HHSN268201500021C
Quantitative Imaging Biomarkers Alliance (QIBA)

PROGRESS REPORT: AS OF MARCH 2016

This progress report is stated in terms given in the accepted Work Plan. This progress report is organized in the following subsections:

A. Review of activities responsive to each objective.

B. Combined list of groundwork projects across the objectives approved by the Steering Committee.

C. Additional descriptions of general committee progress.

A. REVIEW OF ACTIVITIES RESPONSIVE TO EACH OBJECTIVE.

An update on Objectives 1-7 is given below. Note that, in general, the data from each of these efforts have been or will be uploaded to the Quantitative Imaging Data Warehouse (QIDW) identified in the methodology for Objective 6.

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

Selected specifics:

CT Volumetry Biomarker Committee: A Task Force of the CT Volumetry Biomarker Committee is developing a Profile for assessment of small nodules in the context of lung cancer screening. They are developing document text to define evidence-based consensus standards and processes for CT imaging in the setting of lung cancer screening to allow for quantification of biologically meaningful longitudinal volume changes, with acceptable range of variance across vendor platforms. This activity is expected to result in the release of a Profile in 4Q2016.

Groundwork projects focused on volumetry of liver masses have been undertaken for the purposes of extending the first version of the CT Volumetry Profile to include quantitative assessment of liver masses. It is anticipated that a Profile for CT Volumetry of liver masses will continue to develop throughout the first year of the current contract, with a draft for public review in the latter part of 2017.

CT Lung Density Biomarker Committee: A Profile for the measurement of lung density based on quantitative CT measurements is in development and is expected to be released for public comment in 4Q2016 or 1Q2017. The Profile development is being informed by data from 2015-16 Round-5 project L.

fMRI Biomarker Committee: Work is maturing on the QIBA BOLD fMRI Profile v1.0 in efforts to optimize Blood Oxygen Level Dependent (BOLD) fMRI brain mapping for treatment planning prior to surgery or invasive treatment intervention. It is anticipated this Profile will be released for public comment in 2016. The committee is also addressing language mapping based on a Round-5 (2015-16) groundwork project, which will lead to a Profile draft v2.0 in 2017. The language mapping Profile development is being supported by 2015-16 Round-5 projects D1 and D2.

PDF-MRI Biomarker Committee: The DCE-MRI Task Force is drafting Dynamic Contrast Enhanced (DCE)-MRI Profile v2.0, which will extend DCE-MRI Profile v1.0 by addressing 3.0T field strength-specific issues as well as parallel imaging acquisition issues affecting quantitative imaging. This effort builds upon a systematic literature review process, and the success of groundwork projects funded by the previous NIBIB contract. The revised Profile should be available for public comment in 2016.

The DWI Task Force Profile v1.0 is being drafted to address technical performance standards for the acquisition of apparent diffusion coefficient (ADC) measurements in multiple organ systems. ADC phantom scanning and analysis has occurred at multiple sites, informing the Profile, which is slated for release for public comment by mid-2016. 2015-16 Round-5 project G will result in a DWI-DRO that will be critical for the conformance section of this Profile.

Two newer PDF-MRI Biomarker Committee Task Forces are in earlier stages of Profile development, focusing on Diffusion Tensor Imaging (DTI) and Dynamic Susceptibility Contrast (DSC) measures. In these Task Forces, literature review (both task forces) and phantom development (DSC-MRI Task Force, Project H) are being carried out to inform the Profiles. These two Task Forces are working to have drafts of their respective Profiles available for public comment in 2017.

MR Elastography (MRE) Biomarker Committee: The committee is actively developing a draft Profile v1.0 for quantitative MRE measurements in liver. Since substantive groundwork has already been performed and results previously published, Profile development is progressing rapidly and a draft Profile will be available for public comment in 2016.

FDG-PET/CT Biomarker Committee: Field-testing across multiple sites of the *FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy* Profile has resulted in abundant real-world user feedback, as well as a revised checklist of procedure steps. It is anticipated these changes will lead to a revision of the FDG-PET/CT Profile (v2.0), which is expected to be ready for release in 4Q2016. The revisions will be informed by the results from 2015-16 Round-5 projects B, I, and J.

PET-Amyloid Biomarker Committee: A first-generation digital reference object (DRO) and physical phantom have been designed and fabricated for the quantitative assessment of amyloid tracers and successfully imaged on a PET scanner. The committee is now revising their Profile claim based on phantom data and current literature citations, as well as data from 2015-2016 Round-5 projects A and E. This amyloid plaque neuroimaging Profile version is scheduled to be released for public comment in 2Q2016.

SPECT Biomarker Committee: The first Profile (Quantifying Dopamine Transporters with 123-Ioflupane in Neurodegenerative Disorders) addresses Parkinson's disease (PD). PD is a major health problem currently afflicting over one million Americans. The plan is to follow with Profiles addressing (a) Technetium-99m-based SPECT for planning transarterial radiotherapy, (b) SPECT as companion diagnostics for theranostics (a current use case for biopharmaceutical companies). The SPECT BC is performing a detailed review of the existing SPECT quantitative imaging biomarker literature. Methods for achieving compliance with Profile claims for precision and bias are on time-line, with expected near completion by end of 2Q2016. International enthusiasm for participation has been particularly strong from Japan and several European Union states. Multiple task groups, led by deep subject matter experts, have been hosting regular teleconference meetings to define Profile v1.0. The first Profile should be available for public review by 3Q2016.

