HHSN268201000050C, RECOVERY
Quantitative Imaging Biomarkers Alliance (QIBA)

PROGRESS REPORT: AS OF SEPTEMBER 30, 2011

EXECUTIVE SUMMARY.

During Year 1 QIBA has made significant progress toward creating and implementing a process 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 QIBA 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 completed for CT volumetry and DCE-MRI, and are in development for FDG-PET SUV, lung CT densitometry and airway measurements for COPD, and fMRI for pre-surgical mapping. Also during Year 1, in partnership with the FNIH Biomarkers Consortium, we completed and submitted Briefing Documents to FDA for qualification of quantitative FDG-PET and CT volumetry as imaging biomarkers for drug development. We met with the FDA Biomarker Qualification Review Teams (BQRT) in June (FDG-PET) and August (CT volumetry).

To further improve the accuracy and precision of imaging biomarkers, more research is needed re: some of the sources of variability, and on the impact of various proposed mitigation strategies. We solicited, reviewed, approved and implemented 14 projects funded from the NIBIB contract award to address some of these research needs. Status reports on all those projects are given below. QIBA is thus creating 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 that have been allocated NIBIB contract project funding. Sections C-E give 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, and MRI respectively.

A. OVERALL PROGRAM TASKS 11-19.

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 first contract year we held well-attended public and working meetings during the RSNA Annual Meeting in December 2010, five vendor meetings (Siemens, GE, Philips, Toshiba, and smaller suppliers), and our annual QIBA meeting in May 2011.

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

At the 2010 RSNA Annual Meeting, our technical committees each prepared and presented a poster associated with our "Quantitative Imaging Reading Room" exhibit. General updates were also provided in a Special interest Session on Monday, November 29th, 2010.

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

During the contract year, we published the "QIBA Quarterly" in December 2010, as well as March, June, and September 2011.

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.*

In addition to the vendor meetings at RSNA Annual Meeting, we have completed on-site visits with CT, NM, and MR business units at GE in Waukesha, WI; with the MR business unit at Philips in Cleveland, OH. (with video conference feed to Best, NL); the MI business unit at Siemens in Knoxville, TN; and the Toshiba Research Institute-USA with representatives from MR, NM, and CT.

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 also produced a CT volumetry Profile revision 2 and a Profile for DCE-MRI, and are presently coordinating the public comment period on those documents with colleagues from the Pharma Imaging Group (PIG). We hold regular status discussions with the Pharma Imaging Group, 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 during the first contract year is working towards a consensus protocol for quantitative FDG-PET.

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.

We held specific discussions with these groups associated with our September 2010 Imaging Biomarkers Roundtable, with targeted break-out sessions considering neurological diseases and regulatory issues related to contrast agents (in addition to the prior subjects we have raised in that meeting). Additionally, we invited and received reports from the FDA as well as the Critical Path Institute, and also featured a discussion regarding Ultrasound. Since that meeting we have reached out to several key opinion leaders to discuss creation of an Ultrasound effort as well as to potentially expand the MRI effort to address Diffusion Weighted Imaging.

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.

During the first contract year, we have concluded and submitted 100+ page briefing documents to FDA for quantitative FDG-PET as well as CT volumetry. We have prepared for and met with each respective Biomarker Qualification Review Team (BQRT) in June and August respectively.

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.*

During the first contract year, we met monthly by phone and in person on multiple occasions to administer the allocation of NIBIB project funds. In that regard we have completed the first year allocations for all committees, as well as for the second year in CT and MR. Discussions to decide on year-2 projects in FDG-PET have been held.

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

During the first contract year we focused the modality committees on evaluation of funding requests and the recommendations to the Steering Committee on funding. Additionally, two committees (MR and CT) finalized Profile documents for public comment, inclusive of a deliberative voting process by committee members as to readiness.

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).

During the first contract year, a preliminary version of the Process Manual has been posted to the QIBA Wiki and different steps of the process are being refined through experience by the various teams. Also in the reporting period, we created means for sharing content between protocols and Profiles as well as refined formats and writing methods.

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

a. *We have authored a Special Report that will be published in Radiology during the Spring of Year 1 (2011).*

During the first contract year, two Special Reports have been published in Radiology:

Article "A Collaborative Enterprise for Multi-Stakeholder Participation in the Advancement of Quantitative Imaging" has been published by Radiology. This paper is available online at http://radiology.rsna.org/cgi/content/abstract/258/3/906.

