HHSN268201000050C, RECOVERY
Quantitative Imaging Biomarkers Alliance (QIBA)

PROGRESS REPORT: AS OF SEPTEMBER 30, 2012

EXECUTIVE SUMMARY

Note: This is the second Annual Report. The Final Report will be submitted at the end of our NCE in March 2013. This 2nd Annual Report reflects the current status of each of the projects.

During the second contract year QIBA has improved its processes for the development, validation, qualification and use of accurate, repeatable quantitative imaging biomarkers across instruments and settings. The paradigm that has evolved is to create, for each imaging biomarker, documents referred to as the UPICT Protocol and the QIBA Profile. Definitions of these documents can be found on the QIBA wiki at http://qibawiki.rsna.org/index.php?title=What_Are_Profiles_and_Protocols%3F#Definitions_and_Descriptions_for_QIBA_Profiles_and_Protocols. To create these documents, QIBA coordinates broadly with various stakeholders, including professional imaging societies, academic centers, imaging device manufacturers, the pharmaceutical industry and federal agencies. Profiles have been released for CT Volumetry and DCE-MRI, and are in development for FDG-PET SUV, lung CT densitometry and airway measurements for COPD, fMRI for pre-surgical mapping and ultrasound SWS for liver fibrosis. We continued our partnership with the FNIH Biomarkers Consortium during year 2, completing substantial updates to the Briefing Documents for FDG-PET and CT Volumetry, submitting a formal revision on the latter to the FDA in September.

We have completed the majority of the 26 projects funded through this contract to further improve the accuracy and precision of imaging biomarkers. More research is needed regarding sources of variability and the impact of various proposed mitigation strategies. Status reports on all those projects are given below. QIBA is increasingly visible as a collaborative, multidisciplinary infrastructure to foster research, approval, and use of quantitative imaging biomarkers.

This progress report is stated in terms given in the accepted Work Plan. Work Tasks 11-19 in the SOW are associated with the overall program. Some of these do not lend themselves to scheduling in Gantt chart format, but are associated with specific events during the contract term. A status report on those activities is given in Section A below.

Work tasks 1-10 generally comprise the elements of our roadmap for each biomarker. Section B lists specific experimental groundwork projects that are ongoing and/or have been allocated NIBIB contract project funding. Sections C-F provide a high-level statement of what has been done in the period since last report and present updated Gantt charts to reflect the progress and any plan adjustments for CT, FDG-PET, MRI, and our new initiative in Ultrasound respectively.

A. OVERALL PROGRAM TASKS 11-19 (FOR SECOND REPORTING YEAR).

Our initial plan with respect to each numbered task is given in italics, and the status is given in BOLD font:

NIBIB Task 11. Stimulate an interest in disseminating and implementing QIBA solutions to assess their feasibility and efficacy more broadly.

a. *We will schedule two QIBA meetings per year, one in May and the other at the RSNA Annual Meeting in November, with agenda set for this purpose.*

During the second contract year we held well-attended public and working meetings during the RSNA Annual Meeting in November 2011, and our annual QIBA meeting in May 2012. The RSNA Annual Meeting held in November/December 2011 provided opportunities for both formally scheduled as well as informal meetings related to QIBA. Formally scheduled sessions included Special Interest Session - Quantitative Imaging Biomarkers for Clinical Care and Research and a Technical Committees Working Meeting.

b. *We will schedule educational content in the RSNA Annual Meeting to disseminate information to a wide audience.*

At the 2011 RSNA Annual Meeting, our technical committees each prepared and presented a poster associated with our QIBA Kiosk exhibit. General updates were also provided in a Special Interest Session on Monday, November 28th, 2011.

c. *We also publish a QIBA Newsletter electronically.*

d. **During the contract year, we published the "QIBA Newsletter" in December 2011 and March 2012. The March 2012 issue included featured articles "Standardization of Clinical Trial Image Acquisition is Essential for Establishing Clinical Utility" by GARY S. DORFMAN, MD and "Challenges in Tackling Quantitative DCE-MRI" by ALEXANDER GUIMARAES, MD, PhD.**

NIBIB Task 12. Encourage adoption, integration and clinical education of validated QIBA solutions by the research and industry community.

a. *We have begun to schedule company-specific meetings with managers of medical device companies to explain QIBA, and solicit their feedback.*

Our technical committees continue to have broad involvement from the supplier community, including medical device as well as software companies. Building on the meetings we held last year with manufacturers, we have held a discussion to bring together the 3rd party manufacturers of display stations for FDG-PET (with discussion among value-added software companies largely having been driven by CT analysis companies) at the annual RSNA meeting in order to present the QIBA perspective and why the Profiles will matter to them. We also made a presentation to the Nuclear/PET MITA meeting about QIBA, and are planning on doing so again this year.

In the technical committees, several projects involve key supplier participation. In FDG-PET and DCE-MRI, synthetic data objects have been created and are being evaluated by a number of companies. In CT Volumetry, the pivotal algorithm performance "Challenge" has been organized with the following participants (the pilot having concluded earlier with a partially overlapping group of participants):

- **Median Technologies**
- **Fraunhofer Mevis**
- **Siemens**
- **Toshiba**
- **Icon Medical Imaging**
- **Columbia University**
- **INTIO, Inc.**
- **NYU Langone Medical Imaging Center**
- **Perceptive Informatics**

The FDG-PET DRO has been used by the following:

- **GE**
- **Hermes**
- **Keosys Keosys N/A**
- **MedImage**

- **MIM**
- **OsiriX**
- **Philips**
- **PMOD**
- **Segami**
- **Siemens**

b. *We will work with the Pharma Imaging Group to get QIBA solutions integrated into pharmaceutical industry drug trials.*

During the contract year, we completed the field test of our first controlled document, a protocol for CT volumetry in lung cancer. We hold regular status discussions with the Pharma Imaging Group (PIG), and the PIG chair, Jim Conklin, has joined our steering committee.

c. *We will work with ACRIN, the SNM Clinical Trials Network, and other academic organizations to get QIBA solutions integrated into clinical trials.*

We continue to refine the process and to promote the venue of the Uniform Protocols for Imaging in Clinical Trials (UPICT) to discuss details for specific consensus protocols. The most active project in this regard is working towards a consensus protocol for quantitative FDG-PET and we also have made progress with an Alzheimer's protocol.

NIBIB Task 13. Develop an initial consensus on quantitative imaging biomarkers qualification by coordinating broadly with various stakeholders, including professional imaging societies, academic centers, imaging device manufacturers, and drug industry.

a. We will use breakout groups at the annual "Imaging Biomarkers Roundtable" to achieve this objective, as well as collective input from the Pharmaceutical Imaging Group, meetings with individual medical device manufacturers, and recommendations from relevant academic workshops.

In this second year, we have further matured our processes, particularly those associated with review and release of profile documents. We have also made substantial progress on the meaning and actualization of compliance. This continues to be an active area of development for us. Additionally, we have now formed an active Ultrasound Modality Committee, which is currently working on Shear Wave Speed (SWS).

b. For consensus related to formal FDA qualification of imaging biomarkers, we will work with the FNIH Biomarkers Consortium and the Critical Path Institute as well. This collaboration will occur by monthly conference calls, as well as collective work on the Briefing Documents and Data Packages to be submitted to the FDA.

We continued our partnership with the FNIH Biomarkers Consortium during year 2, completing substantial updates to the Briefing Documents for FDG-PET and CT Volumetry, submitting a formal revision on the latter to the FDA in September. We have also continued our engagement of potential data donors, presently including active discussions with Merck, Astra Zeneca, and Genentech/Roche. An approach whereby we prepare and submit quarterly updates to the Briefing Documents highlighting additional study designs and data sets has been assembled.

NIBIB Task 14. Organize and manage relationships in a collaborative, multi-disciplinary environment that fosters communication among imaging groups and other medical disciplines involved in the research, approval and use of quantitative imaging biomarkers.

a. *The QIBA Steering Committee meets once per month by phone and in person twice a year.*

We have held monthly teleconferences with the Steering Committee as well as a face-to-face meeting in Chicago in May 2012. We continued our practice of meeting monthly by phone to monitor project progress.

b. *The Modality Committees convene on an as-needed basis.*

In the second year, we have formed a new Modality Committee for Ultrasound, generalized the MRI work to include "perfusion, diffusion, and flow" (PDF), and started a new CT volumetry initiative in Lung Nodule Assessment in CT Screening. Each of these has been approved by the Steering Committee.

c. *The Technical Committees meet biweekly, with groundwork subgroups meeting as needed, often weekly. All of these QIBA groups are composed of individuals from the named stakeholder groups.*

All of the teams meet by phone at least biweekly, and many meet more frequently.

NIBIB Task 15. Create and implement a process by which standardized and harmonized systems emerge that are sufficient for the development, validation, qualification and use of accurate, repeatable quantitative imaging biomarkers across instruments and settings.

The QIBA Steering Committee, with input from the Technical Committees, has begun to develop such processes. These will be documented in a process manual by the end of year 1 (Sept 30, 2011). We will provide a feedback (public comment) mechanism with a formal update mid-way through year 2 (March 30, 2012).

We have continued to mature our process in this contract year:

Profile Development and Release Stages: The Technical Committee Profiles are at different stages of completion, which needs to be recognized but then harmonized in the QIBA Process. A similar process was employed by IHE. A proposed nomenclature for classifying the evolutionary stage of Profiles based on the intensity of input, testing and consensus achieved to date has been approved by the Steering Committee.