US SWS: An initial draft of the Shear Wave Speed (SWS) Profile v1.0 has been developed. The literature review has been completed, and mitigation strategies to reduce SWS-measuring system variance have been characterized. Comparisons between liver fibrosis measurements using SWS and other techniques have been completed. The Profile is targeted for public review by 3Q2016 and is being informed by 2015-16 Round-5 projects F1 and F2.

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

Selected specifics:

CT Volumetry Biomarker Committee: The committee is evaluating options for a formal field test of the publicly-reviewed *CT Tumor Volume Change* Profile (v2.2). The Profile has been updated to align with the RSNA QIBA Metrology Work Group definitions. Claim language has been modified to reflect the committee consensus on appropriate performance thresholds based on current methods and technology.

PDF-MRI Biomarker Committee: Overseen by the PDF-MRI Biomarker Committee, the DCE-MRI Task Force is awaiting final results of the *DCE-MRI Quantification* Profile (v1.0) field test, implemented in the ACRIN 6701 study. Accrual for this study has been completed, and the results are anticipated to be available in 2016. In addition, based on groundwork projects supported by previous NIBIB contract funds, the Task Force is revising the v1.0 Profile to include 3.0T field strength and parallel imaging. It is anticipated the updated Profile will be released for public comment in 2016.

The DWI-MRI Task Force has completed its literature review as well as the development and dissemination of a NIST-traceable DWI MRI Phantom (along with associated data analysis software) funded by a previous NIBIB contract. The Profile is being recast into preparing a DWI-MRI Profile that is expected to be released for public comment by mid-2016. Key aspects of the draft Profile have been implemented in collaborative studies with the EORTC / IMI and with a group of São Paulo neuroradiologists leading a multicenter, multivendor clinical trial of DWI in glioblastoma patients to allow initial field testing of Profile recommendations.

FDG-PET/CT Biomarker Committee: The Profile was field-tested at multiple academic imaging sites to examine its feasibility and practicality. User-suggested changes to the Profile were made, as well as a revision of the checklist of conformance procedure steps. An updated version (Technically Confirmed Stage) of the FDG-PET/CT Profile will be ready by 4Q2016.

SPECT Biomarker Committee: The specifications for a “fillable” phantom are being developed for rapid deployment in multi-center environments. A concept for a solid phantom, with a traceable source of Tellurium-123 as a proxy for Iodine-123, is being developed in collaboration with subject matter experts from the National Institute of Standards and Technology. A digital reference object (DRO) based on an anthropomorphic basal ganglia plus brain phantom is being developed based on the successful prototype by the FDG PET/CT group.

US SWS Biomarker Committee: Distribution within and approval by the Biomarker Committee is pending while the Profile is converted to the new document template, and system-dependent methods descriptions are provided by the participating manufacturers. Release of the draft Profile for public comment is targeted for 3Q2016.

OBJECTIVE 3. PERFORM INDIVIDUAL GROUND WORK DATA COLLECTION AND ANALYSIS PROJECTS TO FILL GAPS IDENTIFIED DURING WORK DEVELOPING QIBA PROFILES COVERING THE FOUR MAJOR IMAGING MODALITIES, CT, MRI, RADIONUCLIDE, AND ULTRASOUND.

Selected specifics:

Each of the 2015-16 Round-5 Groundwork Projects are underway and will be completed by September 29, 2016.

CT Volumetry Biomarker Committee:

Reference Image Set for Quantification Conformance of Algorithmic Lesion Characterization, PI: Ehsan Samei, PhD – Duke University (CT Volumetry Biomarker Committee) – Project C

A two-part study design informed by an initial combined phantom and simulation-based pilot study has been developed. Appropriate performance measures have been identified and will be applied to assess bias, variance and reproducibility measures.

CT Lung Density Biomarker Committee:

Investigation of Methods of Volume Correction for Lung Density CT, PI: Sean Fain, PhD – University of Wisconsin (Lung Density Biomarker Committee) – Project L

A reference library of CT lung density histograms has been created from test-retest scans in human subjects (from the COPD Gene NLST studies) to assess consequences of inconsistent breath-hold on CT density measures in the lungs. The performance of previously published statistical models for lung volume adjustment of CT density measures is now being tested using these histograms. In addition, an imaging phantom consisting of shredded cork within a 3D printed torso is currently being developed and tested as a means to independently validate the different lung volume adjustment approaches.

PDF-MRI Biomarker Committee:

DWI-DRO Development for ADC Analysis, PI: Dariya Malyarenko, PhD – University of Michigan (PDF-MRI Biomarker Committee / DWI Task Force) – Project G

The overall project goal is to provide a DWI DRO for a relevant range of tissue diffusion values and Rician noise levels, utilizing standard diffusion DICOM attributes for software testing and acquisition optimization. The efforts of the 1st quarter of the project were focused on adequate sampling of DWI parameter space and standard DICOM meta-data definition required by conventional ADC analysis algorithms. The DRO was designed as a 3D array with ADC, SNR and *b*-value parameters varying along the 1st, 2nd and 3rd dimensions, respectively. The selected input SNR and ADC-ranges for DRO derivation were based on tissue-relevant values. A *b*-value range was specified according to the QIBA DWI phantom protocol (0, 500, 900, and 2000 s/mm^2). Diffusion-specific DICOM tags were defined according to standard (vendor-independent) DWI macro (http://dicom.nema.org/medical/dicom/current/output/chtml/part03/sect_C.8.13.5.9.html).