Article "Quantitative Imaging Test Approval and Biomarker Qualification: Interrelated but Distinct Activities" has been published by Radiology. This paper is available online at http://radiology.rsna.org/cgi/content/abstract/radiol.10100800.

b. *We have also initiated formal efforts with FDA/CDER to qualify two biomarkers utilizing these ideas as of this year. We expect to meet with the FDA in a collaborative process and then transition to the formal review phase. As these processes are new to both FDA and us, we are not able to indicate a schedule at this time but will update in our periodic reports. Additionally, early in Year 2, we anticipate formal discussions related to the use of data accumulated for qualification to be contributory to CDRH filing and will update as we get closer to that engagement.*

As mentioned above (Task 13a), we met with the BQRT for each of the two imaging biomarkers on which we seek a qualification result and have started to strategize how to complete the Full Data Packages for them.

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,

In addition to what has already been noted regarding specific topics and breakouts at the Imaging Biomarker Roundtable (Task 13b), the Steering Committee has developed criteria and a procedure for considering and prioritizing new biomarkers to address.

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).*

A panel of experts, convened by the RSNA Board of Directors and chaired by Carolyn Meltzer, MD, Emory University, has met to consider this strategy. A preliminary report is in circulation. It recommends that RSNA continue to support QIBA and makes specific recommendations about such topics as assuring compliance and applicability to clinical care.

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 CTSA Imaging Working Group held a teleconference every other month to facilitate communication and sharing of best practices among funded CTSA sites on issues relevant to imaging in clinical research. On alternate months, the CTSA Steering Committee met. In-

person educational sessions were held by CTSA at the SCTS meeting in April 2011 and at the in-person ACRIN meeting in September 2011.

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.*

This committee has continued to meet and has produced proposals presently being considered by the Steering Committee. The task force has delivered several 'use cases' as well as other documents supportive of defining proposals for implementation. The steering committee decided to form a joint QIBA/Radiology Informatics Committee which met in a face-to-face session in September 2011 to consider how to best move this agenda forward. An action plan is being followed to converge on a specific proposal to the RSNA Board in the March 2012 time-frame.

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.

As noted in Task 18a.

B. ONGOING AND NEWLY FUNDED PROJECTS

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 year project funds in the context of on-going activities.

	Modality	Biomarker	Title	Amount Awarded	Submitter	TimeLine
1a	CT	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
1c	CT	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
2a	CT	VolCT	Assessing Measurement Variability of Lung Lesions in Patient Data Sets	$13,185	Michael McNitt-Gray, PhD (UCLA)	04/01/2011 - 03/31/2012
3a	CT	VolCT	Validation of Volumetric CT as a Biomarker for Predicting Patient Survival	$62,495	Binsheng Zhao, DSc (Columbia Univ)	04/01/2011 - 09/29/2012
4a	CT	VolCT	Development of assessment and predictive metrics for quantitative imaging in chest CT	$50,000	Ehsan Samei, PhD, PhD (Duke)	04/01/2011 - 09/29/2012
5a	CT	VolCT	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.	$42,070	Kavita Garg, MD (U Colorado)	04/01/2011 - 03/31/2012
	CT		TOTAL CT FUNDING AWARDED	$192,750		
6a	MR	DCE-MRI	DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution	$60,347	Edward Jackson, PhD (MDACC)	04/01/2011 - 03/31/2012
7a	MR	DCE-MRI	Software Development for Analysis of QIBA DCE-MRI Phantom Data	$29,975	Edward Ashton, PhD (VirtualScopics)	04/01/2011 - 03/31/2012
8a	MR	DCE-MRI	Digital Reference Object for DCE-MRI Analysis Software Verification	$57,763	Daniel Barboriak, MD (Duke)	04/01/2011 - 09/29/2012
9a	MR	fMRI	Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning	$19,411	Edgar DeYoe, PhD (Med College of Wisc)	04/01/2011 - 03/31/2012
10a	MR	fMRI	Quantitative measures of fMRI reproducibility for Pre-Surgical Planning-Development of Reproducibility Metrics	$33,423	James Voyvodic, PhD (Duke)	04/01/2011 - 03/31/2012
	MR		TOTAL MR FUNDING AWARDED	$200,919		
11a	NM	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
12a	NM	FDG-PET/CT	QIBA FDG-PET/CT Digital Reference	$68,240	Paul Kinahan, PhD (U Washington)	04/01/2011 - 03/31/2012
13a	NM	FDG-PET/CT	Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes	$57,500	Richard Wahl, MD (JHMC)	04/01/2011 - 03/31/2012
	NM		TOTAL NM FUNDS AWARDED	$198,740		
14a	Cross	Cross Modality	Groundwork for QIBA image reference database - QIBA Image Reference	$10,250	Gudrun Zahlmann, PhD (Roche)	04/01/2011 - 03/31/2012
14b	Cross	Cross Modality	Groundwork for QIBA image reference database - QIBA Image Reference	$16,000	Rick Avila, MS (Kitware)	04/01/2011 - 03/31/2012
	Cross	Cross Modality	TOTAL NM FUNDS AWARDED	$26,250		
			TOTAL Round-1 FUNDS AWARDED	$618,659		

