital reference object (DRO), i.e., synthetic data for which ground truth is known.
    c. Assessment of intrinsic scanner variability using single- and multi-center phantom studies:
        i. Same scanner
        ii. Multiple scanners from same manufacturer
        iii. Scanners from different manufacturers
    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") patient studies

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 and was in conformance with 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 consider candidate projects using a deliberative approach that entails an application, with vetting by Biomarker Committees and modality-specific Coordinating Committees, with judgment by the Steering Committee on which projects to fund. The PI and Scientific Liaisons will ensure the portfolio of funded projects apply to six different Profiles covering the four major modalities.

OBJECTIVE 4: DEVELOP AND EMPLOY PHYSICAL AND/OR VIRTUAL (DIGITAL) REFERENCE OBJECTS NEEDED FOR ASSESSMENT OF IMAGING BIOMARKER VARIABILITY AND/OR TO DEMONSTRATE COMPLIANCE WITH QIB PROFILES

We will formalize reference standards and objects (aka physical and/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 deposit such digital reference data sets (empirical and synthetic) into the QIBA Quantitative Imaging Data Warehouse (QIDW) to aid in algorithm comparison and Profile conformance testing. Doing so will provide manufacturers, users, and testing organizations, a process for using freely available simulation data, analysis software, and associated metadata to facilitate demonstration of conformance under consistent conditions while allowing protection of proprietary and confidential information. The PI and Scientific Liaisons will ensure the phantom development projects relate to at least two Profiles.

OBJECTIVE 5: DEVELOP PROCEDURES AND PROCESSES FOR HARDWARE AND SOFTWARE MANUFACTURERS AND USERS TO DEMONSTRATE CONFORMANCE WITH QIB PROFILES

Through conference calls and face-to-face meetings, the QIBA Biomarker, Coordinating, and Process Committees, with ultimate review and approval by the Steering Committee, will jointly develop a general set of procedures and processes to demonstrate conformance with QIBA Profiles as well as to conduct groundwork projects for specific biomarkers to actualize the conformance process. The process will include development of predictive metrics for use in calibration and quality control programs and development of evaluation procedures to verify Profile conformance by imaging equipment vendors and

software companies. At least two funded projects will specifically address this objective, with details to be provided in the Preliminary Work Plan.

OBJECTIVE 6: COLLECT IMAGES AND ASSOCIATED DATA FOR A QIB DATA WAREHOUSE OR OTHER PUBLIC DATA REPOSITORIES, AND PERFORM ANALYSES ON THE DATA TO SERVE QIB COMMITTEES AND THE BROADER IMAGING COMMUNITY.

All data created by QIBA are 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, an *Ad Hoc* Committee on Open Image Archives (Task Force) was created to generate a report containing recommendations regarding available repositories of quantitative imaging biomarker data and needs of the QIBA community.

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 formed a joint QIBA / Radiology Informatics Committee to draft a plan for potential RSNA involvement in the creation of an imaging data warehouse. Imaging data warehouse needs for each of the QIBA Biomarker Committees 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 data sharing, and a business model for long-term sustainability.

Based on approval from the RSNA Board, the "Quantitative Imaging Data Warehouse" (QIDW) was created and is currently in use in support of many QIBA efforts as well as in quantitative imaging efforts of other scientific organizations, e.g., the International Society for Magnetic Resonance in Medicine (ISMRM). As images are collected from clinical trials, groundwork projects funded by this NIBIB contract and other sources, the Biomarker Committees will perform analyses to inform or test details of QIBA Profiles or conformance specifications.

OBJECTIVE 7: PROVIDE SUPPORT FOR THE QIB COLLABORATION PROGRAM STAFF (OUTSIDE ORGANIZATION STAKEHOLDERS AND QIB COALITION MEMBERS), PROJECT MANAGEMENT, MEETINGS, TRAVEL, AND CONFERENCE CALLS.

We will conduct the activities 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 Biomarker Committee, Task Force, and Coordinating Committee conference calls as well as other (e.g., ad hoc) committee calls. Support will also be provided for the occasional workshops or other in-person meetings of the key individuals, as needed. With this new contract cycle we have reappointed, or

appointed new, Scientific Liaisons with responsibilities to each of the modality-specific Coordinating and Biomarker Committees and associated Task Forces. These individuals are:

- Andrew Buckler, MS – CT
- Paul Carson, PhD – US
- Thomas Chenevert, PhD – MR
- Paul Kinahan, PhD – PET/NM

The PI/QIBA Chair, QIBA Vice Chair, and key RSNA staff will meet weekly, and the PI/QIBA Chair, QIBA Vice Chair, and Scientific Liaisons will meet biweekly to monitor and facilitate all QIBA activities, including project management, meetings, travel, and committee conference calls.