Dynamic Susceptibility Contrast MRI Phantom, PI: Ona Wu, PhD – Harvard University / Massachusetts General Hospital (PDF-MRI Biomarker Committee / DSC-MRI Task Force) – Project H

The primary goal of this project is to develop a prototype DSC phantom from which a gradient of susceptibility (χ) values can be measured. A secondary goal is to generate generic acquisition protocols by which one can assess the contrast-to-noise ratio of the susceptibility measurements, as well as stability across time and vendors. Finally, the third goal is to estimate reproducibility and feasibility of performing these measurements across multiple (~5) centers at multiple time points, approximately one week apart.

The project has made progress towards deliverables: meetings between the co-investigators have started, leading to decisions regarding phantom design and components, acquisition protocol, and analysis programs. The already existing DWI phantom shell is being repurposed to accommodate solutions of a gadolinium chelate varying in concentration and in two different orientations (relative to the external magnetic field). An aim is to achieve reference fluids that have similar T_1/T_2 and χ values as does human blood, from when there is no Gd-chelate present to immediately after a double bolus injection, i.e., $\chi=4 \times 10^{-7}$. A preliminary protocol has been worked out on a Siemens Trio system, lasting about 3 minutes, with plans to harmonize protocols across Siemens and GE 3 tesla systems. Collaboration with Tom Chenevert and Dariya Malyarenko at the University of Michigan are guiding development of the DSC phantom analysis software.

Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas, PI: James Voyvodic, PhD – Duke University (fMRI Biomarker Committee) – Projects F1, F2

Subjective quality assessments have been conducted for all reprocessed language fMRI scans. Commonly-used language paradigms have been identified and will be assessed for performance reproducibility. Quality control metrics are being evaluated and a subset will be selected.

PET-Amyloid Biomarker Committee:

Analyses to Support Amyloid Imaging Profile Development, PI: Dawn Matthews – ADM Diagnostics, LLC (PET Amyloid Biomarker Committee) – Project A

Necessary agreements have been put in place between ADM Diagnostics, Siemens, and Avid Radiopharmaceuticals to allow access and transfer of reconstructed amyloid PET scans and associated CT scans for use in the project. Initial scans for misalignment simulation and analysis, including a normal amyloid negative subject, a MCI subject with some amyloid, and an amyloid positive AD subject, have been selected. A specification for translational and rotational misalignments between PET and CT scans from which reconstructed images will be generated for analysis has been developed. Reconstructions are beginning soon. The original scans (selected in part due to a lack of inherent subject motion) will also be used for the other aims examining quantitative impact of ROI and reference region boundary definition.

Amyloid Brain PET Test-Retest Meta-analysis, PI: Rathan Subramaniam, MD, PhD, MPH – Johns Hopkins University (PET Amyloid Biomarker Committee) – Project E

After a systematic review of PubMed, EMBASE, and Cochrane data bases, a meta-analysis was performed to establish a repeatability co-efficient and coefficient of variation for a longitudinal Profile claim. Potential manuscripts and abstracts were identified and were included in the meta-analysis. Authors have been contacted and asked to share additional information to help extract a final repeatability coefficient.

FDG-PET/CT Biomarker Committee:

A Procedure to Facilitate Greater Standardization of PET Spatial Resolution, PI: Martin Lodge, PhD – Johns Hopkins University (FDG-PET Biomarker Committee) – Project J

This project has proceeded rapidly with progress in multiple areas. The method was developed so as to incorporate measurement of axial resolution, as well as transverse resolution (radial component). The analysis algorithm was optimized for more robust quantification. Specifically the numerical differentiation step that was vulnerable to noise in the images has been eliminated. Progress has also been made validating the method using digital reference objects and standardized physical phantoms. More complete validation over a wider range of scanner systems is ongoing. In parallel with these experimental efforts, a software development project produced a beta version that is currently being tested.

Biologic and Reader Repeatability of FDG and CT Volumetric Parameters (ACRIN 6678 & MERCK), PI: Rathan Subramaniam, MD, PhD, MPH – Johns Hopkins University (FDG-PET Biomarker Committee) – Project B

The scope of work has been submitted to ACRIN, and three readers have been assigned to visit ACRIN headquarters during 2Q2016 to perform the case review.

A PET Metabolic Tumor Volume Digital Reference Object (PET-MTV-DRO), PI: Paul Kinahan, PhD – University of Washington (FDG-PET Biomarker Committee) – Project I

The University of Washington team (Larry Pierce and Paul Kinahan) have developed a draft version of a Digital Reference Object (DRO) for testing software that calculates "Metabolic Tumor Volume" (MTV) from a PET image. The PET-MTV-DRO is based on the NEMA NU-2 Image Quality phantom, with some modifications and additional objects added. Sections though the DICOM images are shown below.

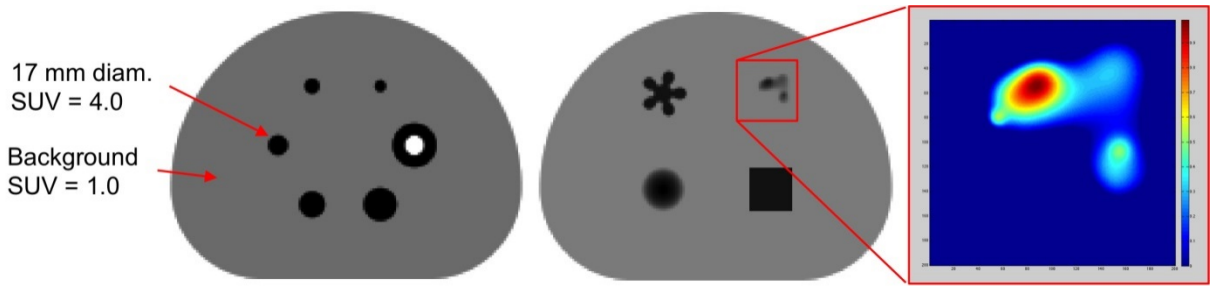

Figure. Two sections through the PET-MTV-DRO. All objects are three dimensional, and one object as indicated has variable SUVs.