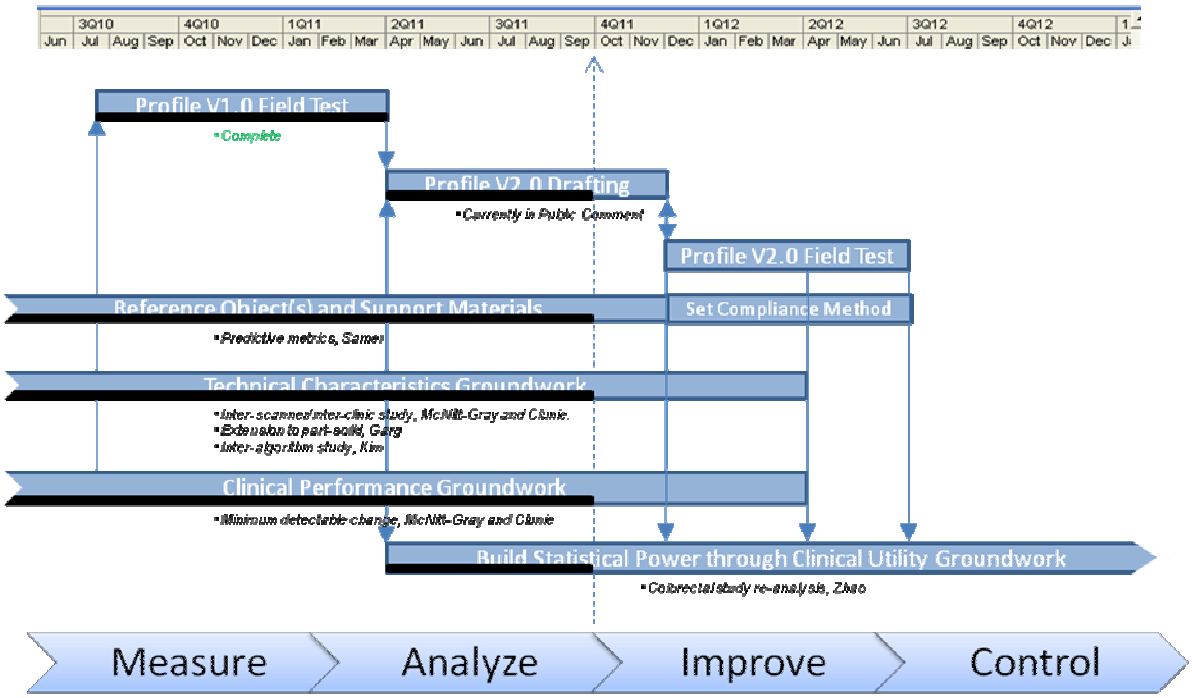
	Modality	Biomarker	Title	Budget request	Submitter	TimeLine
15a	CT	VolCT	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions	$14,110	Michael McNitt-Gray, PhD (UCLA)	08/01/2011 - 07/31/2012
15b	CT	VolCT	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions (1B extenstion)	$13,125	David Clunie, MBBS (CoreLab Partners)	08/01/2011 - 07/31/2012
16a	CT	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	Hyun (Grace) Kim, PhD (UCLA)	08/01/2011 - 07/31/2012
17a	CT	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 - 07/31/2012
3a	CT	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 - 09/29/2012
4a	CT	VolCT	Development of assessment and predictive metrics for quantitative imaging in chest CT **(Carry-over from Round 1)**	$25,000	Samuel Richard, PhD, (Duke)	04/01/2011 - 09/29/2012
	CT		**TOTAL CT FUNDING AWARDED**	**$199,984**		
18a	MR	DCE-MRI	Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects	$175,000	Mark Rosen, MD, PhD (Upenn)	08/01/2011 - 07/31/2012
19a	MR	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)	08/01/2011 - 07/31/2012
	MR		**TOTAL MR FUNDING AWARDED**	**$204,376**		
20a	NM	FDG-PET/CT	Personnel Support for FDG-PET Profile Completion	$16,000	Paul Kinahan, PhD Univ Washington (Dr Perlman)	08/01/2011 - 07/31/2012
	NM		**TOTAL NM FUNDS AWARDED to date**	**$16,000**		
A	NM	FDG-PET/CT	Evaluation of the variability in determination of qPET parameters	$100,000	Richard Wahl, MD Johns Hopkins	
B	NM	FDG-PET/CT		$50,000	Jeffrey Yap, PhD	
C	NM	FDG-PET/CT	PERCIST Validation	$125,000	Otto Hoekstra, MD, PhD (VU MC)	
	NM		**ADDITIONAL NM FUNDS REQUESTED**	**$307,000**		
			TOTAL FUNDS AWARDED	**$420,360**		