Metrology Terminology and Methods: To begin to address challenges deriving from lack of standardized measurement terminology and methods used by QIBA Technical Committees and the imaging field in general, it was decided to convene a QIBA Metrology Workshop, which was held in early April. Groups were formed to address Terminology, Technical Performance Characteristics and Algorithm Comparisons. Varying stages of progress have been made but all groups agreed that the resulting guidelines will be valuable to the QIBA Technical Committees and should be implemented into the QIBA Process. We have conducted many weekly call sessions across three workgroups of this initiative in converging consensus metrology terminology and statistical approach. The group has been working to prepare for a second in-person workshop scheduled for October 15-16, 2012.

Harmonizing Profile Language: Profile editors have been working together to consider uniform format and terminology. Specifically with respect to Claims, the Metrology Workshop participants will provide input on approaches that would provide uniformity.

NIBIB Task 16. Clarify and optimize the regulatory pathway by which quantitative imaging biomarkers enter the market.

As detailed above under Task 13, we have continued the engagement with FDA regarding biomarker qualification. Also during the second year we produced a detailed response to the FDA's public comment period for "Standards for Clinical Trial Imaging Endpoints." In the last 6 months, we have completed projects which produced data capable of being used directly in regulatory pathways. We are also now providing additional specific details on how to establish compliance with QIBA profiles that may use data sourced and/or curated by QIBA efforts.

NIBIB Task 17. Establish a process for relating biomarkers to disease areas, setting the clinical context and, based on the clinical context, identifying and prioritizing what biomarkers to pursue.

We will use breakout groups at the annual "Imaging Biomarkers Roundtable" to achieve this objective.

Our new Modality Committee for Ultrasound is now active, the MR Modality Committee has actualized its extension for other biomarkers beyond DCE, and the CT volumetry committee has extended its effort to the context of Lung Nodule Assessment in CT Screening.

NIBIB Task 18. Create a collaborative, multidisciplinary infrastructure to foster research, approval and use of quantitative imaging biomarkers, including development and maintenance of a national repository of quantitative imaging biomarker data, representation at a variety of workshops and meetings, and provide project management and staff support for same.

a. *The QIBA committee structure and leadership constitutes one component of a collaborative, multidisciplinary infrastructure to foster research, approval and use of quantitative imaging biomarkers. A plan for long-term sustainability will be developed over the next year. (See Task 19).*

We have reorganized the UPICT effort to now be part of QIBA, and we are now actively using a leadership succession policy consistent with RSNA's approach to other sustained committees. This process includes both formal approval of leaders as well as defined terms of service. The first formal transitions are taking place successfully.

b. *In partnership with NCRR/NIH, RSNA provides support for a CTSA Imaging Working Group which constitutes another component of a collaborative, multidisciplinary infrastructure to foster research, approval and use of quantitative imaging biomarkers.*

The RDC has created a Vice Chairs of Radiology committee, and that committee has created three sub-groups that are now addressing the issues initiated within the CTSA IWG.

c. *We have created an Ad Hoc Committee on Open Image Archives which will provide in approximately 6 months a report containing recommendations for creating one or more national repositories of quantitative imaging biomarker data.*

The combined QIBA, OIA and Radiology Informatics Committee (RIC) members have begun the proof-of-concept implementation using a pilot project from the MRI modality committee for demonstration at the RSNA 2012 Annual Meeting. The joint QIBA/RIC committee received approval to deploy an initial seed project for an image warehouse with associated capability

from the RSNA Board. The "Quantitative Imaging Data Warehouse" (QIDW) is currently in pilot phase and is being considered for a demonstration at the RSNA Annual Meeting. Cloud-server technology along with MIDAS and QI Bench software is being used for the proof-of –concept project for the QIDW, intended initially for storing data sets from QIBA projects as well as those that might be contributed by Pharma companies. Data from the DCE-MRI Technical Committee will be the first demonstration project. After completion of the pilot test and before next steps are determined, a report and recommendations will be brought forward for RSNA Board consideration.

d. *RSNA staff supported by this NIBIB contract will provide project management and staff support for same.*

Staff has successfully met the challenges as well as the opportunities afforded by this contract assignment.

NIBIB Task 19. Explore self-funding models to maintain forward progress of the infrastructure and effort described in task 18 above.

We will create an Ad Hoc Task Group to conduct strategy discussions on this topic during Year 1 and will develop a draft proposal by year end. Based on the nature of that proposal we will lay out actions and a plan for Year 2.

An ad hoc task force has been set up to develop the ideas which have been considered for creating a self-funding program. The inaugural t-con of the QIBA Task Force on Commercial Business Models is scheduled for October 31, 2012. This builds on the report of a panel of experts convened by the RSNA Board of Directors and chaired by Carolyn Meltzer, MD, Emory University, which made recommendations regarding sustainable funding among other issues.

B. ONGOING AND NEWLY FUNDED PROJECTS (FULL 24 MONTH SUMMARY)

What follows is a listing of projects that contribute to the summary tasks identified in the charts and information in Sections C-E. They are presented here to demonstrate use of the first and second year project funds in the context of on-going activities.

CT, round 1:

Biomarker	Title	Amount Awarded	Submitter	TimeLine (contract)	Project Description (Abstract)
VolCT	Inter-scanner/Inter-clinic Comparison of Reader Nodule Sizing in CT Imaging of a Phantom	$14,000	Michael McNitt-Gray, PhD (UCLA)	04/01/2011 - 03/31/2012	Project Description Inter-scanner/inter-clinic comparison of reader nodule sizing in CT imaging of a phantom.
VolCT	Inter-scanner/Inter-clinic Comparison of Reader Nodule Sizing in CT Imaging of a Phantom	$11,000	David Clunie, MBBS (CoreLab Partners)	04/01/2011 - 03/31/2012	Project Description Inter-scanner/inter-clinic comparison of reader nodule sizing in CT imaging of a phantom (reader mark-up services).
VolCT	Assessing Measurement Variability of Lung Lesions in Patient Data Sets	$13,185	Michael McNitt-Gray, PhD (UCLA)	04/01/2011 - 03/31/2012	Project Description The purpose of this project is to perform the statistical analysis of data collected under QIBA Volumetric CT committee's 1B experiment, which is investigating the minimum detectable
VolCT	Validation of Volumetric CT as a Biomarker for Predicting Patient Survival	$62,495	Binsheng Zhao, DSc (Columbia Univ)	04/01/2011 - 12/31/2012	Project Description Unidimensional measurements have become a de-facto standard for assessing a patient's response to therapy. In essence, the RECIST measurement is a "surrogate" for tumor burden and change in this metric is used to guide drug discovery. We and other groups have demonstrated that the unidimensional measurement and change in the unidimensional measurement do not always correlate with change in tumor burden. The actual change in tumor burden is better assessed by change in tumor volumes as measured on CT. We plan to retrospectively analyze tumor burden change in patients enrolled on an already completed large, multicenter Phase II/III clinical trial in metastatic colorectal cancer. We are in an excellent position to validate CT volumetric response assessment technique using our computer algorithms and the clinical data in this trial. 451 patients have been enrolled in this trial and have measurable target lesions in the liver as well as in the lungs and lymph nodes. Each patient underwent an average of 5 CT scans (baseline and follow-ups at every 6-week after the treatment and every 3-month starting 49 months until disease progressed or patient died). The trial also collected a number of tissue biomarkers (e.g., markers in the IGF-1R or EGFR signaling pathway) before and at 6-week after the treatment and tumor genotype from blood sample taken pre- and every 6-week post-treatment. Volumetric (as well as unidimensional and bidimensional) measurements of target lesions on all scans of all patients will be calculated using our in-house computer-aided (CA) methods developed for segmentation of lung, liver and lymph node metastases. Intra- and inter-reader variability of the three measurements will be explored in a subset of patients (i.e., the first 50 patients who have more than 3 scans). Finally, correlations of tumor response and time-to-progression assessed unidimensionally, bidimensionally and volumetrically with clinical outcome (overall survival), tissue biomarkers and tumor genotype will be performed. By evaluating the magnitude of measurement variability and the optimal correlation, cut-off value or continuous change variables to identify tumor regression and progression can be established for unidimensional (ie. modified RECIST), bidimensional (ie. modified WHO) and volumetric response assessment methods. If proven successful and accepted by the oncology community and regulatory agencies, this research will aid the discoveries of cancer drugs and tissue biomarkers as well.
VolCT	Development of Assessment and Predictive Metrics for Quantitative Imaging in Chest CT	$50,000	Ehsan Samei, PhD (Duke)	04/01/2011 - 09/29/2012	Project Description: Previous work in our laboratory has developed a framework for predicting quantitative imaging performance from basic system performance measurements.1 These figure of merits (FOM) included metrics that characterize the resolution (modulation transfer function, MTF) and noise (noise power spectrum, NPS) of the image. It was shown that the precision with which medical images can be used to estimate volume of lesions can be predicted from these simpler FOM. By extending this framework to CT, we expect to be able to evaluate how well clinical CT systems perform various quantitative imaging tasks based on measurements of system FOMs (i.e., noise, contrast, and spatial resolution) via conventional QA phantoms. The goal of this project is to utilize these models in the evaluation of existing phantoms in the characterization of quantitative performance of CT and further develop a calibration procedure to assess compliance of quantitative imaging technique in volumetric CT. As part of this project, we anticipate the collaboration with existing QIBA efforts (1a, 1b, and 1c).
VolCT	Measurement of Pulmonary Nodule (Solid, Part-Solid and Ground Glass) Volume, Longest Diameter and CT Attenuation Resulting from Differences in Reconstruction Thickness, Reconstruction Plane, and Reconstruction Algorithm	$42,070	Kavita Garg, MD (U Colorado)	04/01/2011 - 09/29/2012	Recently released initial results of the National Lung Screening Trial (NLST) show mortality reduction by 20% in the CT arm compared with CXR. If screening becomes widely adopted in those at high risk, follow-up investigation of positive scans will impose a major burden on the health care system. In patients with positive scans, a risk stratification strategy or quantitative analysis of lung nodules could reduce this burden by reducing the rate of follow-up in those who are determined to be at lower risk. Quantitative CT analysis for solid nodules has been attempted previously, however there is no significant data available for subsolid nodules.
	TOTAL CT FUNDING AWARDED	**$192,750**			