Noise-free and noisy images have been prepared, and the PET-MTV-DRO is currently being prepared for distribution within the FDG-PET/CT Biomarker Committee for testing on different software analysis packages. After testing, it will be used as a reference check for the Round-5 groundwork project "Biologic and Reader Repeatability of FDG and CT Volumetric Parameters" (PI: Rathan Subramaniam), Project B.

US SWS Biomarker Committee:

Analysis of Sources of US SWS Measurement Inter-System Variability, PI: Mark Palmeri, MD, PhD – Duke University (SWS Ultrasound Biomarker Committee) – Projects F1, F2

Experimental data from all of the sites that participated in the Phase II phantom study are being analyzed, and preliminary statistical analyses are quantifying site and system variables. Viscoelastic digital phantom datasets have been augmented to include more parameters and have been uploaded to the QIDW US SWS Community.

Cross-Modality:

Aggregated Measures of Agreement for QIB Validation: An Open Source Toolkit, PI: Daniel Barboriak, MD – Duke University – Project K

The purpose of this project is develop open-source software to calculate aggregated measures of agreement in order to facilitate image analysis algorithm development, comparative analysis of algorithm output, and demonstrate technical compliance. This project will further develop a toolkit that will calculate the following statistics: concordance correlation coefficient, root mean square deviation, total deviation index, Bland-Altman limits of agreement, and Sigma analysis based on estimates of allowable total error. An existing open-source

package, QIBA DRO Evaluation Tool (QDET), developed by Hendrik Laue, is being used as a starting point. This package's source code has been downloaded, and preliminary analysis of it has been conducted. The software requires some Python modules, such as WxPython and Matplotlib, that are not part of the standard Python installation. These additional modules have been obtained and installed. Python has several ways to package and release software as an executable application; these are currently being investigated to determine which to use.

One early goal was to validate statistics in the existing QDET statistical packages against known results for other software packages. This was accomplished for mean, median, correlation, covariance, and root mean squared deviation. We have implemented some changes including increasing the number of decimal places included in the report. We plan to ensure that NaN values in software output being tested are treated correctly. We are in the process of completing the verification of the statistical figures of merit and performing the programming so that these figures are provided as part of the GUI or .csv files for use in further analysis.

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 QIBA PROFILES.

Selected specifics:

CT Volumetry Biomarker Committee:

Reference Image Set for Quantification Conformance of Algorithmic Lesion Characterization, PI: Ehsan Samei, PhD – Duke University (CT Volumetry Biomarker Committee) – Project C

Development of a two-part study composed of 1) a reference image dataset with synthetic and virtually inserted lesions, and 2) a collection of clinical patient cases with real and virtually inserted lesions has begun. A standard chest CT protocol has been used with the reference image dataset. Clinical cases used in the previous QIBA Group 3A challenge have been identified for use. Virtual lesion insertion techniques previously used in a pilot study have been identified for application in the current framework.

PDF-MRI Biomarker Committee:

The DWI-MRI Task Force has completed its literature review, the development and dissemination of a NIST-traceable DWI MRI Phantom (along with associated data analysis software) funded by a NIBIB Round-3 project. The DWI-MRI Profile that is expected to be released for public comment by mid-2016. Key aspects of the draft Profile have been implemented in collaborative studies with the EORTC / IMI and with a group of São Paulo neuroradiologists leading a multicenter, multivendor clinical trial of DWI in glioblastoma patients to allow initial field testing of Profile recommendations. A manuscript is being drafted on the round-robin study with the DWI phantom.

DWI-DRO Development for ADC Analysis, PI: Dariya Malyarenko, PhD – University of Michigan (PDF-MRI Biomarker Committee / DWI Task Force) – Project G

Development of a DWI-DRO has begun for ADC analysis, as well as identifying DWI tissue diffusion parameter range specifications and defining meta-data (DRO DICOM) formats. (See Objective 3)

Dynamic Susceptibility Contrast MRI Phantom, PI: Ona Wu, PhD – Harvard University / Massachusetts General Hospital (PDF-MRI Biomarker Committee / DSC-MRI Task Force) – Project H

Two phantom prototypes to estimate reproducibility across imaging sites have been designed and are being fabricated. A high-level generalized imaging protocol to be utilized with the phantoms has been developed. (See Objective 3)

SPECT Biomarker Committee:

The specifications for a "fillable" phantom are being developed for rapid deployment in multi-center environments. A concept for a solid phantom, with a traceable source of Tellurium-123 as a proxy for Iodine-123, is being developed in collaboration with subject matter experts from the National Institute of Standards and Technology. A digital reference object (DRO) based on an anthropomorphic basal ganglia plus brain phantom is being developed based on the successful prototype by the FDG PET/CT group.

Groundwork projects are being developed that will propose characterizing the linearity of the confidence intervals surrounding precision and bias, which are suspected of increasing with disease severity. This groundwork can be conducted with the fillable and solid phantoms that are being designed.

OBJECTIVE 5. DEVELOP PROCEDURES AND PROCESSES FOR HARDWARE AND SOFTWARE MANUFACTURERS TO DEMONSTRATE CONFORMANCE WITH QIBA PROFILES.