C. PROGRESS FOR QUANTITATIVE CT AS OF SEPTEMBER 2011

Progress during the first contract year:

- With respect to CT volumetry:
  - Experimental groundwork:
    - The project "Evaluation of 1D, 2D and 3D nodule size estimation by radiologists for spherical and non-spherical nodules through CT thoracic phantom imaging" has completed and been reported at SPIE 2011.
    - Minimum detectable change project has produced initial results and has organized a follow-up project to consider how workflow affects reader performance.
    - Inter-scanner/inter-site imaging has been completed at all sites using both protocols. All image data has been collected and curated; reader randomization and a power study has been done, and 6 of the 7 readers have completed their reads. The data so far will be transferred to the statisticians this week.
    - The inter-algorithm study design has been largely completed; a sequence of "challenge" problems has been articulated; logistics for the first challenge have been worked out with NIST.
    - Verification of a framework for drawing a correspondence between simple FOM and quantitative imaging performance covering a range of reconstruction algorithms (FBP, ASIR, MBIR) and dose levels has been completed; phantoms are being employed for measurements of NPS and MTF across various dose levels and sizes; comparison is underway.
    - Study design to extend results from solid lesions to part solid is drafted, synthetic test-object lesions in support of this are on order.
    - Completed preparation work for retrospective re-analysis of clinical study donated by pharma including a research agreement with donor, IRB waiver, consensus reading, subset image data selection for the variability study, etc.
  - Profiling:
    - For advanced stage disease, the team has completed the field test of our initial lung cancer protocol and completed writing revision 2 of the Profile and Protocol and has issued them for public comment.
    - The team has updated its "Small Pulmonary" nodule Profile.
- 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.
  - Created a first draft Profile.
- NIBIB funds have been allocated to ten projects, as outlined above in section B.

The following updated Gantt chart reflects the CT volumetry Technical Committee progress and plan adjustments in the year.

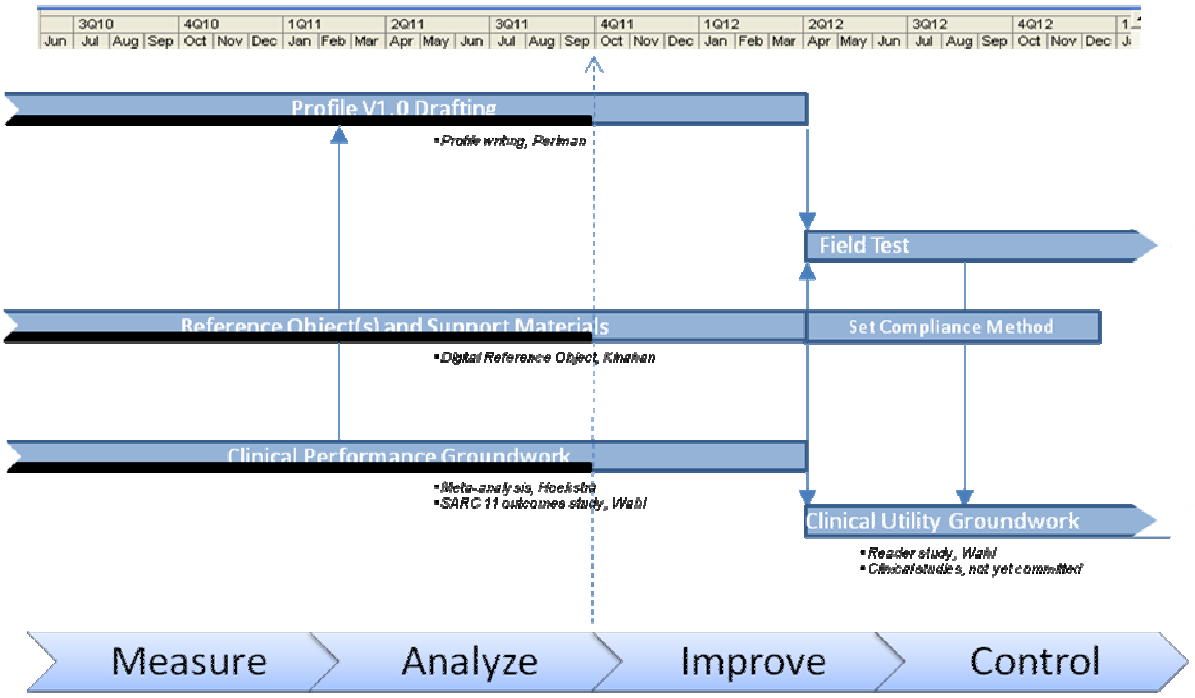


C. PROGRESS FOR QUANTITATIVE FDG-PET AS OF SEPTEMBER 2011

Progress during our first contract year:

- Experimental Groundwork:
    - The Covariates, ROI, Software version tracking, SUV, and QC subcommittees have completed a list of requests that represent requirements to be incorporated into the Profile and have concluded their activities.
    - Two sets of the SARC clinical trial data have been transferred to JHU which has examined its quality. Work has begun on the visual and quantitative analysis. Not unexpectedly, some issues of quality of the entire data set arose. The automated quantitative assessment tool has been refined.
    - With respect to updating and extending cytotoxic- therapy databases related to FDG-PET scans for therapy monitoring:
        - Developed comprehensive search strategy for Pubmed/Embase
        - Extracted relevant studies (reporting individual patient data) by 2 independent readers
        - Developed SPSS database (20 potential variables per study)
        - Completed data-entry on 759 patient data of 27 studies
        - Developed adapted QUADAS tool for analysis of study quality.
    - A virtual (digital) reference test object has been constructed with the following properties: Parametrically defined; contrast, noise and smoothing are adjustable; paired anatomical (CT) and functional (PET) objects.
- Profiling:
    - Considerable progress has been made on a consensus protocol for quantitative FDG-PET in collaboration with people from many societies and geographies.
    - The team has draft Profile text, a gap analysis for completing the Profile has been performed, and an authoring strategy has been set.
- NIBIB funds have been allocated to four projects to author the Profile and build evidence for the biomarker, as outlined above in section B. Three additional projects are under consideration

The following updated Gantt chart reflects the FDG-PET Technical Committee progress and plan adjustments in the year.



E. PROGRESS FOR QUANTITATIVE MRI AS OF SEPTEMBER 2011

Progress during our first contract year:

- With respect to DCE-MRI:
    - Experimental groundwork:
        - The project inter-clinic and inter-scanner study has completed data acquisition and is presently analyzing the results.
        - Specifications for a new phantom design that incorporates experiences from the inter-clinic study have been documented. Resolution of all issues is complete and the phantom is awaiting manufacturing by The Phantom Laboratory.
        - A software package for analysis of phantom data has completed development and unit testing. The final product is now undergoing integration and testing and is scheduled to be complete the second week of October.
    - Profiling:
        - The team completed authoring of the DCE-MRI Profile, ran it through a Public Comment period, and is presently finalizing responses to comments received and issuing of the version of the file for field test.
- The fMRI committee has developed provisional core details for a Profile and has defined tasks and approach to characterize reproducibility in the measurements.
    - Standardized computational sequences are selected, tested and installed including the AMPLE algorithm coordinated between the Voyvodic and DeYoe projects.
    - Data for 8 subjects has been organized in a local imaging database with table entries to facilitate scripted data queries and analysis. fMRI scans are registered with a standard brain atlas, generation of brain activation maps, and calculation of image-based quality assurance QA metrics (image motion, signal drift, signal spikes, task activation).
    - Early versions of a Profile have been discussed, including both the nature of the Claim(s) and how the Details would be determined.
- NIBIB funds have been allocated to seven projects, as outlined above in section B.

The following updated Gantt chart reflects the DCE-MRI Technical Committee progress and plan adjustments in the year.