CT, round 2:

Biomarker	Title	Budget request	Submitter	TimeLine (contract)	Project Description (Abstract)
VolCT	Validation of Volumetric CT as a Biomarker for Predicting Patient Survival (Carry-over from Round-1)	$62,495	Binsheng Zhao, DSc (Columbia Univ)	04/01/2011 - 12/31/2012	Project Description The purpose of this project is to extend the data collection and statistical analysis of the QIBA Volumetric CT committee's 1B experiment, which is investigating the minimum detectable change in lesion size from patient datasets imaged on CT. That project used: (a) "Coffee Break" CT image datasets from 32 NSCLC patients who were imaged twice over a short (15 minute) interval on the same scanner using thin (1.25 mm) slices; (b) one lesion was identified for each patient, (c) Image data was marked up by five radiologists at RadPharm (now CoreLabs); (d) each reader marked the lesions on each of the repeat scans to obtain measures of volume, single longest diameter and bi-dimensional diameters. This data was previously collected and initial analyses have been performed.
VolCT	Development of Assessment and Predictive Metrics for Quantitative Imaging in Chest CT (Carry-over from Round -1)	$25,000	Ehsan Samei, PhD (Duke)	04/01/2011 - 09/29/2012	Project Description The purpose of this project is to extend the data collection and statistical analysis of the QIBA Volumetric CT committee's 1B experiment, which is investigating the minimum detectable change in lesion size from patient datasets imaged on CT. That project used: (a) "Coffee Break" CT image datasets from 32 NSCLC patients who were imaged twice over a short (15 minute) interval on the same scanner using thin (1.25 mm) slices; (b) one lesion was identified for each patient, (c) Image data was marked up by five radiologists at RadPharm (now CoreLabs); (d) each reader marked the lesions on each of the repeat scans to obtain measures of volume, single longest diameter and bi-dimensional diameters. This data was previously collected and initial analyses have been performed.
VolCT	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions	$14,110	Michael McNitt-Gray, PhD (UCLA)	08/01/2011 - 09/29/2012	Project Description QIBA 1A study investigated the bias and variance using CT images of an anthropomorphic phantom and obtained measurements using only one algorithm. However, image processing algorithms have been developed in many organized activities from a number of groups using many different approaches with varying amounts of human interaction and different levels of segmentation success. This study proposes to investigate the effects of different algorithms in bias and variance using reference data sets of both phantoms and patients; in addition, this study proposes to investigate the performance of different methods and degree of automation in the algorithm. This study can increase knowledge for the QIBA Profile and to provide a context in which multiple parties have incentives to participate. (1) manual analysis in which sites perform required measurement task and manually supply data back to QIBA 3A project personnel and (2) scripted analysis that would apply to multiple data sets to invest in a re-usable infrastructure for large-scale algorithm testing
VolCT	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions (reader mark-up)	$13,125	David Clunie, MBBS (CoreLab Partners)	08/01/2011 - 07/31/2012	
VolCT	Comparative Study of Algorithms for the Measurement of the Volume of Lung Lesions: Assessing the Effects of Software Algorithms on Measurement Variability	$35,500	Michael McNitt-Gray, PhD (UCLA)	08/01/2011 - 07/31/2012	
COPD	Impact of Dose Saving Protocols on Quantitative CT Biomarkers of COPD and Asthma	$49,754	Sean Fain, PhD (Univ of Wisconsin)	08/01/2011 - 12/31/2012	Longitudinal clinical research studies that depend on quantitative measures of CT (qCT) number and structures depend on stable and reproducible image fidelity in often young, radiation sensitive, populations. Quantitative image measures of CT number and structural dimensions in ongoing lung studies, such as parenchymal density and airway wall thickness, have been shown to vary substantially according to the CT scanner make and model due to factors that differentially affect image noise, artifacts, and other image quality parameters, such as low contrast detectability and MTF. Imaging at the lowest possible dose, while maintaining diagnostic accuracy, is important to reduce the patient's risks from radiation. While image noise is normally adversely affected by adjusting scan parameters to decrease radiation dose, there now exist methods that allow decreased dose with no significant effect on image quality. However, there are significant questions as to effects of these techniques on qCT measures. These dose reduction techniques include automatic exposure control (AEC) systems, such as Smart mA on the GE systems, which produce mA modulation in the Z and angular directions, and iterative reconstruction (IR) techniques such as ASIR (GE).
	TOTAL CT FUNDING AWARDED	**$199,984**			

CT projects that have been granted NCEs:

- *Validation of Volumetric CT as a Biomarker for Predicting Patient Survival*, 09/31/2012 $\Delta\rightarrow$ 12/31/2012
- *Impact of Dose Saving Protocols on Quantitative CT Biomarkers of COPD and Asthma*, 07/31/2012 $\Delta\rightarrow$ 12/31/2012

MR, round 1:

DCE-MRI	DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution	$60,347	Edward Jackson, PhD (MD Anderson CC)	04/01/2011 - 12/31/2012	Project Description The DCE-MRI Technical Committee has developed a prototype DCE-MRI phantom that is proposed for use in DCE-MRI clinical trial site qualification as well as ongoing quality control processes. When it was initially formed, the DCE-MRI Technical Committee identified the need for such a robust DCE-MRI contrast response phantom as a top priority. Since that time, the committee developed a "generic" DCE-MRI acquisition protocol, developed a protocol for quality control / initial site qualification, each process a key component of the first DCE-MRI Profile, and has evaluated the use of a modified ADNI MagPhan phantom and, upon initial multicenter testing of two copies of this phantom design, found the phantom to be insufficiently robust to shipping and handling, too limited in its evaluation of R1 (longitudinal relaxation rate) contrast response assessment, and not time efficient in routine application. A new phantom design was proposed to address each identified weakness of the modified ADNI MagPhan phantom for DCE-MRI contrast response characterization, relaxometry, and quality control.
DCE-MRI	Software Development for Analysis of QIBA DCE-MRI Phantom Data	$29,975	Edward Ashton, PhD (VirtualScopics)	04/01/2011 - 03/31/2012	Project Description This project will address the development of a distributable software package to allow the analysis of QIBA DCE-MRI phantom data.
DCE-MRI	Digital Reference Object for DCE-MRI Analysis Software Verification	$57,763	Daniel Barboriak, MD (Duke)	04/01/2011 - 09/29/2012	Project Description One barrier to implementation of dynamic contrast-enhanced (DCE) MRI in multi-center clinical trials is that available software packages used to analyze the images may differ in their approach and implementation, causing variability in the extracted quantitative parameters. Because no standardized image analysis method is available, results obtained using DCE-MRI in different laboratories are difficult to compare, and the rational choice of one software implementation over any other for use in a multi-center trial is exceedingly challenging. As a first step in providing a standardized analysis process, it is necessary to ensure that software implementations are extracting parameters accurately. In this project, we propose to create digital reference objects (DROs) using synthetic data in order to help verify software packages for use in DCE-MRI analysis, and to initiate the development of verification protocols as a method to qualify software packages for use in clinical trials of DCE-MRI.
fMRI	Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning	$19,411	Edgar DeYoe, PhD (Med College of Wisconsin)	04/01/2011 - 08/31/2012	Project Description This subproject will provide quantitative measures of reproducibility for a unique set of vision- and motor-related fMRI brain maps using a set of data manipulations, computations, and the AMPLE normalization algorithm that will be standardized in coordination with subproject 1. In addition, this subproject will provide a unique analysis of the reproducibility of fMRI functional specificity and will compare reproducibility measures over different time durations both within and across subjects. The results of this study will help address NIBIB Tasks 1, 3, 6, 7, and 9 in the context of fMRI as a biomarker of brain function/dysfunction.
fMRI	Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning-Development of Reproducibility Metrics	$33,423	James Voyvodic, PhD (Duke)	04/01/2011 - 07/31/2012	Project Description This sub-project will develop metrics for quantifying reproducibility within and across fMRI scans, and it will apply those metrics to existing data sets to assess the reproducibility of fMRI results both within and across scanning sessions. The metrics to be developed will be based on using the AMPLE normalization algorithm (Voyvodic, 2006) to assess reproducibility and will include both voxel-wise and ROI-based measures of the consistency of fMRI activation maps over time. The results of this study will help address NIBIB Tasks 1, 3, 6, 7, and 9. Demonstration and quantification of reproducibility is an essential step in the development of the QIBA Profile for fMRI.
	TOTAL MR FUNDING AWARDED	**$200,919**			

MR, round 2:

DCE-MRI	Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects	$175,000	Mark Rosen, MD, PhD (ACR/U Penn)	08/01/2011 - 02/28/2013	Project Description In order to evaluate the profile claims for the repeatability of tumor DCE-MRI metrics, it is ultimately necessary to evaluate the performance of the QIBA DCE-MRI protocol in human subjects with tumors. This process would include not only implementing the imaging protocol, but also introducing site imaging personnel to proper procedures for magnet qualification, the selection of tumor-bearing human subjects, and the implementation of the proper DCE-MRI imaging exam to these subjects. Through discussions within the DCE-MRI subcommittee, it has been decided to seek a partnership with the American College of Radiology Imaging Network (ACRIN) to facilitate the development and ultimately the implementation of the test-retest DCE-MRI human study. The overall project, including the completion of the protocol, selection of participating sites, central and site regulatory approval, and implementation is expected to last two years.
fMRI	Validation of Breath Hold Task for Assessment of Cerebrovascular Responsiveness and Calibration of Language Activation Maps to Optimize Reproducibility	$29,376	Jay Pillai, MD (Johns Hopkins MC)	08/01/2011 - 09/29/2012	Project Description Assessment of the integrity of cerebral vascular responsiveness (CVR) is a critical problem in clinical applications of fMRI brain mapping, and must be addressed in any attempt to quantitate fMRI results in patients. Neurovascular uncoupling (NVU) associated with brain tumors and other brain diseases may result in regional variations in CVR that affect the ability to generate a BOLD signal and thereby reliably and reproducibly localize eloquent cortex during presurgical mapping. Multiple studies have demonstrated that a breath-hold (BH) hypercapnia task is a reliable tool for assessing CVR and normalizing BOLD response among different subjects, different brain regions and various features of the scanning environment. In this project we plan to 1) validate use of a BH task for mapping of brain CVR and 2) use such maps to calibrate language task-based BOLD activation maps in order to both reduce intersubject variability and increase intrasubject reproducibility across scan sessions. For the first objective, we will compare BH CVR maps with T2* DSC MR perfusion imaging maps using quantitative region of interest analysis to assess concordance of regions of decreased CVR with regions of abnormal perfusion in a cohort of 10 brain tumor patients. For the second objective, we plan to apply the normalization/calibration technique described by Thomason et al. (2007) to an existing dataset of approximately 10 normal right-handed native English speaking subjects who performed two BOLD language tasks--silent word generation and sentence completion--in addition to a breath hold (BH) task, as well as to a cohort of a similar number of brain tumor patients who performed similar tasks. Furthermore, for the patient cohort, analysis of multiple runs of the same language activation paradigms will assess intrasubject BOLD activation variability utilizing CVR-calibrated activation maps. The results of this study will help fill the high priority gaps of evaluation of neurovascular responsiveness, reproducibility and protocol optimization, defined by the QIBA fMRI subcommittee, and address NIBIB Tasks 1, 3, 6, 7, and 9 in the context of fMRI as a biomarker of brain function/dysfunction.
	TOTAL MR FUNDING AWARDED	**$204,376**			

MR projects that have been granted NCEs:

- *DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution*, 03/31/2012 $\Delta\rightarrow$ 12/31/2012
- *Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects*, 07/31/2012 $\Delta\rightarrow$ 02/28/2013

NM, round 1:

FDG-PET/CT	Meta-analysis to Analyze the Robustness of FDG SUV Changes as a Response Marker, Post and During Systemic and Multimodality Therapy, for Various Types of Solid Extracerebral Tumors	$73,000	Otto Hoekstra, MD (VU Med Ctr, NL)	04/01/2011 - 03/31/2012	Project Description Meta-analysis on the association between FDG uptake changes and histopathological response. Validated qualitative and quantitative statistical model of quantitative FDG PET to predict response of neoadjuvant therapy in solid tumors.
FDG-PET/CT	QIBA FDG-PET/CT Digital Reference Object Project	$68,240	Paul Kinahan, PhD (U Washington)	04/01/2011 - 03/31/2012	Project Description Construct a common reference DICON PET/CT test image (Digital Reference Object or DRO) as if generated by each vendor's PET/CT scanner. This will then be read on PET/CT display stations to check SUV computation fidelity and region of interest (ROI) analysis performance. This is motivated by the vendor-specific variations in the standardized uptake value (SUV) calculations. It is well known that variations in the implementation of DICOM standards produce substantial quantitative differences in SUVs for the same image on different display stations. In addition, the behavior of ROI analysis tools, (e.g., due to image interpolation) is rarely, if ever, quantitatively understood.
FDG-PET/CT	Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes	$57,500	Richard Wahl, MD (Johns Hopkins MC)	04/01/2011 - 02/28/2013	Project Description The insulin-like growth factor (IGF) pathway plays an important role in a variety of physiological processes in humans and animals, including normal growth and development. Additionally, this pathway has been shown to play an important role in the development of conditions like cancer. IGF signaling has been proposed to play a major role in the very aggressive nature of certain sarcomas, like Ewing's sarcoma family of tumors (ESFT) and synovial sarcomas The SARC 11 trial prospectively evaluated the utility of an anti Insulin like Growth Factor Human Monoclonal Antibody (R1507) as monotherapy for Sarcomas of several types (Recurrent or Refractory Ewing's Sarcoma, Osteosarcoma, Synovial Sarcoma, Rhabdomyosarcoma and Other Sarcomas.) . All patients received R1507 9mg/kg i.v. . This single arm study evaluated the efficacy and safety of R1507 in patients with recurrent or refractory sarcoma Clinical efficacy of the trials was judged by: Objective response rate [Time Frame: Week 24, and every 12 weeks thereafter] , Progression-free survival in patients with Ewing's sarcoma [Time Frame: Week 18] , Duration of response, PFS, and overall survival. In this multicenter study, a baseline PET scan was obtained as well as a PET scan at approximately 9 days post therapy initiation. A follow up scan at 12-18 weeks was obtained in those remaining on study. A total of 311 patients entered the study. Importantly, the PET was not used to alter the therapy. Thus, the PET data can be used to determine prognostic ability. Accrual to the study is now complete and the full PET data set have been collected and are available in DICOM form for analysis. Details of the SARC 11 trial and the rationale for anti IGF antibody therapy are detailed at Clinical Trials. gov and the SARC website. http://www.clinicaltrials.gov/ct2/show/related/NCT00642941?term=r1507 and http://www.sarctrials.org/SARC011r1507 We propose to analyze the PET data quantitatively (and qualitatively) using PERCIST and EORTC response criteria to determine how predictive PET, notably changes in PET signal between baseline and the first follow up scan, is of clinical outcomes. We will also examine inter-observer consistency. We will apply commercial software and our in house developed software for analysis. This trial is particularly suitable for analysis of PET data as they are not
	TOTAL NM FUNDS AWARDED	**$198,740**			

NM, round 2:

FDG-PET/CT	Personnel Support for FDG-PET Profile Completion	$16,000	Eric Perlman, MD (Perlman Advisory Group)	10/01/2011 - 12/31/2011	Project Description This is a proposal for expert support as a 'Profile Writer' to convert the considerable amount of material accumulated by the FDG-PET TC into a QIBA Profile.
FDG-PET/CT	Evaluation of the Variability in Determination of Quantitative PET Parameters of Treatment Response across Performance Sites and Readers	$100,000	Richard Wahl, MD (Johns Hopkins MC)	10/01/2011 - 02/28/2013	Project Description There is very limited data on the performance of varying readers and quantitative imaging workstations in determining cancer treatment response using FDG PET/CT. We propose a study design using well-defined anonymized pre-treatment and post-treatment FDG PET scans of cancer patients as an analysis set. All
FDG-PET/CT	PERCIST Validation	$50,000	Otto Hoekstra, MD (VU Med Ctr, NL)	04/01/2012 - 12/31/2012	Project Description Validate PERCIST metrics using peer-reviewed patient cohorts.
FDG-PET/CT	Evaluation of FDG-PET SUV Covariates, Metrics, and Response Criteria	$34,000	Jeffrey Yap, PhD (Dana-Farber Cancer Institute)	02/01/2012 - 12/31/2012	Project Description We have developed a large database of more than 25,000 PET oncology studies, which includes critical acquisition parameters, patient information, and DICOM CT and PET images.1 Many of these studies are from multi-center trials that included PET scanner qualification, phantom imaging, central review and PET SUV analysis, and collection of clinical outcome data. We propose to perform a retrospective meta-analysis to compare different PET metrics, response assessment criteria (EORTC, PERCIST), PET SUV covariates (FDG dose, glucose, fasting time, patient size, etc.), and clinical outcome. A small component of this activity has already been performed in a subset of data comparing the impact of metabolic response assessment using SUVmax vs. SUVmean (Figure 1) and SUV patient size normalization using lean body mass vs. body weight (Figure 2).2,3,4 The requested resources that are needed to complete this work include the compilation of images, meta-data, and clinical trial outcome measures from a research miniPACS archive, multiple clinical trial MS Access databases, a clinical PET database, and various sources of clinical trials results such as Excel spreadsheets. In addition to the existing results, additional image analyses will be performed to generate normal tissue ROIs (e.g. liver) as well as multiple tumor ROIs for studies that only included single tumor per patient in the original analysis. A software package will be developed in IDL to establish a DICOM server research archive and automatically extract and compare various PET metrics (e.g. SUVmax, SUVmean, SUVlbm) from previously performed ROI analysis. This will address a major limitation in commercial software that only allows the use of a single metric and/or response criteria for a given study and facilitate the automated generation and comparison of different PET metrics and response criteria. Lastly statistical analysis will be performed on the results of multiple clinical trials in order to evaluate the impact of covariates, PET metrics, and response criteria on the performance of FDG-PET SUV as an imaging biomarker of therapeutic response. This will yield critical results for supporting claims in the QIBA profile with such as the variability in response assessment using different methods as well as justify consensus recommendations in the UPICT protocol, e.g. with regards to image analysis and response assessment.
	TOTAL NM FUNDING AWARDED	**$200,000**			

NM projects that have been granted NCEs:

- *Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes*, 03/31/2012 $\Delta\rightarrow$ 02/28/2013
- *Evaluation of the Variability in Determination of Quantitative PET Parameters of Treatment Response across Performance Sites and Readers*, 09/29/2012 $\Delta\rightarrow$ 02/28/2013
- *PERCIST Validation*, 09/29/2012 $\Delta\rightarrow$ 12/31/2012
- *Evaluation of FDG-PET SUV Covariates, Metrics, and Response Criteria*, 07/31/2012 $\Delta\rightarrow$ 12/31/2012

Cross-modality:

Cross Modality	Groundwork for QIBA Image Reference Database	$10,250	Gudrun Zahlmann, PhD (Roche)	04/01/2011 - 03/31/2012	Project Description QIBA profiles of all technical committees describe what the imaging process for a certain quantitative imaging biomarker should look like in order to fulfill the profile claims. The claims state how accurate and reliable the respective quantitative imaging biomarker can be expected if the profile is followed. The so-called bull's-eye principle is used for describing ideal, target and acceptable quality. All teams deal with phantom imaging to assess the scanner quality. In addition clinical images are captured and analyzed in order to define the claims. It would be beneficial to support the QIBA profiles with a repository of phantom and clinical images illustrating the QIBA understanding of ideal, target and acceptable quality in real life image examples.
Cross Modality	Groundwork for QIBA Image Reference Database	$16,000	Rick Avila, MS (Kitware)	04/01/2011 - 10/31/2012	Project Description QIBA profiles of all technical committees describe what the imaging process for a certain quantitative imaging biomarker should look like in order to fulfill the profile claims. The claims state how accurate and reliable the respective quantitative imaging biomarker can be expected if the profile is followed. The so-called bull's-eye principle is used for describing ideal, target and acceptable quality. All teams deal with phantom imaging to assess the scanner quality. In addition clinical images are captured and analyzed in order to define the claims. It would be beneficial to support the QIBA profiles with a repository of phantom and clinical images illustrating the QIBA understanding of ideal, target and acceptable quality in real life image examples.
	TOTAL CROSS FUNDS AWARDED	**$26,250**			

Cross-modality projects that have been granted NCEs:

- *Groundwork for QIBA Image Reference Database*, 03/31/2012 Δ→ 10/31/2012

C. PROGRESS FOR QUANTITATIVE CT (FOR SECOND REPORTING YEAR)

Snapshot at this time:

- With respect to CT volumetry:
  - Experimental groundwork:
    - ***Inter-scanner/Inter-clinic Comparison of Reader Nodule Sizing in CT Imaging of a Phantom*** (Fenimore): Project complete. Conclusions: The Figure shows that for nearly all scanners, the absolute percent relative error was well below 15% for spherical lesions that are ≥ 10 mm in diameter, regardless of scanner or protocol used; for spiculated lesions, the absolute percent errors were higher, but only a few exceeded 15% (5 out of 154 and most of those were confined to one scanner, regardless of protocol). In the spiculated lesions, 10 out of 154 were greater than 15%.
    - ***Validation of Volumetric CT as a Biomarker for Predicting Patient Survival*** (Zhao): Accomplishments: Part 1. Measurement Variability. Completed the intra- and inter-reader variability study and successfully delivered the proposed report. Since variability in interpretation of change in total tumor burden can occur during both selection and measurement of target lesions, study was designed to consider both of these factors. Outstanding: Part 2. Clinical Correlations. To date, have completed computer-aided tumor volume measurements (uni- and bi- as well) on all available CT scan time-points (4 - 5 scans per patient, on average) in all of the received 560 patients. After locking longitudinal tumor measurements, project was provided the patient survival data and further clinical information by the company. Out of the 560 patients, 478 patients (147 died and 331 alive) have a baseline and at least one follow-up scan and are qualified for further analysis in terms of the comprehensiveness of imaging data.
    - ***Development of Assessment and Predictive Metrics for Quantitative Imaging in Chest CT*** (Samei): Project complete. Conclusions: Publications: Chen B, Richard S, Barnhart H, Colsher J, Amurao M, Samei E. Quantitative CT: technique dependency of volume assessment for pulmonary nodules. Physics in Medicine and Biology 57: 1335–1348, 2012; and Chen B, Richard S, Samei E. Relevance of MTF and NPS in quantitative CT: towards developing a predictable model of quantitative performance. SPIE International Symposium on Medical Imaging, San Diego, CA, February 2012, Proc. SPIE Medical Imaging, 2012.
    - ***Quantifying Variability in Measurement of Pulmonary Nodule (Solid, Part-Solid and Ground Glass) Volume, Longest Diameter and CT Attenuation Resulting from Differences in Reconstruction Thickness, Reconstruction Plane, and Reconstruction Algorithm*** (Garg): Project complete. Conclusions; Hypothesis One: The absolute percent error in part-solid nodule tumor measurements will be less than or equal to 15% (the QIBA Solid Nodule > 10mm claim). In this study, the absolute percent error for part-solid nodule measurements was found to be 20.38 (17.75), for nodules of diameter 10 and 20mm. This value was significantly dependent on the reader, nodule diameter, nodule outer shape and nodule core density. Further work is needed to investigate these dependencies for part solid

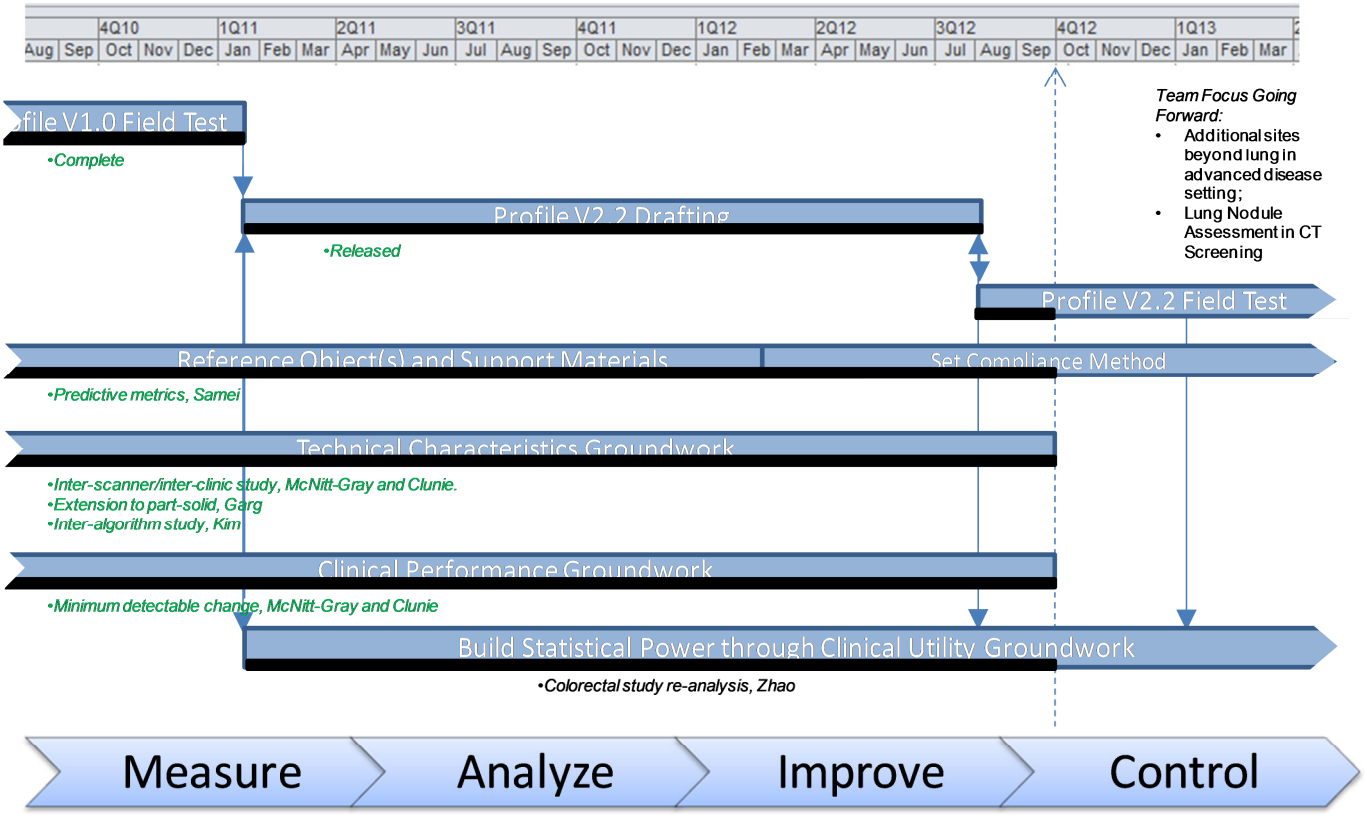
measures. It was also noted that the readers consistently obtained volumes that were larger than the actual volume. Further study is needed on the proper display for visualizing the PS lesion with respect to the displayed segmentation outline. Concerns have been raised regarding the actual "ground truth" values of the nodules; this will be investigated further. Absolute bias measures for solid lesions were found to be significantly worse than those of the part-solid lesions. In addition to lesion size differences, it would be important to see if the algorithm designed for part-solid lesions performs less effectively on solid lesions. Finally, the one-dimensional measure, SA-RECIST exhibited significantly less absolute error than the volume measure. Noting that the 1-D measure results from the same segmentation as the volume measure and for a spherical lesion, the volume goes up as radius-cubed, one might actually expect that the volume measures should be worse than they were. For this study, all of the cores and 50% of the part-solid lesions were spherical. There was also a significant dependence on nodule outer shape; further study is required to understand this trend. Hypothesis Two: Dose will not significantly affect the part-solid absolute percent error measurement for the nodules chosen for this study. This study confirmed a lack of significant dependence of any morphometric measure on dose. Hypothesis Three: Part-solid nodules will exhibit increased inter-reader and intra-reader measurement variability, compared to solid nodule studies. This study confirmed greater reader variability for all nodules measured and a poor ICC for measuring small changes in lesion volume. Further investigation into the user interface and process are needed to determine the reason for this.