Selected specifics:

CT Volumetry Biomarker Committee:

The committee has prepared a checklist of actions for each "actor" to establish Profile conformance, divided into activities related to 1) patient handling activities, 2) scan acquisition and reconstruction, 3) image quality checks, and 4) segmentation and analysis. Procedures for claiming conformance have been completed and are now part of the profile.

Conformance assessment will be conducted through a challenge to the imaging science community. Each participant is to use their segmentation algorithm to perform volume estimation on lesions with locations that are provided *a priori*. This will involve performing image-based segmentation on datasets generated using (1) an anthropomorphic phantom with synthetic and virtually inserted nodules, and (2) clinical images containing real lung lesions and virtually inserted lesion models.

CT Lung Density Biomarker Committee:

Committee members are actively working with vendors to develop models for harmonizing CT lung density measures across different scanner manufacturer and model. This effort primarily uses the COPD Gene phantom modified to contain NIST-certified foam standards that fall within the ranges expected for CT density of lung parenchyma. A first round of scans were performed by the vendors and a preliminary correction model was developed to achieve consistent performance within 2 Hounsfield units across four vendors (GE, Siemens, Philips, and Toshiba). A second round of phantom scans with a greater number of scanner models and an updated anthropomorphic phantom is currently under way involving sites in Iowa and Wisconsin.

PDF-MRI Biomarker Committee:

The conformance section of the DWI Profile will be updated according to the revised Profile template. The DTI, DSC, and DCE v2.0 efforts are fairly early in their Profile development, but conformance will be something they address as their claims and protocols become more firm.

fMRI Biomarker Committee:

The Round-5 language fMRI groundwork projects (D1, D2) will identify reproducibility benchmarks for language function tasks that can be used as goals for conformance testing by manufacturers of fMRI task software. Currently there are no standards for such tasks, nor benchmarks for evaluating the quality of data produced by different tasks.

FDG-PET/CT Biomarker Committee:

Representatives of each of the four vendors of PET/CT scanners systematically reviewed and commented upon their current and future ability to achieve conformance with the FDG-PET/CT profile as part of the field-testing project. Specific comments and suggestions from the vendors regarding feasibility and practicality were provided to the committee who will discuss and incorporate appropriate changes, potentially as part of the technically confirmed document draft to be released by 2017.

PET-Amyloid Biomarker Committee:

A full draft version of the Profile provided to all BC members is undergoing final internal review with incorporation of the feedback in preparation for public comment. As part of this review, the group will identify the necessary Profile conformance procedures as the logistics for the stage of feasibility testing are developed.

SPECT Biomarker Committee:

Hardware:

Groundwork projects are being constructed that will propose characterizing the linearity of the confidence intervals surrounding precision and bias, which are suspected of increasing with disease severity, that is, increasing with decreasing signal-to-noise ratios, as the signal becomes lost in patients with Parkinson's disease. This groundwork can be conducted with the fillable and solid phantoms that are being designed.

Software:

In addition to analyzing the phantom and DRO data, it is anticipated that the SPECT Biomarker Committee will be able to quickly assemble a test set from patients and matched controls with which all software vendors can test their analytical processes. There are several potential sources of human data that can be donated. Several sample populations are known in which subjects signed informed consent to allow their data to be contributed for future imaging research before their trials started. This will be yet another example of the SPECT Biomarker Committee moving rapidly based on trails blazed by other groups, as this project would be constructed to resemble the software comparison exercise pioneered by the CT Volumetry Biomarker Committee.

US SWS Biomarker Committee:

Requirements for demonstrating conformance are under discussion. It is currently standard operating procedure for manufacturers to demonstrate performance of operational modes, such as blood flow imaging, with phantoms. Therefore, it is anticipated that phantom tests of shear wave speed estimation under various operating conditions will be an acceptable test for vendor conformance.

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

Note that in general the data from each of these efforts have been, or will be uploaded to the Quantitative Imaging Data Warehouse identified in the Methodology for Objective 6.

Selected specifics:

CT Modality:

Reference Image Set for Quantification Conformance of Algorithmic Lesion Characterization, PI: Ehsan Samei, PhD – Duke University (CT Volumetry Biomarker Committee) – Project C

Reference image set data and associated metadata will be uploaded to the QIDW upon completion of the groundwork project.

MR Modality:

Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas, PI: James Voyvodic, PhD – Duke University (fMRI Biomarker Committee) – Projects D1, D2

This Round-5 language fMRI project will allow the upload of representative human fMRI data sets (in anonymous form) to the QIDW to support our reproducibility findings. We will include examples of 2 language tasks from different subjects, representing different quantitative levels of reproducibility metrics.

DWI-DRO Development for ADC Analyses, PI: Dariya Malyarenko, PhD –University of Michigan (PDF-MRI Biomarker Committee) – Project G

The DWI-DRO will be uploaded to the QIDW, as was the previous MR modality DRO developed with the support of NIBIB contracts, i.e., the DCE-MRI DRO.

Ultrasound Modality:

Analysis of Sources of US SWS Measurement Inter-System Variability, PI: Mark Palmeri, MD, PhD – Duke University (SWS Ultrasound Biomarker Committee) – Projects F1, F2

Elastic and viscoelastic digital phantom data (finite element simulation data) has been uploaded to QIDW, which has been downloaded by academic and industry members of the QIBA community.

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

Support for all the above committee work, funded project management meetings, conference calls and travel continue to be administered and provided by the RSNA/QIBA staff, QIBA Chair / Vice-chair, and Scientific Liaisons.

B. COMBINED LIST OF GROUNDWORK PROJECTS APPROVED BY STEERING COMMITTEE ACROSS THE OBJECTIVES FOR ROUND-5 (2015-2016) FUNDING.

Project Number	Biomarker Cmte	Project Title	Investigator
A	PET Amyloid	**Analyses to Support Amyloid Imaging Profile Development**	Dawn Matthews, ADM Diagnostics, LLC
B	FDG-PET	**Biologic and Reader Repeatability of FDG and CT Volumetric Parameters (ACRIN 6678 & MERCK)**	Rathan Subramaniam, MD, PhD, MPH, Johns Hopkins University
C	CT Volumetry	**Reference Image Set for Quantification Conformance of Algorithmic Lesion Characterization**	Ehsan Samei, PhD, Duke University
D1, D2	fMRI	**Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas**	James Voyvodic, PhD, Duke University Jay J. Pillai, MD, Johns Hopkins Univ
E	PET Amyloid	**Amyloid Brain PET Test-Retest Meta-analysis**	Rathan Subramaniam, MD, PhD, MPH, Johns Hopkins University
F1, F2	SWS US	**Analysis of Sources of US SWS Measurement Inter-System Variability**	Mark Palmeri, MD, PhD, Duke Univ Shigao Chen, PhD, Mayo Clinic
G	PDF-MRI (DWI TF)	**DWI-DRO Development for ADC Analysis**	Dariya Malyarenko, PhD, University of Michigan
H	PDF-MRI	**Dynamic Susceptibility Contrast MRI Phantom**	Ona Wu, PhD, Harvard/Mass General Hospital
I	FDG-PET	**A PET Metabolic Tumor Volume Digital Reference Object (PET-MTV-DRO)**	Paul Kinahan, PhD, University of Washington
J	FDG-PET	**A Procedure to Facilitate Greater Standardization of PET Spatial Resolution**	Martin Lodge, PhD, Johns Hopkins University
K	Cross Modality	**Aggregated Measures of Agreement for QIB Validation: An Open Source Toolkit**	Daniel Barboriak, MD, Duke University
L	Lung Density	**Investigation of Methods of Volume Correction for Lung Density CT**	Sean Fain, PhD, University of Wisconsin

C. GENERAL PROGRESS ON ACTIVITIES BEYOND THE FUNDED PROJECTS

Additional updates from the committees are as follows.

CT Volumetry Biomarker Committee

The CT Profile describing measurements of change in tumor volume for advanced disease (the “CTV” Profile) has been updated to align with the Metrology Work Group definitions, and extensive additional public comments have been incorporated. The claims have been updated to reflect the committee consensus on appropriate thresholds of performance based on the state of the current methods and technology, as demonstrated in prior groundwork projects.

A protocol for a field test of the QIBA Profile is being re-evaluated to incorporate considerations of funding and logistics. The intent is to first carry out a feasibility assessment to determine whether sites can take the QIBA Profile and execute its requirements. The goal after this will be to collect data on the precision of clinical lesion measurements so the precision can be combined with prior information on bias to provide a more complete description of measurement variability.

A CT liver phantom has been designed and fabricated. Scans have been performed on the phantom, and analysis of the resulting scan data has been carried out.

The algorithm challenge group (Task Force 3A) has prepared a manuscript for publication and secured permission to publish. A publication from the phantom data project is in the revision process after submission. The group dedicated to this project is now organizing to provide support for the upcoming "field test" of the CT volumetry biomarker profile.

The Lung Nodule Assessment in CT Screening Task Force has been working to ensure that the small nodule claims are consistent with the established claims of the advanced disease CT Volumetry Profile. Published results and unpublished data from members of the group have been used to inform development of claim details. The committee has collaborated with manufacturer representatives to obtain technical parameter guidance for individual scanner models for quantitative applications. The small nodule Profile will be released for public comment in 2016.

CT Lung Density Biomarker Committee

A draft Profile and claim development are in progress, based on critical evaluation of literature, for a lung density protocol. The acquisition and reconstruction specification of CT images has been completed and is being evaluated by a working group of vendor scientists who are developing compliance procedures using the COPDGene Phantom. The image analysis section of the Profile is nearly completed.

The group has developed recommendations for pulmonary quantitative CT (qCT) protocols to be used on multiple vendor scanners using automatic exposure control (AEC) and iterative reconstruction (IR). These protocols should guide efforts to lower CT dose for ongoing and future clinical research studies with qCT of the lungs focused on measures of parenchymal density. These protocols may be used in conjunction with low dose screening for lung cancer, and will be immediately implemented in the COPDGene study.

A Task Force of CT vendor scientists has been formed to develop a compliance checklist and to suggest changes to the acquisition and reconstruction parameter specifications in efforts to mitigate measurement bias. The Task Force has organized a project that involves scanning the same COPDGene Phantom using three radiation doses on two models of each vendor's CT scanners. The CT Vendor Task Force has completed a first round of scanning and is planning to complete a second more rigorous round of scanning by March 2016.

The Biomarker Committee has completed a meta-analysis of the CT lung density repeatability literature, thus finalizing their measurement repeatability claim for assessing emphysema progression. The meta-analysis may be the basis for a submission of a manuscript for publication in the peer-reviewed literature.

PDF-MRI Biomarker Committee

PDF-MRI Biomarker Committee Task Forces (TFs) have been formalized for the development of a v2.0 DCE-MRI Profile (which will address 3.0T and parallel imaging applications), DWI Profile activities, DSC Profile efforts, and anisotropic diffusion MRI (DTI) Profile development. In addition, the PDF Biomarker Committee

has developed a suite of digital reference objects (DROs) for DCE-MRI, along with tools for quantitatively comparing the bias and precision of DCE software analysis packages.

The DCE-MRI TF is presently focused on defining systematic literature review procedures, and their application for select organ/tumor sites, to support the DCE-MRI v2.0 Profile claims. The DWI TF is recasting its Profile language into the revised QIBA Profile template. The DWI TF successfully developed a physical phantom and related analysis software, and has started development of a DWI DRO. The DSC and DTI task forces are identifying appropriate QIBs for claim development.

An open-source software package to facilitate comparison of parametric images generated by different DCE-MRI analysis packages when utilizing the DRO created as part of a previous funded project. This software is capable of importing 2D and 3D DICOM images, or binary data formats, as well as imaging formats such as TIFF and PNG. It generates difference and ratio maps (exportable as PNG), scatter diagrams and box-plots, and ANOVA statistics to more easily compare analysis packages. The summary results are exported to a pdf file. This software is available for Mac, Windows, and Linux operating systems, and further development continues past the original project timeline. The software is available on the QIDW and can be used for demonstrating compliance of software.

An automated software analysis package was developed to be used with the QIBA DCE-MRI Phantom for site qualification / conformance as well as ongoing quality control for DCE-MRI studies. The software was tested using phantom data acquired for site qualification for the ACRIN 6701 clinical trial. The analysis software and user manual have been uploaded to the QIDW, along with example data from various scanners and the associated reports produced by the software.

A DCE-DRO extension project resulted in a broader range of baseline T1 values to better simulate lesions in breast or bone marrow, the addition of 3.0T DRO data (adjusted baseline tissue and vascular T1 values), and the incorporation of an option for a vascular input function simulating reduced cardiac output. This project provides a more comprehensive set of DCE-MRI and T1 relaxometry DROs for compliance evaluation of analysis packages.

The DWI TF is finalizing the initial version of the isotropic diffusion-weighted imaging (DWI) QIBA Profile, which incorporates results from two Round 3-funded (2013-2014) groundwork projects (DWI-MRI ADC Phantom, PI Michael Boss, and Software Development for Analysis of QIBA DWI-MRI ADC Phantom Data, PI Thomas Chenevert). A production phantom for DWI was finalized, fabricated, and disseminated across 13 QIBA test sites to assess reproducibility of phantom data collected over time. Acquired phantom data has been aggregated on the RSNA QIBA/RIC QIDW, downloaded by NIST scientists, and reduced to repeatability/reproducibility/bias statistics using the Round-3 funded DWI analysis software to further support DWI Profile claims. Results were presented at the 2015 RSNA Annual Meeting. DWI phantom scan procedure instructions are being further refined specifically for each MRI vendor platform. This process will enable systematic and consistent comparison of results, better establishing the reproducibility of the ADC biomarker.

fMRI Biomarker Committee

The fMRI Biomarker Committee continues work on v1.0 of its Profile for pre-surgical mapping of eloquent brain tissue. Refinements to the clinical claims and context were made, particularly the acquisition guidelines, as well as accompanying appendices with detailed performance specifications. Likewise, members are in the process of completing Section 3, Profile Details, specific to the mapping of motor cortex. To inform conformance procedures, members are conducting groundwork studies focused on software analysis specifications.

The fMRI Bias Task Force meets bi-weekly to focus on the issue of bias in the fMRI measurand. This activity will inform the Profile claims definition and guide development of methodological sequences for image analysis that best achieve the claims.

fMRI-DRO testing was completed at 8 sites, all analyzing the same bilateral hand motion DRO but with each site employing its own standard fMRI processing and analysis workflow. The activation map results accompanied by data analysis forms describing workflow were collected from each site. For the period through September 2015, generation and testing of advanced DROs for head motion in fMRI were performed. These include DROs from various combinations of selected empirical and synthetic datasets wherein amplitude and spatial distribution of task-related fMRI signals and associated fMRI noise were controlled. By fully specifying "ground truth" in this way, subsequent post-processing and display methods can be tested for the ability to accurately recover the original signal distributions and to quantify any inaccuracies that might be present. These DROs, containing realistic task signal and noise variability (including motion, performance, and neurovascular uncoupling sources of variance), have been uploaded to the QIDW.

DROs from various combinations of task-related fMRI signals of known ground truth and containing realistic task and noise variability (including motion, performance, and neurovascular uncoupling (NVU) sources of variance) have been uploaded to the QIDW. These can be used for trial and comparison of fMRI analysis and correction methods for coping with the variance of the BOLD signal in the primary motor cortex as a function of presence or absence of NVU.

Members of the fMRI Biomarker Committee contribute to the DICOM Working Group 16 fMRI task force. The proposed DICOM work item will build on recent quantitative imaging support added to the standard, with new elements created as necessary to represent fMRI acquisition, activation maps, and task paradigms. The functional requirements incorporated by WG-16 fMRI were drawn from work done in the QIBA fMRI Biomarker Committee.

FDG-PET/CT Biomarker Committee

An FDG-PET/CT Profile Field Test was performed to thoroughly examine the feasibility and practicality of the QIBA Profile in the specific context of three academic PET imaging centers using imaging equipment from three different manufacturers. The field test resulted in Profile revisions and identified impractical or ambiguous specifications, and initiated discussion regarding how to formalize this QIBA profile revision workflow procedure. A reduced list of 36 specifications was extracted from the QIBA FDG-PET Profile that can serve as a simple checklist for imaging sites to determine their QIBA conformance. This distillation from the much longer set of QIBA Profile specifications was based on feasibility and relevance to quantitation. Profile specifications relevant to PET/CT devices were sent to the four manufacturers to evaluate their own system's compatibility with the Profile.

A follow-up field test was initiated, in which the site-relevant Profile specifications were evaluated for feasibility at 11 sites (academic and non-academic). Additional incompatibilities between Profile specifications and imaging site practices were identified. From this, follow-up discussion amongst committee members was held to determine whether individual specifications should be modified to be more compatible with sites' practices, or whether sites should be encouraged to modify their practices.

A QIBA/NIBIB funded DRO extension project increased the functionality of the previous PET-CT DRO in efforts to test for (a) PET/CT display alignment (b) SUVpeak calculation and (c) Region of Interest (ROI) fidelity.

PET-Amyloid Biomarker Committee

The committee has made substantive progress in drafting a Profile whereby 18F-Amyloid tracers may be used in clinical trials for assessing subjects with cognitive impairment. The Profile is based on a longitudinal claim and uses the change in SUVR as the measurand. There continues to be excellent participation on the teleconferences by members of all 18F-PET radiotracer manufacturers and equipment manufacturers as well as key subject matter experts from clinical, academic, imaging core lab, medical physics and systems engineering backgrounds. The draft Profile is currently undergoing the final phase of internal committee review.

The claim language is being revised based on current literature citations reviewed by a Task Force within the committee. The Profile is slated for distribution for public review during the 2Q2016.

One of the previous NIBIB projects was for co-development of a first generation digital reference object (DRO) and physical phantoms for quantitative assessment of amyloid tracers. The Amyloid committee felt that amyloid imaging, in particular, and the field of neuro-PET imaging in general, would significantly benefit from a well-designed quantitative brain phantom. Co-development has been completed for (1) a PET Brain DRO with separate gray and white matter anatomic compartments plus CSF, with well-defined reference regions for SUVR calculations, and (2) a precision physical brain phantom with anatomic compartments identical to the DRO. The physical phantom has been successfully imaged on a PET scanner.

SPECT Biomarker Committee

Driven by mounting evidence that quantification adds value to SPECT, and the accelerating production of commercial software packages to capture that value, a large group of physicians and scientists, from industry, academia, and governmental agencies have now begun developing a SPECT Profile. International enthusiasm for participating has been particularly strong from Japan and several European Union states. The initial focus will be on dopamine transporter brain scans to assist in the evaluation of patients with parkinsonian symptoms. Use cases that are expected to follow include quantification of trans-arterially administered macro aggregated albumin for radiotherapy planning in patients with liver metastases, and targeted theranostics for selecting candidates for treatment with companion therapeutics in the emerging fields of antibody and small molecule drug conjugates. Four Task Forces, led by deep subject matter experts, hold regular meetings to define the first Profile and claim language. Although this is a relatively new initiative, solid progress has been made toward the completion of the first Profile (v1.0), which is expected to be released to public comment by 3Q2016.

US SWS Biomarker Committee

The original goal of the SWS US Biomarker Committee was to develop a QIBA Profile for a single biomarker: ultrasound shear wave speed (SWS) as a measure of liver stiffness which correlates with the degree of liver fibrosis/cirrhosis present. Major efforts center on completing groundwork studies and publishing results, continuing to understand and account for sources of bias in SWS estimation with ultrasound imaging systems, continuing to determine sources of variance in these estimates, minimizing those contributions, and finalizing the draft Protocol and Profile documents.

Three recent areas of groundwork efforts were: (1) Validation of simulations and phantoms mimicking elastic and viscoelastic properties of liver, (2) Comparison of SWS measurements in uniform liver-mimicking phantoms using ultrasound imaging systems, the established US non-imaging system, and, initially, MR elastography, and (3) Sources of measurement variability in shear-wave elasticity techniques. It is anticipated that the physical and digital phantoms will be part of these efforts, as well as of the conformance procedures.

Simulation data sets have been developed and posted on the QIDW for use by research groups and manufacturers. The goal is to find approaches that allow different ultrasound systems to achieve the same SWS results from data generated using appropriate simulated visco-elastic materials. Simulated data representing elastic (lossless) and viscoelastic (tissue-mimicking) media have been released for download by interested parties, and several manufacturers have begun to look at the materials to determine if it is technically and economically feasible to analyze test data using their proprietary software. A comprehensive comparison of simulation results obtained with two common commercial finite element modeling software has been performed, and the corresponding code to process the data are available on GitHub. If this plan is successful, use of digital reference objects (DROs) to analyze ways to achieve better agreement in SWS values will become a real possibility.

Data have been acquired to investigate sources of variance from comorbidity, biological variability, and measurement methods that might affect shear wave speed estimate correlation with fibrosis. Studies were based on a literature analysis of 1548 publications from which 102 SWS papers included a study of one or more confounding factors. A further analysis of the potential for steatosis and/or inflammation to affect the correlation of SWS with liver fibrosis was performed using results obtained for 242 subjects.

A standardized plan for archiving clinical and phantom data into the QIDW is being devised and will be included as an appendix to the QIBA Profile.

A first draft of the QIBA ultrasound Profile “SWS Estimation of Liver Fibrosis” has been created. Distribution within and approval by the Biomarker Committee is pending while the Profile document is converted to the new document template provided by the Process Committee and system-dependent methods descriptions are provided by the participating manufacturers. A standardized SWS data collection report form has been developed for inclusion in the Profile appendices.