- ***Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions*** (McNitt-Gray and Clunie): Project complete. Discussion and Conclusion: These results demonstrate that the measurement variability has decreased markedly when using the sequential locked reading paradigm of this study when compared to the independent reading paradigm of the previous study. The decrease in measurement variability was seen for all lesions and for all measurements, but the reduction in variability appears to have been greatest in volumetric measurements. The results from this study should be directly applicable to the QIBA profile and its descriptions regarding "best practices" for clinical trials and the reduction of measurement variability. Specifically, the use of a sequential locked reading paradigm rather than independent randomized reading may allow for a smaller biological change to be detected in an individual subject. Further analyses yet to be performed include the reduction in measurement variability of lung lesions that meet the QIBA profile criteria (i.e. that a "given tumor is measureable [tumor margins are sufficiently conspicuous and geometrically simple enough to be recognized on all images in both scans] and the longest in-plane diameter of the tumor is 10 mm or greater"), as well as clear determination of the statistical significance of the difference in reading paradigms.
- ***Comparative Study of Algorithms for the Measurement of the Volume of Lung Lesions*** (Athelogou PI, statistical analysis Kim): Project complete. Conclusion: The performance of analysis methods were highly differentiated, but with the majority fell within 15% absolute percent error across participants. These results match with QIBA performance and target levels, with providing insight for variation of software programs in measuring volumes. Next Steps of the QIBA 3AGroup: Paper preparation for pilot and pivotal study and preparation of the next challenge. For the next challenge clinical data will be used (QI-Bench datasets).

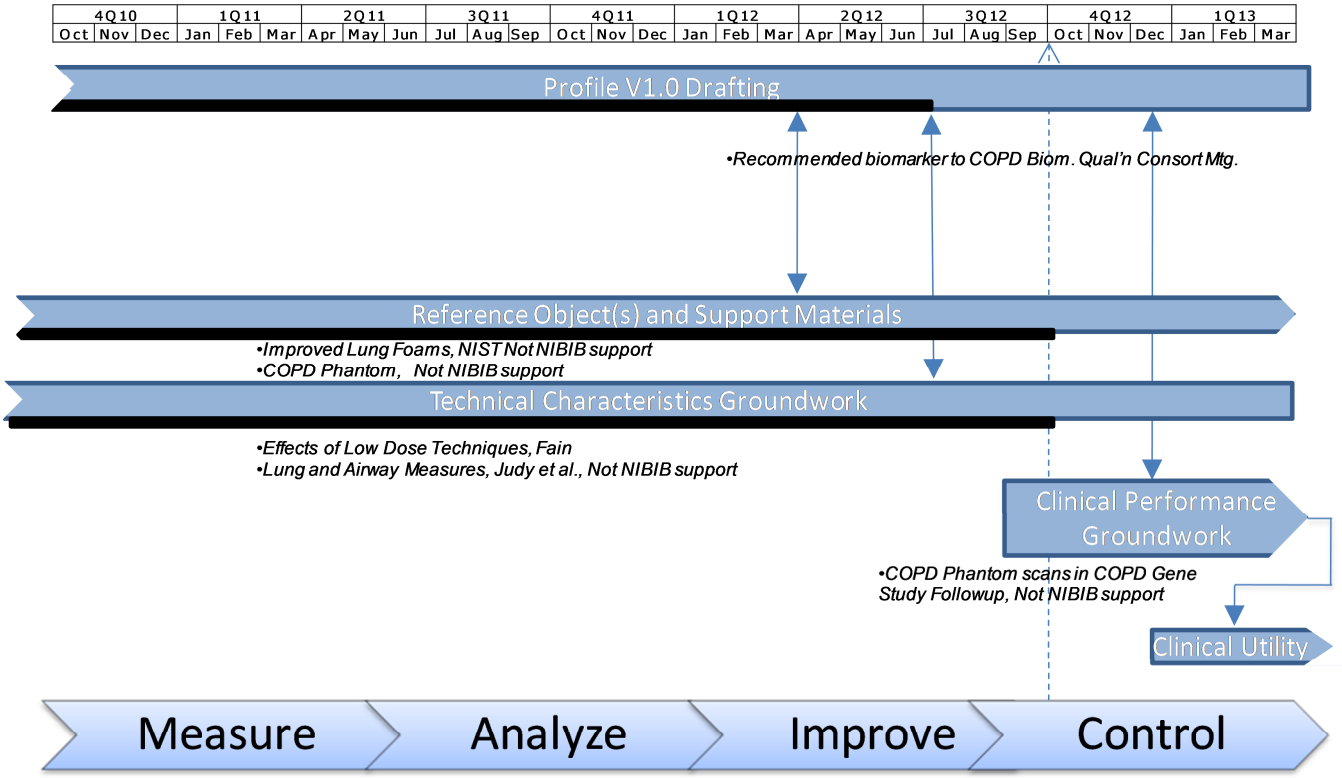
- Profiling:
  - The team conducted a public comment period, addressed all comments, and released its advanced disease profile in August 2012.
  - A new writing group has started, covering Lung Nodule Assessment in CT Screening.

- The COPD/Asthma committee has:
  - Characterized various foam inserts and other aspects of phantom design for effective calibration and quality control in lung densitometry studies.
  - ***Impact of Dose Saving Protocols on Quantitative CT Biomarkers of COPD and Asthma*** (Fain): Project has been granted a NCE. Accomplishments: 1. We have established the impact of dose on quantitative measures of wall thickness, and microstructural density using the COPD gene CT phantom. 2. We have also established the impact of a product non-linear iterative reconstruction (ASIR) designed to preserve image quality under low x-ray dose image acquisition conditions on quantitative measures of wall thickness, and microstructural density using the COPD gene CT phantom for low and high radiation dose scans. 3. We have also extended the results of measurements in phantoms established in 1 and 2 above to human lung images utilizing raw data reconstructions of human lung studies. We have been able to reproduce results for sampling density with a reduced display FOV reconstruction to improve measures of wall thickness; demonstrate the impact of measurement kernel on wall measures using Airway Inspector vs. VIDA; and have determined the consequences of nonlinear reconstruction (ASIR) on quantitative airway and microstructural lung parenchymal density measures. Outstanding: We have not yet completed the analysis, but recently (Sept. 27, 2012) completed data acquisition of the COPD gene phantom with different sized density rings surrounding the foam insert both with and without Smart mA methods of x-ray tube current modulation for reducing radiation dose. These measures are intended to determine the impact of smart mA tube current modulation methods on quantitative measures of wall thickness and density. Additionally, these measures will determine the consequences of off-center FOV positioning of the COPD gene phantom on identical quantitative measures as the CT images of the phantom were also acquired with differing degrees of magnification by shifting the position +/- 5 cm away from center.
  - First draft Profile is in progress.

The following updated Gantt chart reflects the CT volumetry Technical Committee progress and plan adjustments through the reporting period:



The following updated Gantt chart reflects the COPD/Asthma Technical Committee progress and plan adjustments through the reporting period:



D. PROGRESS FOR QUANTITATIVE FDG-PET (FOR SECOND REPORTING YEAR)

Snapshot at this time:

- Experimental Groundwork:
  - ***Meta-analysis to Analyze the Robustness of FDG SUV Changes as a Response Marker, Post and During Systemic and Multimodality Therapy, for Various Types of Solid Extracerebral Tumors*** (Hoekstra): Project Complete. Results: sixty-nine studies were identified reporting on 88 data sets (20 during-treatment PET assessments, 68 end-of-treatment PET assessments). QUADAS revealed heterogeneity but it was not useful to stratify studies according to quality aspects relevant for the study question. Of these 36 (52%) reported individual level data and 44 (64%) used SUVmax as the measure of uptake. The most common tumor types were esophagus 18 (26%), rectal 15 (22%), sarcoma 14 (20%) and breast (14%), with 30 (43%) studies reporting chemotherapy (CT) treated, 36 (52%) reporting chemoradiotherapy (CRT), and 3 (4%) reporting combined CT /CRT cohorts. A heterogeneity test indicated excessive variation in the ratio of PET values (post-therapy/baseline) for responders and non-responders in breast cancer cohorts, potentially due to differences in

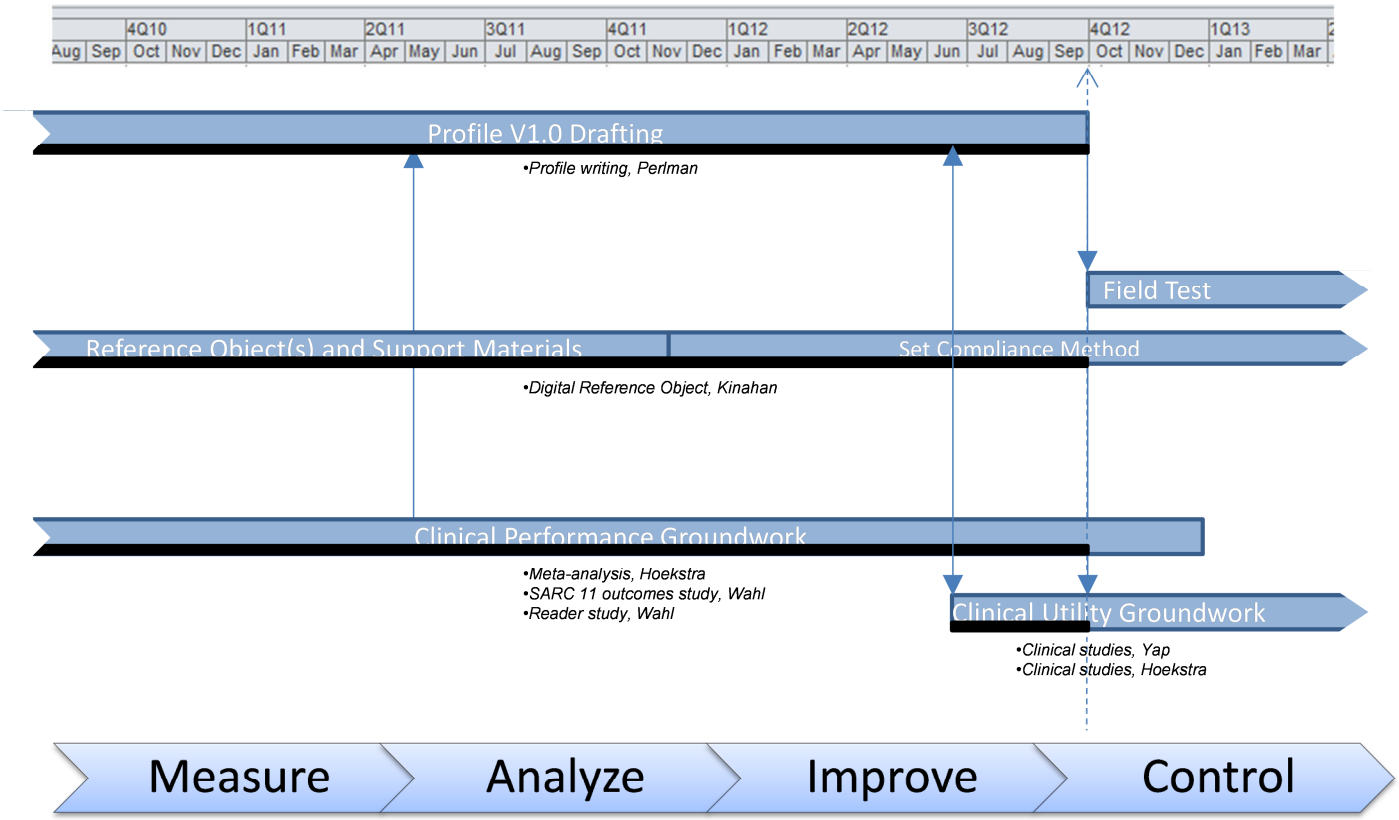
histopathological response definitions. Excluding these studies a mixed effects logistic regression indicated differences due to baseline uptake level (high vs. low repeatability) and treatment (CT vs. CRT). Summary receiver operating characteristic (SROC) analyses indicated that on studies and individuals with high baseline values (i.e. high repeatability) had better discrimination of responders than respectively CRT studies and individuals with low baseline values. For end-of-treatment (during treatment) FDG PET, a decrease of 65%-70% (40%-50%) provided maximal discrimination.

- ***QIBA FDG-PET/CT Digital Reference Object Project*** (Kinahan): Project complete. Summary: The QIBA FDG-PET/CT Digital Reference Object (DRO) provides a method for testing the SUV based calculations performed by PET/CT display software platforms. It is not intended as a ranking approach, but rather to verify nominal performance in a transparent and objective manner. The anecdotal evidence of failures (or otherwise) during evaluation of new software versions is a demonstration that the DRO has already succeeded in this manner. Even so, initial DRO tests have identified some variation in performance.
- ***Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes*** (Wahl): Project underway. Current results: The SARC 11 data show that scans from a diverse group of SARC performance sites are of variable quality and that meeting the detailed PERCIST guidance for scan performance is not the norm. Further, analysis of PET scans qualitatively and quantitatively, at least in the more completely analyzed Ewing's data set, shows that quantitative PET at less than 2 weeks after treatment has been begun can identify good and poor responders to anti IGF immunotherapy, even from far less than optimal PET data sets. Outstanding: Linkage to clinical outcomes is under way. 115 cases with clinical outcomes available are Ewings sarcoma. 163 cases are other histologies of sarcoma. The PERCIST criteria appear able to separate 1 year survivors from non survivors in Ewing's sarcoma and appear more robust than EORTC in preliminary assessments. The qualitative assessments of progression or non-progression on PET also appears prognostic. Analysis of the other sarcomas is ongoing.
- ***Evaluation of the Variability in Determination of Quantitative PET Parameters of Treatment Response across Performance Sites and Readers*** (Wahl): Project underway. Current results: IRB approval was required at Johns Hopkins which delayed the start of the project. This has now been approved, so we can anonymize data and send to performance sites. US and European sites have been identified. In the US, both CRO and academic sites have been identified. The QIBA technical committee sites and the QIN sites have been given priority. To date, 15 interested sites of performance have been contacted and their qualifications informally queried. Clinical datasets have mainly been selected and are in the process of being de-identified. The sites will soon be able to initiate interpretation of these studies. Outstanding: Sites will include the QIN sites. We expect we will determine that the SUV max change measures are highly reproducible and expect an ICC of .90 to result. We expect repeatability among sites to be less robust for SUV peak and volumes of tumors. These data in which each site examines real human data and must select the "hottest" tumor for analysis with a variety of workstations, will allow us to determine what degree of variability is due to the reader, software and workstation, as opposed to being due to the intrinsic variability among test re test scans. These data will inform the QIBA community on what key gaps exist in our analytical approaches, thus helping drive our future studies in quantitative imaging.

- ***PERCIST Validation*** (Hoekstra): Project underway. Current results: completed re-analysis of bevacizumab/erlotinib and sorafenib/erlotinib datasets using PERCIST metrics. Outstanding: re-analysis of Cisplatinum and erlotinib datasets and final report.
- ***Evaluation of FDG-PET SUV Covariates, Metrics, and Response Criteria*** (Yap): Project underway. Current results: 1. Compiled a research archive and database that supports FDG-PET imaging results, covariates, and clinical outcome data. 2. Developed software to facilitate retrospective analysis of previously defined regions-of-interest (ROIs) in order to automate the comparison of different SUV metrics and response criteria. Outstanding: Due to the complexities of performing volumetric analysis in GI stromal tumors, additional tumor analysis of the imatinib trial has been postponed until the imminent release of a new software version that will expedite the analysis and enable automated extraction of multiple SUV metrics. Instead, a multicenter trial of breast cancer patients treated with lapatinib has been used for additional analyses as this is a very robust data set that has been recently completed with survival analysis since the time of the original RSNA proposal submission. ROI analysis has been performed to estimate liver background SUV in all patients except those that cannot be used due to the presence of liver disease (21/85 patients).

- Profiling:
  - The QIBA FDG-PET Profile for the therapeutic area of oncology is all but finalized for the public comment phase.

The following updated Gantt chart reflects the FDG-PET Technical Committee progress and plan adjustments through the reporting period:



E. PROGRESS FOR QUANTITATIVE MRI (FOR SECOND REPORTING YEAR)

Snapshot at this time:

- DCE-MRI, progress has been exceptional on all fronts:
  - Experimental groundwork:
    - ***DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution*** (Jackson): The project is complete. Four copies of the QIBA DCE-MRI phantom have been manufactured successfully by The Phantom Laboratory. Data from multiple MR scanner vendors have been acquired and analyzed.
    - ***Software Development for Analysis of QIBA DCE-MRI Phantom Data*** (Ashton): The work is complete. A number of software improvements and fixes have been implemented in the period.
    - ***Digital Reference Object for DCE-MRI Analysis Software Verification*** (Barboriak): Project underway. Status: Extension of simulations to generate more realistic DROs. Advanced DROs have been produced taking into account less frequent imaging and temporal jitter. Use of these DROs will give more realistic predictions of the actual

performance of software in clinical applications. A DRO which realistic levels of image noise is currently in pre-release evaluation. Development of verification protocols and integration into profiling activities. Developing verification protocols will be challenging because of disagreements on how exactly this should be accomplished and the complexity of the task. Progress is being made, however, on three fronts: first, we are collecting data from software packages in the field to document performance across a broad range of parameter space. This will provide the source data for the protocol verification process. Second, we are cooperating with the QIBA Metrology initiative to help define figures of merit that can summarize performance in this multi-dimensional dataset. Third, we are cooperative with follow on projects which if funded will help automate the data acquisition. Creation of open source archives. We have created an open source archive on our own website (https://dblab.duhs.duke.edu/modules/QIBAcontent/index.php?id=1) and are working cooperatively with RSNA efforts to store data in a data warehouse.

- ***Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects*** (Rosen): Project underway. Status: CTEP approved protocol in March 2012; First amendment (coffee-break DWI) added and approved in September 2012; First site qualification (Univ. Penn) in September 2012; Remaining Site selection and approval anticipated November 2012.

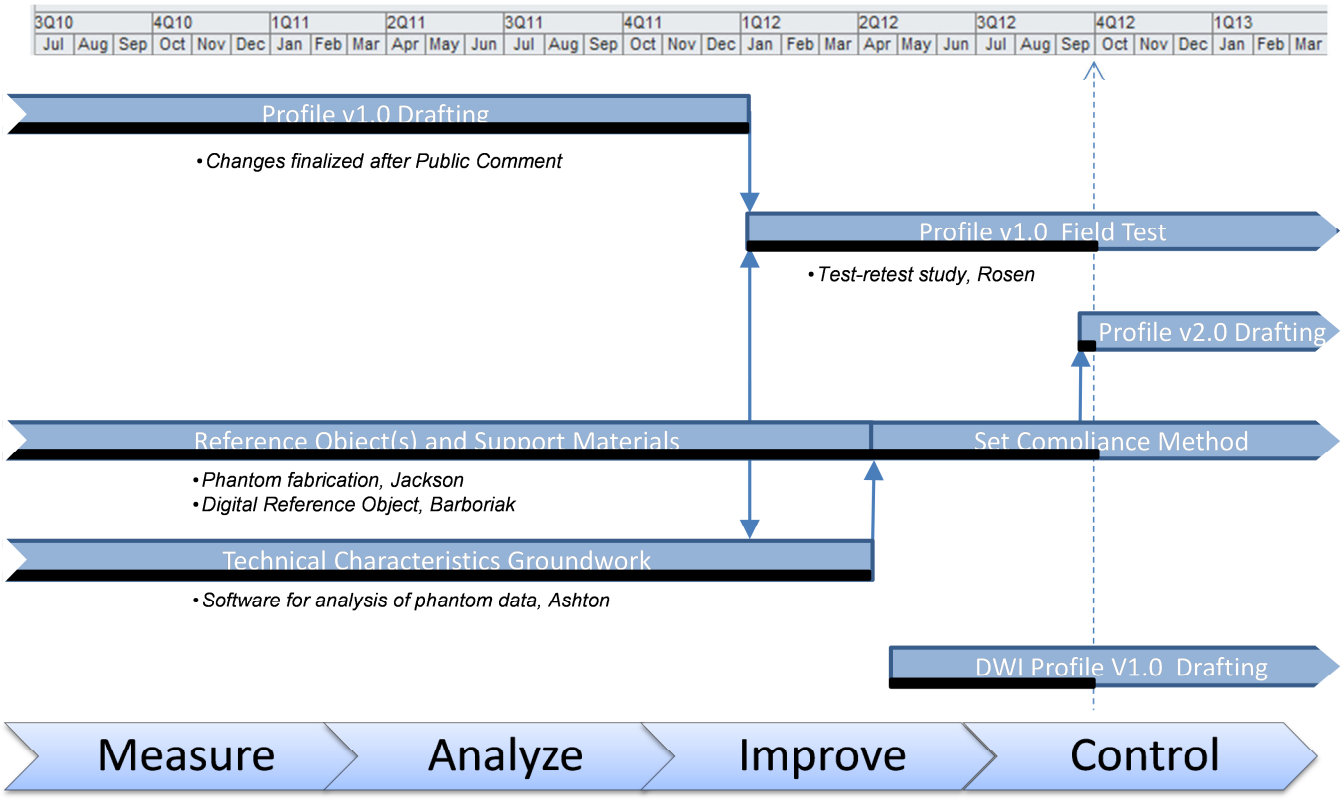
- Profiling:
  - The MR Technical Committee has completed its first QIBA Profile on DCE-MRI and has changed its focus to diffusion-weighted MR imaging. Accordingly, the Technical Committee has renamed itself the Perfusion Diffusion and Flow MR Technical Committee (PDF-MR). This committee has a new co-chair, Marko Ivancevic, PhD. There is a one year timeline for developing the DWI profile, and a second version of the DCE-MRI profile has a two-year timeline. The DCE-MRI profile is not organ-specific; a new profile that is specific to the prostate will be developed for the ACRIN trial. The DCE-MRI profile has been implemented in some Roche clinical studies.

- The fMRI committee has developed provisional core details for a Profile and has defined tasks and approach to characterize reproducibility in the measurements.
  - ***Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning-Development of Reproducibility Metrics*** (Voyvodic): Project complete. Results: AMPLE normalization did greatly increase quantitative reproducibility of fMRI language mapping, which compares standard t-maps and AMPLE maps for a single subject scanned 6 times. Quantitative measures of reproducibility showed that the brain location for the peak of activation in AMPLE-normalized maps was highly reproducible across scan sessions. We found that peak location of language areas varied by less than 10mm in almost all pair-wise comparisons, and by less than 5mm when both scans were acquired using the same scanner model and the same pulse sequence. Reproducibility of the spatial extent of activation was not correlated with acquisition procedures, but was positively correlated with the strength of the task activation signal itself. Reproducibility of hemispheric laterality index in AMPLE normalized maps was very good, with over 90% agreement between scans in frontal and temporoparietal language areas. The data sets used in this project could be made available for sharing via QIBA's Open Image Archive Initiative. New

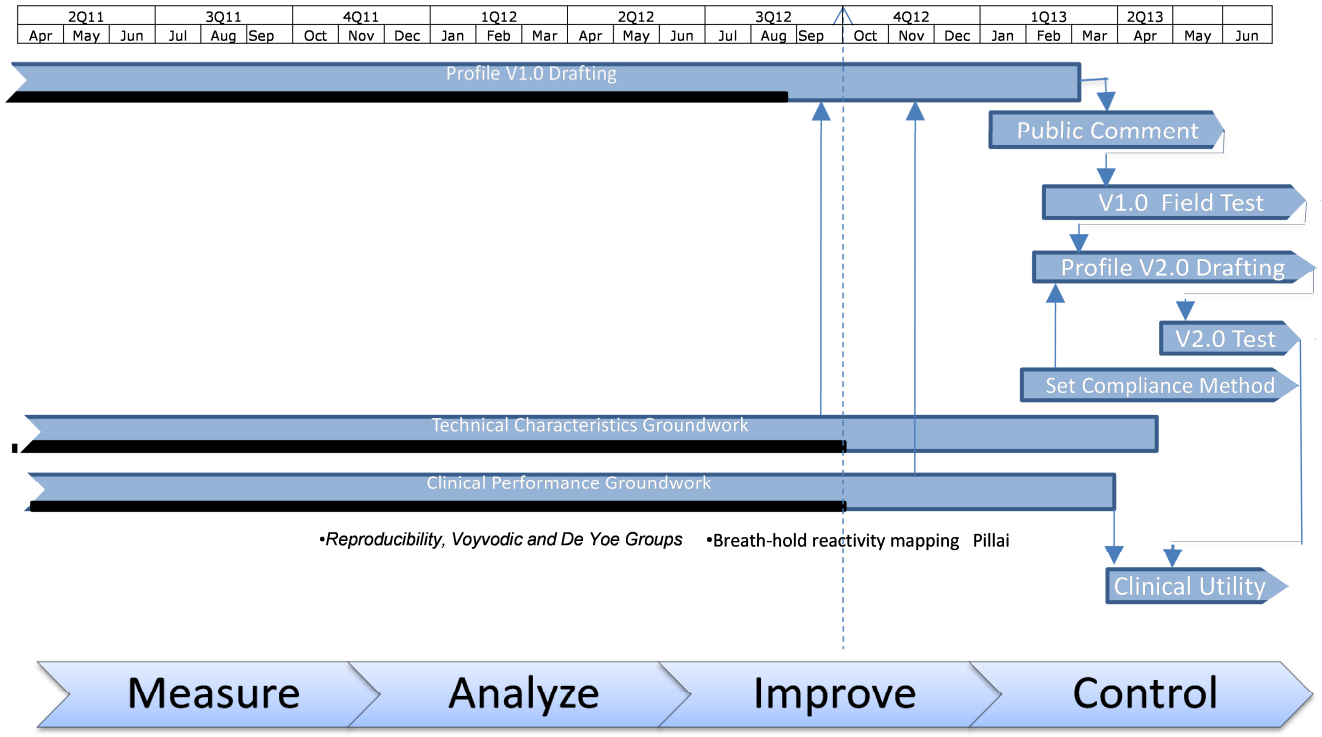
data sets should be acquired using a QIBA supported fMRI protocol, incorporating our recent findings, which could then provide publicly available support for the claims in our Profile.

- ***Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning*** (DeYoe): Project complete. Discussion: Overall, the results of this study indicate that visual cortex fMRI activation foci are, on the whole, quite reproducible with respect to the location of the weighted center-of-mass, the number of voxels within the focus and the spatial overlap of repeated observations. AMPLE normalization can improve repeatability relative to conventional T-valued data at 7 comparable statistical thresholds. However, anecdotal observations with other visual mapping data not presented here suggest that AMPLE normalization may at times suppress weak activation in portions of a broad pattern of activity (e.g. extrastriate cortex) that might be important for clinical interpretation in the context of presurgical planning. A manuscript for journal publication is in preparation that will describe additional details and results from this study that go beyond the items described above which most directly impact the claims being considered for inclusion in the QIBA fMRI profile.
- ***Validation of Breath Hold Task for Assessment of Cerebrovascular Responsiveness and Calibration of Language Activation Maps to Optimize Reproducibility*** (Pillai): Project complete. Conclusion and future work: The CVR calibration approach used in this sample dataset has demonstrated its potential to minimize false negatives for motor mapping in brain tumor patients with reduced CVR. A further development of the technique is needed to make it completely threshold independent and also to extend its application to mapping of eloquent cortex other than simply primary sensorimotor cortex in patients. Specifically, the technique needs to be further evaluated and optimized for application to intrinsically less symmetric and more strongly lateralized functional networks in the human brain such as the more complex language network in patients with focal resectable brain lesions such as brain tumors. We have already shown that in normal volunteers this approach is useful for calibration of language activation maps, but in the setting of brain lesions, more work needs to be performed in order to establish this algorithm as a viable calibration/normalization approach for use in the clinical setting. Clinical validation is also needed via comparison with intraoperative electrophysiological mapping and correlation with patients' functional status.

The following updated Gantt chart reflects the DCE-MRI Technical Committee progress and plan adjustments through the reporting period:



The following updated Gantt chart reflects the fMRI Technical Committee progress and plan adjustments through the reporting period:



F. FIRST REPORT OF ULTRASOUND/SWS (FOR SECOND REPORTING YEAR)

The ultrasound biomarker Technical Committee has been formed, and it has decided that sheer wave speed will be the first biomarker addressed.

For ultrasound, the challenges are well known. We need to develop an understanding of how to obtain comparable numbers across platforms. Three subcommittees have been formed:

- System dependencies-looking at how each system makes their measurements and the sources of variability
- Clinical applications- looking at making the measurement in humans and sources of variability
- Phantoms.

When appropriate, a Reporting subcommittee might be added.

The suggestion has been to have a clinical use case in mind when developing Claims. The Profile can take a broader approach.

The following updated Gantt chart reflects the US/SWS Technical Committee progress and plan adjustments through the reporting period: