

**NISTIR 7434**

# **Imaging as a Biomarker: Standards for Change Measurements in Therapy Workshop Summary**

September 14-16, 2006  
National Institute of Standards and Technology  
Gaithersburg, MD 20899

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Ram D. Sriram

**NIST**

**National Institute of Standards and Technology**  
Technology Administration, U.S. Department of Commerce

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# **Imaging as a Biomarker: Standards for Change Measurements in Therapy Workshop Summary<sup>1</sup>**

**Technical Co-Chairs:** Laurence Clarke (NCI) and Ram D. Sriram (NIST)

**General Coordinator:** Linda Beth Schilling (NIST)

## **Executive Summary**

**Background:** Biomarkers are biological indicators of disease or therapeutic effects that can be measured by *in vivo* biomedical/molecular imaging, as well as other *in vitro* or laboratory methods. Recent work has shown that biomedical imaging can provide an early indication of drug response by use of X-ray, computed tomography (CT), positron-emission tomography/CT (PET/CT), or magnetic resonance imaging (MRI). There are three primary sources of uncertainty in using imaging as a biomarker: 1) the biological variability, 2) the variability associated with the clinicians interpreting the images, and 3) the physical measurement variability associated with image data collection and analysis across the same or different imaging platforms. Although biological variability is a large source of error, the physical uncertainty often significantly reduces the robustness of the imaging methods and the clinical decision tools required for quantitative measurement of therapy response over time. Physical and biological measurement uncertainties may be addressed prior to designing a clinical trial and thus help in reducing the case size and cost of a clinical trial associated with a drug submission to the Food and Drug Administration (FDA).

The National Institute of Standards and Technology (NIST) has been approached over the last few years by several industry and medical stakeholders to address the physical sources of measurement uncertainty. NIST's initial research discovered that the characterization of measurement uncertainty poses many complex metrology and standardization problems on a scale that appears to need significant collaboration across the different medical imaging stakeholders. Many of the issues are similar to other scientific domains that NIST has addressed as part of its mission to provide metrology standards to enhance the competitiveness of U.S. industries. To better assess the measurement and standards needs for using imaging as a biomarker, NIST engaged leading representatives from many of the different imaging societies, the imaging, pharmaceutical and e-health and other healthcare stakeholders, as well as other key federal agencies (the National Institutes of Health Institutes and Centers (NIH ICs), and FDA) to organize and conduct a United States Measurement System (USMS) workshop: <http://usms.nist.gov/workshops>. The workshop entitled "*Imaging as a Biomarker: Standards for Change Measurements in Therapy*," was thus held on September 14-15, 2006 at NIST in Gaithersburg, Maryland. (Workshop agenda, presentations and final workshop report will be available at <http://usms.nist.gov/workshops/bioimaging.htm>.)

**Report:** This meeting was the largest USMS workshop held by NIST. It was attended by more than 250 researchers from the medical imaging community including: academia, clinicians and research physicians, imaging and pharmaceutical companies, contract research organizations (CROs) and trade

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<sup>1</sup> This workshop was sponsored by the following organizations: National Institute of Standards and Technology, National Institutes of Health, Food and Drug Administration, PhRMA, Radiological Society of North America, American Association of Physicists in Medicine, Society of Nuclear Medicine, National Electronics Manufacturing Association, American College of Radiology, International Society of Magnetic Resonance in Medicine, The International Society for Optical Engineering, and Digital Imaging and Communication in Medicine.

organizations (NEMA, PhRMA Consortium), representatives from many different imaging societies (RSNA, ACR, AAPM, SNM, ISMRM) and key agencies of the federal government were represented (NIH: NCI, NIBIB, NIA, NIAMS, NIGMS, NCRR; FDA: CDRH, CDER; and NIST: CSTL, EEEL, PL, MSEL, MEL, ITL).

The workshop was organized as follows: (a) presentations from current or planned public-private partnerships that included imaging as a biomarker and the need for associated metrology and standards for Alzheimer's disease, osteoarthritis and cancer, followed by an FDA discussion of these and related clinical trial issues associated with imaging; (b) presentations on the NIST U.S. Measurement System activity; (c) presentations from several of the key stakeholders that outlined their level of interest in supporting standards for biomedical imaging; and finally (d) presentations from the National Electronics Manufacturer's Association (NEMA) and three leading medical imaging companies outlining their interest in collaboration with other stakeholders. Six breakout sessions were organized over the two-day workshop to specifically address emerging imaging modalities being used in the clinical setting for drug or radiation therapy response, and related resources needed to meet the imaging metrology and standards needs for measuring change. Each breakout session was chaired by four representatives from the different stakeholder groups. The breakout session summaries are described in this report. The final workshop session summarized key points from all the speakers and breakout sessions and opened discussion with panel representatives from the stakeholder groups.

The physical measurement uncertainties for monitoring therapy response as applied to different diseases and the need for quantitative measurements were recognized as an important problem to be collectively addressed by the different agencies of the federal government, with NIST recognized as having an important role in the development of needed metrology. There was also very strong expression of interest by all the academic and industry stakeholders to become collectively engaged in finding solutions for these measurement and standards challenges, such as through the different scientific (volunteer) task groups within academic societies and industry trade organizations (PhRMA, NEMA). In addition it was recognized that there was an opportunity to collaborate in other interagency efforts that address the role of biomarkers for drug discovery and response, including potential FDA Critical Path, and NIH roadmap and partnership initiatives, which are described at:

[http://www.fnih.org/Biomarkers%20Consortium/Biomarkers\\_home.shtml](http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml)

<http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html>

<http://www.fda.gov/cdrh/ocd/criticalpath.html>

<http://nihroadmap.nih.gov/>

The workshop concluded with agreement to organize several follow-up meetings between the federal agencies and the academic/industry stakeholders to continue development of a roadmap of how to address both short-term and long-term challenges. One such stakeholders' meeting was held by the leadership of the Radiological Society of North America (RSNA) on November 28, 2006.

Highlights from key workshop findings are given below, in no particular order. Many of the opportunities can be addressed in the short term, and others on the longer term, depending on the complexity of the imaging modality, the particular measurement challenge and the value that the solution could bring to drug development.

- Identify and characterize the physical performance requirements of emerging imaging platforms that are required to measure therapy response, in order for the imaging industry to consider responding to these requirements during new platform introduction or system upgrades.
- Develop open architecture standards, such as that initiated by NEMA-DICOM, that permit the interoperability of software tools for both data collection and analysis, thus encouraging harmonization or ideally greater standardization for targeted imaging drug trials.

- Develop standardized imaging phantoms that are designed to better characterize time-related changes in the physical performance of imaging systems, and to include anatomical, functional and molecular-based measurements.
- Develop and share open-source tools to encourage more standardized methods for phantom data analysis.
- Encourage imaging companies to cross-license biomarker-specific software for data integration and clinical decision tools, as required for the measurement of drug and radiation therapy response.
- Develop public federated image database resources to help standardize image data acquisition, analysis, and related annotation and mark-up methods developed by academia and industry. One example is to permit standardization of methods to benchmark the performance of user-developed or commercial clinical decision tools for the measurement of drug or radiation therapy response. This resource should therefore permit accelerated FDA approval and/or usage of clinical decision change analysis tools and facilitate their broad dissemination and implementation in future clinical therapy trials.
- Develop comprehensive interoperability standards for both user-developed and commercial information technology solutions, such as research and clinical Picture Archiving and Communication Systems (PACS), knowledge-based or decision support systems that support clinical therapy trial data collections and meta-analysis as required for FDA drug submissions.

**Workshop Sponsors:**

NIST	National Institute of Standards and Technology	FDA	Food and Drug Administration
CSTL	Chemical Science & Technology Laboratory	CDER	Center for Drug Evaluation and Research
EEEL	Electronics & Electrical Engineering Laboratory	CDRH	Center for Devices and Radiological Health
PL	Physics Laboratory	AAPM	American Association of Physicists in Medicine
MSEL	Materials Science & Engineering Laboratory	ACR	American College of Radiology
MEL	Manufacturing Engineering Laboratory	DICOM	Digital Imaging and Communications in Medicine
ITL	Information Technology Laboratory	ISMRM	International Society for Magnetic Resonance in Medicine
NIH	National Institutes of Health	NEMA	National Electrical Manufacturers Association
NCI	National Cancer Institute	PhRMA	Pharmaceutical Research and Manufacturers of America
NCRR	National Center for Research Resources	RSNA	Radiological Society of North America
NIA	National Institute on Aging	SNM	Society for Nuclear Medicine
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases	SPIE	The International Society for Optical Engineering
NIBIB	National Institute of Biomedical Imaging and Bioengineering		
NIGMS	National Institute of General Medical Sciences		

## 1 Introduction

Biomarkers are biological indicators of disease or therapeutic effects that can be measured either *in vivo* by biomedical/molecular imaging or *in vitro* by imaging or laboratory methods. Imaging as a biomarker of drug response is becoming an increasingly important field of research, particularly for the emerging trend toward personalized medicine, i.e., patient-specific diagnosis and drug treatment. Recent work has shown that biomedical imaging can provide an early indication of drug response by use of X-ray, CT or FDG PET/CT.

Many sources of uncertainty exist in imaging as a biomarker. Biological variability, for example, is a factor that is both drug- and patient-dependent, thus difficult to characterize or model. However, other uncertainties are associated with the image data collection platform and the robustness of software tools required for reliable, quantitative measurement of change over time, such as tumor volume, radioactive tracer activity, or contrast agent dynamics. All these sources of uncertainty significantly affect the statistical power of clinical drug or therapy trials. Measurement of change over time with imaging for a variety of disease models can be used to identify common factors that give rise to sources of uncertainty.

The development of standards for image quality control, image data collection, and benchmarking of change analysis software tools, as well as image-specific statistical methods, could significantly reduce the size of clinical trials for drug response. The cost of drug development and submission to the FDA by the pharmaceutical industry may soon exceed \$1 billion. Standardized imaging methods may reduce these costs.

A workshop was held at the National Institute of Standards and Technology on September 14 – 15, 2006 in order to understand the measurement and standard needs for imaging as a biomarker, with specific focus on imaging methods for data collection and data analysis in the context of drug or radiation therapy trials. Ram D. Sriram (MEL) and Laurence Clarke (NCI, Detail NIBIB, and Guest Scientist at NIST) served as technical co-chairs, while Linda Beth Schilling (NIST) served as the General Chair. More than 250 scientists from academia, imaging and pharmaceutical companies (PhRMA), Contract Research Organizations (CROs), Trade Organizations (NEMA) and representatives from different imaging societies, and the different agencies of the Federal Government (NIH Institutes and Centers, FDA CDRH, CDER), attended the workshop.

Dr. William Jeffery, Director, NIST, Dr. Belinda Seto, Deputy Director, NIBIB, and Dr. Larry Kessler, Director Office of Science and Engineering Laboratories, CDRH, FDA provided the opening remarks. This was followed by various presentations (which can be found at <http://usms.nist.gov/workshops/bioimaging.htm>) and six breakout sessions.

The breakout sessions addressed the following issues:

- Instrument quality control over the time sequence of a trial (modalities include: X-Ray, X-Ray CT, PET, PET/CT, MRI, MRS, DCE and Diffusion MRI, and other emerging modalities)
- Harmonization of data collection across different commercial imaging platforms
- Creation of standardized, objective performance metrics for image-analysis software using reference image databases or test beds
- Standardized statistical methods for change measurements
- Archival and access methods for image storage, related metadata, and clinical outcome data
- Innovative methodologies for the integration of image and other data for clinical decision making

Workshop participants were asked to address the following questions with respect to the above topics:

- What technological innovations are at stake?
- What is the economic significance of the innovations?
- What technical barriers to the innovations impede progress to the marketplace?

- At what stages of innovation (R&D, Production, Marketplace, End-use) do the technical barriers appear?
- What parts of the technical barriers (current problems) are measurement science or standards development?
- What are the potential solutions to the measurement and standards development problems?
- Who are potential providers of solutions?
- Are there critical roles for agencies of the federal government?

We summarize the presentations and the breakout sessions in the following sections.

## 2 Presentations

On the first day, four presentations described various public--private partnerships, and seven presentations provided stakeholder perspectives including: PhRMA, various societies, software developers, and contract research organizations. On the second day, three presentations provided an outlook from the medical device industry, and the final presentation summarized the workshop, followed by a summary discussion panel.

### 2.1 Standards and Needs from Public--Private Partnerships

The focus of this session was to articulate the measurement science and standards needs of various public-private partnerships and related government efforts.

#### *Alzheimer's Disease Neuroimaging Initiative (ADNI) (Michael W. Weiner, MD)*

ADNI is a \$60 million dollar (over five years) Public-Private Partnership (PPP), with funding from NIH's National Institute of Aging (NIA), National Institute of Bio-Imaging and Bioengineering (NIBIB), the pharmaceutical industry (PhRMA) and other private foundations. The goals of ADNI are to: (a) define the rate of progress of mild cognitive impairment and Alzheimer's disease, (b) develop improved methods for clinical trials in this area, and (c) provide a large database which will improve design of treatment trials (<http://www.adni-info.org>). The long-term intent is to develop a validated biomarker for Alzheimer's Disease clinical trials. Other aims include: developing standards for imaging; improving methods for clinical trials; determining optimum methods for acquiring and processing images; validating imaging and biomarker data by correlating with neuro-psychology and behavioral data; and providing database and biological samples for PhRMA. There are 450 subjects enrolled in 55 sites and all studies will be completed by 2010. Dr. Weiner explained that clinical trialists have to make their own decisions concerning MRI pulse sequences, phantom measurements, choice of sites, and methods to qualify sites. These efforts always delay the startup of any study by several months. He proposed that a database, library, or archive of images be set up where he and all the other scientists can simply "park" the images, so that the rest of the world could also have access to them. He also recommended that NIST, NIH and FDA develop uniform standards for brain MRI and PET clinical studies, so that site performance could be more readily monitored.

#### *The Osteoarthritis Initiative (OAI) (Charles Peterfy, MD, PhD)*

Osteoarthritis (OA), characterized by the erosion of articular cartilage, is a highly prevalent, chronic, debilitating, and costly disease. Currently 13% (35 million) of the U.S. population is afflicted with this disease. It is estimated that this number will increase to 20% (or 70 million people) by 2030. Only symptomatic therapy is available. No preventative or disease modifying therapies with proven efficacy and safety have been introduced. The main barrier to drug development in OA is inadequate understanding of the pathophysiology of the disease, particularly the link between structural abnormalities and clinical outcomes. This has made it difficult to identify potentially modifiable therapeutic targets. Moreover, there is a lack of biomarkers which are suitably validated, discriminative and feasible for studying the disease and putative therapies. The Osteoarthritis Initiative (OAI) (<http://www.oai.ucsf.edu/datarelease/About.asp>) is a public--private partnership (NIAMS, NIA and other NIH institutes, GlaxoSmithKline, Merck, Novartis and Pfizer), with goals to create a publicly accessible resource of images (radiographs and MRI), biochemical and genetic specimens, and associated clinical data to: (a) identify and validate imaging, biochemical and genetic biomarkers for OA; (b) characterize

early natural history and progression of OA; and (c) evaluate risk and prognostic factors for OA onset and progression. The OAI will address these aims by following a cohort of approximately five thousand subjects with OA or at risk of developing OA over a period of four years. Current focus is on knee OA.

Three main components of OAI are:

1. Clinical centers (University of Maryland / Johns Hopkins University, Ohio State University, University of Pittsburgh, Memorial Hospital Rhode Island / Brown University)
2. A data coordinating center led by Michael Nevitt, University of California San Francisco: <http://www.oai.ucsf.edu/datarelease>; and
3. An imaging quality assessment (QA) center led by Charles Peterfy, Synarc Inc.

The imaging protocol for the database is designed to do the following:

1. Provide imaging data on as many joint structures and features believed to be relevant to OA as possible.
2. Provide images able to support as broad a range of existing and anticipated measurement methods for each structure and feature as possible.
3. Balance scientific requirements for image quality and consistency against practical needs of high throughput and patient retention.

Several considerations for an MRI protocol approach, presented at the OMERACT-OARSI workshop for Consensus on OA imaging, December 2002, were discussed. These include the following:

1. articular structures and OA features to focus on
2. measurement methods (quantitative and semi-quantitative) support for these features
3. subject tolerance for these tests
4. generality of the results
5. support for future analysis techniques

The goals of the image quality component include:

1. obtaining uniform, high-quality artifact-free images from all participating sites
2. ensuring longitudinal consistency of key parameters (e.g., signal-to-noise ratio, signal homogeneity, spatial distortion, etc.)
3. developing metrics to compare images from all sites
4. obviating need for repeating imaging by preemptive correction of slowly developing problems

When completed, the OAI will represent the largest publicly accessible scientific and drug discovery resource to date for OA.

*Reference Image Database to Evaluate Response (RIDER)  
and Related Oncology Biomarker Initiatives (Laurence Clarke, PhD)*

The Reference Image Database to Evaluate Response (RIDER) to therapy, initially targeting lung cancer, began as a highly leveraged and collaborative pilot project, initiated in September 2004, by the NCI's Cancer Imaging Program. The goal is to create a web-accessible federated image database resource that is specifically designed and validated to benchmark the relative performance of change analysis tools for drug response using imaging in a standardized manner. This resource could permit accelerated FDA approval of clinical decision change analysis tools and allow their broad dissemination and implementation in future clinical therapy trials.

The RIDER project was organized as a trans-agency effort that involves investigators from several academic sites, and scientists from the NCI's Center for Bioinformatics, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the FDA (CDRH, CDER), and NIST. All of these stakeholders are engaged as active participants of the RIDER steering committee to permit a broad

consensus on the creation of this resource and its planned implementation as an internationally recognized reference standard. Additional RIDER support has been provided by the Cancer Prevention and Research Foundation, as well as information technology (IT) support from the Radiological Society of North America (RSNA). (For details: [http://imaging.cancer.gov/images/Documents/eb7bee83-9e9f-47f8-ab39-2e998bf8a95d/RIDER%20white%20paper\\_071306.pdf](http://imaging.cancer.gov/images/Documents/eb7bee83-9e9f-47f8-ab39-2e998bf8a95d/RIDER%20white%20paper_071306.pdf) ).

The RIDER goals include the following.

1. Rapidly populate this resource by collecting data from currently supported NCI and privately funded (PhRMA) cancer clinical therapy trials, for a range of targeted organ systems and imaging modalities (CT, PET/CT, MRI, Optical). The initial data collections include CT and PET/CT as applied to lung cancer. The RSNA MIRC software (DICOM and caBIG compatible) is being modified as a cost effective open source tool for remote data collection and annotation.
2. Design the case collection and case mark up of the resource and web query methods to permit training and testing of clinical decision tools for change analysis in an objective way, namely to allow this resource to be recognized by both academia and industry as a reference standard. The project therefore involves collaboration with both FDA and NIST scientists to meet these objectives.
3. To include in this resource collections of image calibration data, such as phantom measurements, and other imaging platform performance data, to encourage more standardized methods for both data collection and analysis across different imaging platforms.
4. Develop a scaleable informatics infrastructure for the creation and implementation of this reference resource, including access to open source validation tools, with a goal of meeting the IT needs for not only NCI, but other NIH IC's, FDA and NIST. The long term goal is to encourage an inter-agency effort to create international standards for imaging as a biomarker in collaboration with NIH IC's, FDA and NIST.

The intent of the RIDER project is to seek a second public-private partnership with support from the imaging and pharmaceutical industries during 2006-2007, through a submission of proposals to the NIH Biomarkers Consortium to help create this resource:

([http://www.innovation.org/documents/File/Biomarkers\\_Press\\_Release.pdf](http://www.innovation.org/documents/File/Biomarkers_Press_Release.pdf)). The first NCI Public--Private Partnership directed at lung cancer screening has already been implemented and is to be completed by September 2008 ([http://www.fnih.org/partners/research\\_environment/IDRI.shtml](http://www.fnih.org/partners/research_environment/IDRI.shtml)).

### *FDA Perspective – The Necessity for Standardization of Imaging in Multi-center Clinical Trials for Investigational Drugs and Biologics (George Mills, MD)*

George Mills (currently with Perceptive Informatics) opened his talk by the disclaimer that he is participating as an individual and not as a representative of the FDA, and that his comments should not be construed as any official policy of the FDA. Dr. Mills focused on imaging standards as related to multi-center imaging trials. The FDA's Critical Path Initiative underscores the following issues:

1. Imaging is a key technology for assessing, accelerating the development of, and guiding the use of new therapeutic options.
2. FDA believes that synergy between current drug development programs and current imaging techniques can be created for drug development to work in a more cost effective manner.

Currently, multi-center trials suffer from the fact that participating clinical sites are typically not standardized with any other participating centers in the following areas: imaging technique, imaging

platforms, and imaging archives. Reliable decision making based on medical imaging requires comprehensive standards and tools to maintain integrity and ensure quality of results. Dr. Mills stated that there is a need to specify “in detail” the specific imaging procedures and provide at the minimum the following (both within a site and across sites):

1. Full description of the required imaging parameters
2. The imaging output—hard copy and digital
3. The imaging intervals – formal timeline schema
4. Imaging data archives (databases)

Clinical trial sponsors and contract research organizations (CROs) / should ensure that all specifications are unambiguously articulated. The clinical sites normally do multiple trials. One must ensure that all protocols are properly followed.

Key elements of standardization are as follows:

1. Ensure that all participants in the trials are identified
2. Establish the level of cross site-consistency and the known variances across clinical sites (make sure independent readers are trained appropriately)
3. Clinical sites imaging manuals should be clearly written and must include metadata information
4. Prepare/train/monitor the clinical sites to avoid “drift” (i.e., different interpretations by different imagers)
5. The imaging archive should track and record all steps and document all deviations (transparency)
6. Implement the same, detailed imaging acquisition protocols at all clinical sites
7. Optimize image processing and reconstruction software.

## 2.2 Stakeholder Perspectives

The focus of this session was to review different perspectives on “standardization and harmonization of imaging for clinical trials” from various industry and scientific society stakeholders.

*Pharmaceutical Research and Manufacturers of America (Mostafa Analoui, PhD)*

There are lots of questions that can be raised regarding imaging, but the focus here is on clinical trials for imaging as a biomarker. The key challenges from PhRMA’s perspective are as follows (<http://www.phrma.org>):

1. Image acquisition: high cost associated with optimal acquisition protocols, insufficient plans for re-utilization and sharing, inconsistent image quality.
2. Image analysis: large uncoordinated investments for tool development and validation, lack of standards and guidelines for PhRMA, subjective and sub-optimal analysis, manual measures requiring large number of technicians, and long delay for execution.
3. Image archival and management: lack of standards for image archival and access, repeated investment across PhRMA and clinical trials, increased interest from regulators for access to original and analyzed images, disconnect between clinical data and imaging for access and archival, potential loss of opportunity for development of large clinical imaging databases to support biomarker strategy and future developments.
4. Radio labeling of biologicals: extensive safety assessment may be required to deploy radio-labeled versions of large biologicals, and need for guidance for assessment of radio-labeled version of a biological.

There is a need for consensus and partnership toward developing an industry standard, regulatory and clinical guidelines for *harmonizing* with existing standards and *standardizing* through new standards the quality, cost and time associated with managing imaging in clinical trials.

In order to answer the question on the need for standards, including harmonization, we need to develop a list of areas where guidelines would be required, and identify various partners and players (e.g., PhRMA, NEMA, government agencies [NIH/FDA/NIST], medical imaging instrumentation makers, CROs, and clinical imaging sites).

*From DICOM to IHE and Beyond:*

*Radiological Society of North America (R. Gilbert Jost, MD, President-elect RSNA)*

The DICOM standard was demonstrated at the 1992 annual RSNA (<http://www.rsna.org>) meeting. This demonstration involved a partnership with the device manufactures, the academia and RSNA, and thus laid foundations for the importance of an impartial provider (RSNA) for creation of DICOM infrastructure. At that time DICOM successfully demonstrated the scope of image interoperability. It was soon realized that purely transferring images is not enough. Rather, we need to have a framework for all the computer systems in a medical enterprise to communicate with one another. Along with HIMMS, RSNA put forth the idea of integrating the health care enterprise (IHE). After several years (starting in 1996), a vision was created by December 1999 with a plan for multi-year demonstrations, starting with an initial functional systems architecture in the first year. To date there are over 100 vendors involved worldwide in IHE, which includes five technical frameworks, 37 integration profiles, and nine domains within the IHE IT infrastructure (<http://www.ihe.net>). Key lessons learned are: industry should drive the process, a neutral party should act as a facilitator, and publicity is key to maintaining momentum and for attracting new partners. The biomarker initiative could benefit from above lessons, with the different agencies of the federal government playing a supporting role.

*Standards for Clinical Image Data Collection: ACRIN Vision*

*American College of Radiology (Mitch Schnall, MD, PhD, Chair-elect ACRIN)*

American College of Radiology Imaging Network (ACRIN) (<http://www.acrin.org>), an NCI funded cooperative agreement (U01), represents a network of over 100 institutions in the U.S., Canada, and Europe that has accrued over 70,000 subjects onto imaging clinical trials. ACRIN's IT infrastructure consists of a network of PCs (at local institutions), where security and privacy of records are ensured and a central image store supports image archiving. Currently, there are over 14 million images (13.1 terabytes), gathered from over 76,000 patients, in the central imaging archive. ACRIN is developing several internal standards for analyzing and processing data: 1) image quality assessment, such as for system qualification (calibration and performance) and for image exam quality (protocol compliance and image quality); 2) qualitative imaging interpretation, such as developing standards of practice; and 3) qualitative imaging analysis, such as standards for process documentation and various test suites for reproducibility.

Challenges to image analysis include the following:

1. Variable image reconstruction from different vendors results in variable partial volume effects.
2. It is difficult to validate algorithms across manufacturers as the data is generally processed with manufacturer specific procedures.
3. There is no agreement on what "signal" to measure or how to represent it.
4. There are no means of validating analysis (e.g., precision/accuracy against performance standards).

5. Image metadata should be incorporated in image archives: we need standards for representing this metadata over time and standards for linking features to images.

In summary the ACRIN vision is for standards and support for: images, metadata, structure for tracking lesions/findings, imaging common data elements (CDE), query standards based on CDE (including access control/authorization), and compliance with FDA's 21 CFR 11. ACRIN has considerable test data and is willing to act as a testing facility. As a neutral entity, ACRIN can act as a nice playing field for various stakeholders and is interested in collaborating in the imaging as a biomarker effort.

*AAPM: Imaging and Phantom Standards for Data Collection and Analysis*  
*American Association of Physicists in Medicine (James Purdy, MD, PhD)*

AAPM (<http://www.aapm.org>) is a scientific, educational, and professional organization of over 5000 medical physicists. Its mission is to advance the practice of physics in medicine and biology by encouraging innovative research and development, disseminating scientific and technical information, fostering the education and professional development of medical physicists, and promoting the highest quality medical services for patients. AAPM has a strong history with working with NIST, such as the protocols for the determination of absorbed dose from high-energy photon and electron beams. The Radiological Physics Center (RPC), a part of AAPM, has been funded continuously by NCI since 1968 to provide quality auditing of dosimetry practices at institutions participating in NCI cooperative group clinical trials. (See <http://rpc.mdanderson.org/rpc/>.)

There is a critical need for an Imaging Physics Center (funded by NCI) to provide imaging practices in a similar manner. AAPM's Imaging/Therapy Physics Committees could serve as the scientific advisory body to this center. There is a transition happening in radio-therapy (RT), from two-dimensions (2D) to three-dimensions to intensity modulated (IMRT) to image guided RT(IGRT). Using portals for 2D RT is not a very good idea, due to insufficient resolution. IMRT requires a physician to more clearly (quantitatively) define volumes and treatment objectives at beginning of the planning process. There are many challenges for image-based RT: defining basic technical/clinical QA criteria necessary for protocol participation, and dealing with heterogeneous and proprietary data formats. There is a need to accurately characterize/specify volumes in the evolving image-based RT.

Key challenges for radiation oncology are as follows:

1. Radiation oncology department digital data storage needs increase dramatically with the use of IGRT.
2. IGRT clearly points to a need for a new IT infrastructure for radiation oncology, i.e., something similar in some ways (but uniquely different in other ways) to a diagnostic PACS.
3. Multiple data types need to be archived, and data types, data/work flow and software tool issues must be addressed.

In summary, AAPM has played a key role in standardizing dose delivered, RT nomenclature, QA, etc., in 3D CT/IMRT/IGRT clinical trials, along with ATC (Advanced Technology QA Consortium). The AAPM can play a similar role in helping imaging standards and needed informatics infrastructure to further develop imaging to measure therapy response and efforts to achieve these aims are already in progress.

The AAPM has formed a new working group for exploring how to develop standards for imaging as a biomarker, formally voted upon at the last AAPM annual meeting, and has formed a joint task group for PET/CT in collaboration with the SNM as mentioned below.

*Imaging and Phantom Standards for Data Collection and Analysis.*  
*Society for Nuclear Medicine [SNM] (Sandy McEwan, MD, President-elect SNM)*

The idea of molecular imaging is becoming increasingly important, due to recent trends toward personalized medicine. Currently we use  $^{18}\text{F}$ -FDG as the radio tracer and results are generally binary, i.e., either there is uptake or not. However, we need to know the level of uptake. Over the next few years, we will witness the arrival of new radiotracers (FDG may not be the primary tracer). Molecular imaging with these radiotracers will allow us to:

1. Understand normal functioning of molecules, cells, organs, and organisms; assess the biological nature of disease early and throughout its evolution; assess progressive developmental, degenerative, and disease changes *in vivo*.
2. Facilitate drug discovery and development; provide biological information for the development and assessment of innovative therapies.
3. Predict, monitor and measure treatment response; and help in clinical practice.

Workman P. et al., JNCI 2006; 98(9):580-598, have provided an excellent list of measurable endpoints for various trial objectives. Examples include expression of molecular target (erbB2) if the objective is patient selection, pharmacokinetic properties in plasma and/or tissue if the objective is determination of concentrations for activity at the site of action, etc. Unless we can link some quantitative measure to an objective it reflects the lack of confidence in our ability to measure and quantify.

There are three issues associated with the dissemination of PET radiotracers/MI into clinical practice:

1. Clinical trials: what are the measures of validating tracers with patients outcomes, and how do we tie new imaging methodologies into “omic” profiling and treatment planning and stratification? How do we data that prove clinical effectiveness?
2. How do we develop standards for quantitative data to support clinical trials and routine applications?
3. How do we address regulatory, IP and clinical translation issues to ensure the development of the next generation of molecular imaging probes?

SNM has set up a clinical trials group that addresses issues associated with MI radiotracers. This group will deal with development of PET tracers, validation and standardization of quantitative tracer uptake, design and conduction of clinical trials, integration with other imaging modalities, among other issues. In terms of standardization requirements, we need quantification measures of radiotracer uptake and develop validation procedures to ensure that these measures are compliant across platforms and between sites. At the end of the day we need to define correlative outcomes required for imaging biomarkers.

We are looking at a series of stages to approach this problem:

1. Stage 1 will assess our current capability in measuring radiotracer uptake. This would involve a 9-12 center study representing all major manufacturers, where two phantoms will be shipped to each center and various data analysis performed on the output. This stage will allow us to perform: cross platform comparison and validation, comparison and validation between centers, inter-center temporal comparison and validation, SUV (standardized uptake value) vs. non-SUV based quantification. Additionally, we may be able to determine the sources of error and provide recommendations for correcting variables.

2. Stage 2 will involve correlating phantom data with  $^{18}\text{F}$ -FDG and other radiotracers uptake in patients. The outcomes here would be to validate Stage 1 data, correlate biological and phantom data, understand variables between radiotracers, difference between SUV and non-SUV quantification, determine sources of error, and provide recommendations.
3. Stage 3 will correlate the quantified biomarker with an outcome; this is where the rubber meets the road. Here, we determine whether we can make a difference in clinical management.

In summary we believe we have developed a series of experiments that can take quantitative imaging and understand errors right away, through to outcome measures that may well impact the way a new drug is either accepted, validated, approved, or rejected.

*Information Technology and Architectures for Imaging Biomarkers*  
(Michael Hehenberger, PhD)

Information-based medicine is an approach that transforms existing medical and pharmaceutical practices with actionable knowledge generated from the integration of clinical and biomedical data. It involves integration of information from life sciences, such as those generated by genomics, proteomics, and information generated through clinical practice, such as electronic health records, image data, and predictive medicine. Hence, information-based medicine would require access to diverse information in heterogeneous repositories in an integrated manner. Biomedical imaging data must be integrated with clinical, research, and environmental data to enable the desired transformation of healthcare toward “personalized medicine.”

There are several challenges for IT in support of biomedical and molecular imaging. At the image acquisition stage, there is a need to handle thousands of images per patient case, which requires considerable processing power and high input/output/network bandwidths. During image processing and visualization, innovative methods are required from image visualization, quantitative analysis, and 3D reconstruction. Routing of images from multiple sources requires intelligent workflow management and appropriate secure transfer techniques, including dealing with large object transmission and exchange using standard formats. Storage and retrieval management will need to deal with very large file systems, standard, controlled, and regulated access (including HIPAA compliance), data mining from heterogeneous sources, image versioning, semantic annotation, etc.

There are standards requirements in each of the above stages. In the image acquisition stage, we need adapters for image capture, including normalization to DICOM 3.0, metadata formats, and support for data cleansing, compression, privacy. Integration of image data into existing standards, such as HL7, and frameworks, such as IHE, is a must. This is also true for storage management. In addition we need standard plug-ins for various heterogeneous data and integration between repository and storage infrastructures. A personalized web-based access with appropriate security features to this infrastructure is required. The entire IT infrastructure should support regulatory compliance, such as full audit trail, electronic signatures, role-based security, controlled import/provisioning.

IBM has an important role to play in the imaging as a biomarker venture, including organizing various biomarker summits. It has developed several software modules to facilitate the integration and management of various information sources. Finally, the role of various healthcare stakeholders is to agree on imaging biomarker strategies and standards needed to move ahead.

*Imaging Contract Research Organizations, Clinical Trials, and Standards*  
(David A. Clunie, MD)

Contract Research Organizations (CROs) provide a wide range of research services to pharmaceutical companies. The clinical trials are normally outsourced to a CRO. Hence, CROs play a very important role in clinical trial management. As CROs deal with multiple companies, standards are very important to them (i.e., imaging CROs love standards). Imaging CROs generally target specific markets. For example, they don't deal with medical devices. The standards needs for clinical trials which seek to prove technology and concepts are different from commercial (pharmaceutical trials) which seek to register a new agent. Commercial trials recruit patients wherever they can get them. These trials need independent reads, are strictly regulated, must have data integrity and reduced variance, and have strict software validation requirements.

CROs involve thousands of sites, as opposed to a few hundred sites (mostly academic) such as with ACRIN. The on-site PIs are generally Internists in these clinical trials (we might not even see a radiologist in the actual clinical trial team). The information flow in a clinical trial is as follows: various sites generate images and send these images, along with other information, to an imaging CRO; these images are analyzed and the results, images, and associated measures, are sent to the sponsor (usually a pharmaceutical company); the sponsor files this with an appropriate regulatory agency. This flow is not strictly linear and includes feedback loops. There are many functions that an imaging CRO performs: trial design, logistics of trial conduct, independent review, submission publishing, and archival of data. The independent review is both quantitative and qualitative and involves human subjectivity. There are several opportunities for standardization, apart from the change detection focus of this workshop:

1. Trial design and conduct (e.g., RSNA's Uniform Protocols for Imaging in Clinical Trials)
2. Site equipment qualification (e.g., American College of Radiologists accreditation)
3. Acquisition of images (e.g., UPICT)
4. Transfer of images from sites (e.g., DICOM, IHE, RSNA's MIRC)
5. Internal use within core labs (DICOM)
6. Conduct of independent reads (for FDA)
7. Response criteria and change detection (considerable gaps exist and we need to look to beyond RECIST)
8. Tools for reading and analysis (considerable gaps)
9. Quality control, assurance and improvement (considerable gaps)
10. Submission to regulators (considerable gaps)
11. Compliance and certification (easy to talk about standards, but who is going to police these standards and ensure compliance with the standards)
12. Archival and re-use (no standards for long term retention)
13. Audit trials (no standards for interoperability).

In terms of standards for image transfer between sites, there are three issues that need to be addressed: 1) content and media; 2) network; and 3) film. DICOM seems to satisfy the requirements for media transfer. Network transfer poses several challenges, such as lack of a standard network infrastructure, de-identification, workflow issues, and security technology and policy. Perhaps, we can leverage off the recent Nationwide Health Information Network Initiative. One key problem that we need to address is that standards are poorly supported in cutting-edge academic research. For example, these centers tend to focus on innovative algorithms and don't give much thought to a number of issues important to the commercial world, e.g., robustness, ease of use, data transfer, documentation, etc. This may, in part, be mitigated by the caBIG eXtensible Imaging Platform (XIP) effort, which plays a considerable emphasis on interoperability of software tools standards. Finally, standards are needed if they add value and used. Otherwise, there is no point in developing standards.

## 2.3 Medical Imaging Integrated Solutions

Andrew Whitman, Vice President, National Electrical Manufacturers Association (NEMA), chaired this session. He provided a short overview of NEMA, whose mission is “to promote the competitiveness of its member companies by providing quality services that will impact positively on standards, government regulations and market economics.” NEMA publishes over 500 standards and plays a key role in medical imaging. NEMA promotes the value of medical imaging to the external community. One of the standards that NEMA helped develop is the DICOM standard. NEMA views standards as facilitating technology innovation. Andrew Whitman volunteered to put together a workshop for phantom manufacturers. He also indicated that NEMA is very interested in working with various stakeholders in the imaging as a biomarker thrust and as a potential industry partner in the trans-agency Biomarker Consortium ([http://www.innovation.org/documents/File/Biomarkers\\_Press\\_Release.pdf](http://www.innovation.org/documents/File/Biomarkers_Press_Release.pdf)). A transcript of the question and answer session following the imaging industry speakers is presented in Appendix A.

### *The Development of Imaging Agents for Diagnosis and Therapy Monitoring: General Electric Health Care (Jonathan Allis, PhD)*

General Electric Health Care, headquartered in United Kingdom, is a \$15 billion dollar unit of the General Electric Company. It has expertise in medical imaging and information technologies, medical diagnostics, patient monitoring systems, performance improvement, drug discovery, and biopharmaceutical manufacturing technologies. General Electric Health Care is organized into three thrusts:

1. Imaging, monitoring
2. Medical diagnostics
3. Life sciences.

The R&D in medical diagnostics includes:

1. Development of next generation X-ray and MR contrast agents
2. Polarized gases for respiratory disease
3. Molecular agents for Angiogenesis, Alzheimer's, Parkinson's, Heart failure, Bladder and Prostate Cancer (SPECT, PET, Optical, MR, Ultrasound, CT).

The issues GE faces are the same issues regarding variation and recruitment in the pharmaceutical industry, complicated by multi-center imaging and combination of various products (i.e., imaging agent + hardware + software). The statistical challenge for clinical trials is to calculate the number of subjects (N) needed for a trial. This number is dependent on multiple factors. The only factor that can be controlled is the variance in imaging. This can be achieved by building in quality into the study, reducing the number of trial centers, and improving analysis software. GE's six sigma technique proved useful in improving quality of data acquisition and interpretation. In traditional imaging, a scan is taken and then several radiologists read the images; this creates variability due to different observer interpretations. The technique that GE would like to adopt is a model-based approach, where biological models and statistical models are incorporated into the analysis process.

In terms of standardization, vendors try to differentiate themselves (i.e., be competitive) and implement imaging techniques taking into account their system imperfections. Unlike DICOM, where there was a

user demand, there does not seem to be a user driven requirement for standardizing machines. However, standards for system performance would drive quality and “raise all boats.” There is also a demand for a common lexicon (ontology) of imaging and a forum to discuss cross-vendor imaging for the pharmaceutical industry. GE would be very happy to be a part of this effort.

*Medical Imaging-Integrated Solutions: Measurements in Therapy*  
*Philips Medical Systems (David Rollo, MD)*

A Med-Pac (<http://www.medpac.gov>) report in 2005 to the Subcommittee on Health, Committee on Ways and Means, U.S. House of Representatives, indicated that there is an escalating utilization of diagnostic imaging and that diagnostic imaging is a major cause of the increases in healthcare costs. This report also pointed that there is inadequate evidence that diagnostic imaging actually improves clinical outcomes. Med-Pac further asserted that “setting standards should increase the quality of imaging services provided to Medicare beneficiaries, not decrease access, and potentially decrease spending by reducing duplication of images and eliminating unnecessary services.”

David Rollo (currently with CellPoint) testified to the committee on the behalf of the device manufacturers and was challenged by the committee to provide evidence that imaging could reduce healthcare costs. He found out that such evidence is not clearly articulated in the literature. He believes that molecular imaging could provide clear documentation for demonstrating the benefits of imaging. Some examples of the lack of standardization brought out by a NEMA consultant include the lack of:

1. Patient preparation protocols
2. Acquisition protocols
3. Clinical validation of post acquisition processing
4. Guidelines for applying post acquisition processing
5. Recommendations on how to optimize image quality and diagnostic content for devices which vary in performance (between manufacturers and devices by a manufacturer across time). For example, for PET (in terms of device variance) there are seven different detector types, eight different reconstruction alternatives, spatial resolution variance between 4.5-6.9 mm, and noise-equivalent counts (NEC) variance between 30-80 keps at clinical dose.

SPECT (Single Photon Emission Computed Tomography) has recently emerged to be of considerable use. It is similar to PET, but the radioactive substances (agents) used in SPECT have longer decay times than those used in PET. Currently, there are more than 15 types of SPECT agents that have been approved; each of these is target specific. SPECT agents can be used in molecular medicine, which can be viewed in three stages:

1. Molecular diagnostics, where a biological marker such as PSA first identifies predisposition to a particular disease
2. *In vivo* molecular imaging, where the disease specific SPECT agent can target the site
3. Therapeutic molecular imaging, where SPECT agents can be used with chemotherapy or radiation therapy as a guided missile to treat the disease.

SPECT needs the addition of CT to provide the exact location of the disease (or tumor). Hence, CT is necessary for SPECT. The goals for biomarker imaging in general are two fold:

1. Consistency in image quality and reproducibility of diagnostic content resulting in:
  - a. increased diagnostic accuracy

- b. increased confidence in physicians interpretation
  - c. improved decisions regarding most appropriate therapy
  - d. improved capability to quantify Rx dose and efficacy
2. Repeatability of diagnostic decisions for the most appropriate therapy independent of the geographical location, vendor or site for service.

Standardized reconstruction algorithms, in collaboration with the pharmaceutical industry, will be needed for effective SPECT/CT use. For successful biomarker imaging, the recommendations for various stakeholders include:

1. Vendors need to collaborate with the pharmaceutical industry to develop clinically validated software solutions which optimize image quality, diagnostic content and provide for quantification measures on tumor viability, and they need to cross license software solutions to assure optimized outcomes at all points of care.
2. Government agencies need to establish accessible databases for software development and require that new reconstruction software be clinically validated and certified in terms of diagnostic accuracy for intended applications.
3. Professional medical societies must establish standardization guidelines for: clinical indications for performing studies, recommended acquisition and processing protocols, and training and certification requirements for staff and facilities.

In summary, we need to:

1. Validate biomarker imaging as providing improved diagnostic accuracy and more appropriate therapy decisions than traditional imaging for oncology, cardiovascular, and neurological diseases.
2. Validate consistency and reproducibility of biomarker imaging independent of geographic location, device manufacturer, and clinical setting for the device.

*Imaging as a Biomarker: Industry Perspective on Data Integration Requirements.  
Siemens Medical Solutions (Heinrich Kolem, PhD)*

Extending the points made by the previous two speakers, Heinrich Kolem focused on the integration issues, and the development of standards for integration. Siemens believes that the innovation in molecular medicine will be possible through the seamless integration of *in vitro* diagnostics, molecular imaging, knowledge-driven healthcare, and clinical trials. Siemens clinical trial solution involves five stages: 1) protocol development; 2) site/patient recruitment; 3) trial execution; 4) data management; and 5) trial analysis/submission. Different types of data are generated through this process and these data need to be integrated properly.

Siemens currently provides multi-modality fusion software for data collection and data management-collaboration solutions to the NCI's Network for Translational Research in Optical Imaging (see the NCI website for more on this initiative:

<http://imaging.cancer.gov/programsandresources/specializedinitiatives/ntroi>).

Siemens' REMIND (Reliable Extraction and Meaningful Inference from Non-structured Data) extracts and combines data from various databases, unstructured text, and images, and produces, through probabilistic inference, high quality structured clinical patient data. Finally, standardization of imaging protocols may be feasible for widely used clinical techniques, but is very hard for evolving technologies. The recommendation for integrated systems is to first standardize data exchange formats, and then standardize processes and workflows.

### 3 Breakout Sessions

The following six parallel breakout sessions, focused on the issues outlined in Section 1, were held:

1. X-Ray and X-Ray CT: What can be measured over time?
2. PET and PET/CT: What can be measured over time?
3. MRI, MRS, DCE, and Diffusion MRI: What can be measured over time?
4. Open architecture and software tools: Image and metadata collection and analysis, data integration and display
5. Resources for imaging systems, benchmarking of image processing and data integration tools, and related statistical methods
6. Data archival and access methods.

Based on the input provided by the session chairs and co-chairs, the deliberations were reported out to the full workshop in four categories: 1) customer needs; 2) current problems and measurement issues; 3) solutions, for addressing the gaps; and 4) suggested contributions from government agencies.

#### 3.1 Breakout Session 1: X-Ray and X-Ray CT: What can be measured over time?

Chair: Charles Peterfy, MD, PhD, Co-chairs: Robert Ford, MD, Xiang (Sean) Zhou, PhD, NIST Support: Lisa Karam, PhD and Herb Bennett, PhD

*Topic 1: Characterization of structural change of pathology by quantitative analysis of CT images.*

Customer needs: Lung cancer kills more people than any other cancer in the U.S. It is estimated that approximately 170,000 thousand cases are diagnosed with lung cancer each year; total estimated new cancer cases—not including basal and squamous cell skin cancers -- is approximately 1.4 million. In 2006, it is estimated that 162,460 deaths will occur due to lung cancer; the total deaths due to all cancers is estimated to be 564,830 (<http://www.cancer.org/>). Several studies indicate that the number of people having lung nodules range from 50 to 100 million (not all of these are malignant). CT imaging plays an important role in detecting these nodules.<sup>2</sup> Further, about \$14 billion dollars are spent each year in the treatment of osteoporotic fractures; CT is widely used to detect these.

Current problems and measurement issues:

There are several barriers to innovation for CT due to the lack of:

1. Understanding of the error sources in CT, which affects quantification
2. Performance standards in CT or standard means to assess performance
3. Understanding of uncertainty of minimally significant change thresholds in relation to scanner variability
4. Information about tumor biology (i.e., tumor structure)
5. Standard phantoms (similar to MRI group) and scanning protocols to assess scanner performance
6. Measurement and understanding of voxel characteristics between scanners

Proposed solutions:

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<sup>2</sup> A study indicating that annual spiral CT screening will result in detecting lung cancer that is curable was published in the October 26, 2006 issue of the New England Journal of Medicine.

1. Create a standard image database with “ground truthed” data for investigating clinical significance thresholds and image processing methods (such as LIDC, IDRI, RIDER, etc.). For example, for lung cancer, one can measure size (volume or area), function (perfusion), or structure (tissue characterization).
2. Standardize the basic unit of measurement across scanners, such as the voxel for CT. The variance in this measure needs to be understood with an “intensity and spatial/geometrical phantom”, as well as with a “biological tissue phantom.”
3. Develop appropriate phantoms for scanner performance evaluation.

Suggested government roles:

1. NIH and NIST to facilitate and support research where needed to address the above.
2. NIST could provide guidance on phantom development based on common metrology methods.

**3.2 Breakout Session 2: PET and PET/CT: What can be measured over time?**

Chair: Paul Kinahan, PhD, Co-chairs: David Mozley, MD, Merck, David Rollo, PhD, MD, Philips Medical Systems, Saara Tooterman, PhD, Virtual Scopics (could not attend), NIST Support: Brian Zimmerman, PhD and Jeffrey Cessna, PhD

*Subtopic 1: Imaging response to lung cancer therapy with <sup>18</sup>F-FDG (Fluorodeoxyglucose-18).*

Customer needs: PET/CT (with FDG, which is used in many trials) has considerable potential for assessing the response of drug therapy (more than 10% of the CT scanners used are PET/CT scanners). However, for trials of new therapies multi-center trials are needed for greater accuracy. Hence, there is a need to standardize protocols and reduce variability. This will result in reduced costs and better quality in drug development.

Current problems and measurement needs:

1. Significant variability in estimating tracer uptake due to differences in scanner algorithms, processing parameters, partial volume effects, across-tumor heterogeneity, and method of reporting (e.g., max vs. mean Specific Uptake Value or SUV).
2. Unknown longitudinal stability of scanners.
3. Operator errors in protocol compliance, calibration, acquisition, process of measurement, analysis, etc.
4. Variations in DICOM interpretation/implementation and insufficient information in DICOM headers needed for change management in clinical trials.<sup>3</sup>
5. Integration of trial protocol into on-site clinical practice.

Proposed solutions:

1. Develop standardized phantoms relevant to imaging tasks with different lesion sizes. At a minimum this would be imaged on representative scanners (i.e. one from each manufacturer) or potentially imaged as a qualification step by every participating imaging site. (Potentially combined with CT DQC phantom.)
2. Introduce QA trending tools to plot QA results as a routine procedure.
3. Generate digital phantom images to test manufacturers’ display and analysis tools, in particular SUV values and ROI definitions and estimated values.

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<sup>3</sup> David Clunie pointed out that this is being currently addressed and a draft specification is out for comments.

4. Incorporate information needed into daily QA/QC.
5. Develop on-site operator manual and/or training.
6. Use FBP (Filtered Back Projection) for images used to report quantitative results, in addition to iterative methods, if desired by site.
7. Introduce timing standards traceable to NIST.
8. Calibrate patient weight properly.
9. Form standards group for site qualification for assessment of response to therapies.
10. Need a RIDER-like database for comparison of results.

Suggested government roles:

1. Scientific and programming support by NIH and NIST.
2. NIST assistance with phantom definition and longitudinal scanner calibration and timing standards time, weight and activity.
3. NIST assistance with standards definitions.

*Subtopic 2: Imaging progression of Alzheimer's Disease in ADNI (Alzheimer's Disease Neuroimaging Initiative) study.*

Customer needs: America is graying. The number of Americans over 65 years of age is expected to reach 70 million by 2030<sup>4</sup>. Alzheimer's Disease is likely to have a profound effect on this population. The ADNI, sponsored by NIH, is a major research venture that aims to study whether "brain imaging can help predict onset and monitor progression of Alzheimer's Disease." Leading research laboratories are currently in the process of acquiring PET/CT images for this study. This will eventually lead to a considerable dataset, which needs to be managed properly, in particular for drug therapy. An effective database management strategy would aid in the design of imaging trials with fewer patients and provide an increased ability to detect smaller changes.

Current problems and measurement issues: In addition to the problems outlined in *Subtopic 1: Imaging response to lung cancer therapy with <sup>18</sup>F-FDG (Fluorodeoxyglucose-18)*, two issues were raised:

1. Patient motion between emission and transmission/CT scan, leading to potentially confounding errors in FDG uptake. Small head motions between emission and transmission/CT scan lead to inaccuracies in attenuation correction. These resulting effects in the tracer uptake image are small, but Alzheimer's studies can rely on changes of only a few percent per year. Amount of motion and consequent impact on PET brain image is unknown on a patient-by-patient case;
2. Considerable variability in normal patients.

Proposed solutions:

1. Develop a more stable holder for the patient's head.
2. Automate estimation of motion (i.e. rigid-body image registration using mutual information cost functions), followed by re-alignment of emission and transmission/CT scan data before attenuation correction.
3. Require head motion tracking with position-sensing devices (e.g. Polaris, Varian RPM), which should be followed by re-alignment of emission and transmission/CT scan data before attenuation correction.
4. Use an open source normal case database to determine statistical significance.

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<sup>4</sup> *Digitally Monitoring Mom*. Available at: <http://www.forbes.com/2003/08/14/0814monitorpinnacor.html>

Suggested government roles:

1. Scientific and programming support by NIH.

*Subtopic 3: Development of specific molecular probes, such as hypoxia markers, nucleoside transporters, and steroid receptor assays.*

Customer needs: Several promising new molecular probes (e.g., F-18 fluoromisonidazole (FMISO) and F-18 fluorodeoxythymidine (FLT), etc.), which can expand the role of PET/CT in cancer detection, are currently being developed. There is a considerable need for standardized protocols and measurement techniques for tracer uptake.

Current problems and measurement issues:

1. Currently viewed as a “cottage industry” in academia and industry leading to uncoordinated efforts (only counter-example is NCI sponsored F-18 Fluorothymidine [FLT] trial). This also leads to IP-driven lack of information sharing.
2. Lack of methods to analyze various studies using new molecular probes? (i.e. ranging from full kinetic models with arterial sampling to 'simple' SUV).
3. Lack of standardized protocols for clinical trial design.
4. Lack of techniques for correlation of outcomes from multi-center trials.
5. Variability in estimating tracer uptake due to differences in scanner algorithms, processing parameters, partial volume effects, and method of reporting (e.g. max vs. mean SUV or other metrics, as well as ROI definition for smaller lesions).

Proposed solutions:

1. Develop standardized phantoms relevant to imaging task.
2. Develop standardized analysis and reporting methods.
3. Need an independent facilitator for standards.
4. Accelerate introduction of new probes in conjunction with larger clinical trials.

Suggested government roles:

1. Scientific and programmatic support can be provided by NIH.
2. FDA involvement is needed in approval process of new tracers.
3. NIST could provide the independent facilitator for standards.

*Other areas not covered in the breakout sessions, but recommended for study:*

1. Not clear about the impact of new technology over next 1-5 years, e.g., Time of flight PET
2. SPECT - many more tracers, but non-quantitative
3. SPECT/CT - new technology, not widely distributed
4. Cardiac Imaging:
  - a. Difficulties introduced by PET/CT with CT-based attenuation correction
  - b. Integration of PET and CT angiography
5. New tracers/Drug discovery
6. Respiratory motion
7. Pre-clinical validation

8. Image data for IGRT (image guided radiation therapy), IMRT (intensity-modulated radiation therapy) and RIT (radioisotope therapy)
9. Tumor heterogeneity

### **3.3 Breakout Session 3: MRI, MRS, DCE, and Diffusion MRI: What can be measured over time?**

Chair: Jeffrey L. Evelhoch, PhD, Co-chairs: Derek Hill, PhD, Jonathan Allis, PhD, and Chun Yuan, PhD, NST support: Ron Goldfarb, PhD and Steven Russek, PhD

Two primary topics were considered: 1) standard system phantoms, and 2) application specific phantoms.

*Subtopic 1: Standard system phantoms for MRI use.*

Customer needs: Phantoms are anthropogenic objects that can be used to evaluate the performance of various MRI scanners and techniques. Types of phantoms include resolution phantoms for testing spatial properties, such as in-plane resolution, slice thickness, linearity, etc. of MRI scanners, and RF homogeneity phantoms. Use of standardized phantoms can result in reduced costs to the pharmaceutical industry.

Current problems and measurement issues:

1. Lack of consensus in defining, characterizing, manufacturing and assessing stability of a phantom.
2. Lack of a uniform acquisition protocol.
3. Paucity of measurement standards relating SNR (signal-to-noise ratio) and image resolution.
4. Lack of standard metrics for measuring geometric accuracy.
5. Instability in MRI signal from pulse to pulse.
6. No traceability to fundamental quantities.
7. Inadequate characterization of phantoms.
8. Lack of performance measures for software analysis packages.

Proposed solutions:

1. Develop and use standard reference materials.
2. Generate well-defined specifications.
3. Develop web-based software analysis tools.
4. Identify performance metrics for software tools.
5. Develop consensus-based standards for above problems outlined.

Suggested government roles:

1. NIST can play a very important role in standard reference materials.
2. Support for national and international standards bodies.

*Subtopic 2: Development of application specific phantoms*

Customer needs and measurement issues: Same as Topic 1, except the analysis software would be more complex than for the system phantom.

Proposed solutions: In addition to the ones proposed in Topic 1, the following are recommended:

1. Form application specific working groups.
2. Prioritize applications.

Suggested government roles:

1. Same as for system phantom with increased role for NIST, especially for traceability.
2. NIH funding for basic research that will support efforts to create standards for imaging.
3. FDA involvement critical for potential health care applications.
4. The cross-industry nature of program impact on U.S. population and regulatory process necessitates significant contribution.

### **3.4 Breakout Session 4: Open Architecture and Software Tools: Image and Metadata Collection and Analysis, Data Integration and Display**

Chair: Laurence Tarbox, PhD, Co-chairs: Howard Foster, PhD, John Pearson, PhD, Gary Mallow, PhD, NIST support: Alan Bond, PhD, and Afzal Godil, M.S.

On day 1, the following measurement needs were identified:

1. Management of metadata and ontologies (near and mid-term)
2. “Plug-in” or service oriented architectures (near term)
3. Reference implementations (near term)
4. System quality management or data collection quality control management (mid term)
5. Interacting with workflow engines (mid term)
6. Data collection protocol management (mid term)
7. Automation of processing (long term).

On day 2, two subtopics were discussed in more detail: system quality management (item 4) and data collection protocol management (item 6).

*Subtopic 1: System quality management or management of data collection quality control*

Data collection quality control includes consideration of not only the measurement system but also how the measurement system was used.

Customer needs: There is a need for mechanisms to move fundamental quality checks to scan time (rather than off-line processing) and for collecting quality control (QC) data along with measurement data. Further, analysis of QC data needs to be more automated. Immediate feedback about quality and reduced variability will result in a reduction in the number of non-valuable studies, thus reducing the number of participants that must be enrolled to get statistically sound data.

Current problems and measurement issues:

1. Resistance of manufacturers to sharing of QC data.
2. Lack of access to the data needed for QC assessment.
3. Outside provider providing criteria for QC (there is a considerable time lag, in addition to communication problems).
4. Lack of open source plug-and-play software architectures.
5. Untimely communication of QC analysis to operators.

6. Inadequate data interoperability among various scanners.
7. Various performance measurements are not directly traceable to standards.
8. Paucity of user friendly tools.

Proposed solutions:

1. Develop a common ontological framework for data representation.
2. Create standard methods for:
  - a. describing phantoms,
  - b. automating measurements, and
  - c. automating the analysis of measurements.
3. Implement methods for timely returning of measurement results to the site, which will facilitate the incorporation of corrections into the measurement process.

Suggested government roles:

1. Create appropriate measurements (phantom specification, acquisition setup, analysis, etc.) to characterize quality of scans.
2. Characterize and/or mandate particular measures.
3. Manage ontology, cooperating internationally.
4. Provide reference implementations of the collection, analysis, and dissemination architecture, as manufacturers currently have little incentive to do this.
5. Provide neutral archives (e.g., for tracking, for improving equipment).
6. Provide [secure] communications infrastructure.

*Subtopic 2: Data collection protocol management*

Customer needs: Many clinical trials are done at multiple sites with equipment that have similar capabilities. Hence, there is a need to consistently produce measurable and comparable images at these different sites. Doing so will produce more consistent data collection, reducing variability, and thus reducing the number of participants needed to obtain statistically significant data.

Current problems and measurement issues:

1. Proprietary nature of how manufacturers control their measurement instruments.
2. Variability in the equipment capabilities.
3. Variability in how different equipment accomplish similar tasks.
4. Lack of consistent ontologies for describing acquisition and other data collection parameters.
5. Non-standard methods for representing low level settings.
6. Lack of standard protocols for patient preparation, monitoring, etc.
7. Inadequate feedback loops between data collection operators and data analysis specialists.

Proposed solutions:

1. Provide documentation on imaging systems performance (e.g., Word document) for distribution for the high level portion.
2. Develop sample scanner settings (one for each scanner type in the trial) for the low level settings for acquisition (scanner translates into the internal representation).

3. Include “plug-in” distribution for analysis methods needed by the protocol.

Suggested government roles:

1. Provide archive for data collection protocols (e.g. NCI/NLM).
2. Manage ontologies, coordinated internationally (e.g. NLM).
3. Perform gap analysis and provide metrics for measurement, i.e., are there units of measure that would be needed to characterize a data collection protocol, including acquisition parameters? (e.g. NIST)

**3.5 Breakout Session 5: Resources for Qualification of Imaging Systems, Benchmarking of Image Processing and Data Integration Tools, and Related Statistical Methods**

Chair: Nick Petrick, PhD, Co-chairs: Colin Miller, PhD, Ruzena Bajcsy, PhD, Dorin Comaniciu, PhD, Paul Maguire, PhD, NIST support: Charles Fenimore, PhD, and Mala Ramaiah, MD

Qualification refers to an appropriately validated and benchmarked performance for an imaging system and associated algorithms. One issue with current systems is the lack of standard metrics to compare outputs from different vendors and standard benchmarking measures. This becomes very important in multi-center, multi-vendor trials. Key discussion points from Day 1 were as follows:

1. Need to harmonize output from different vendors.
2. Develop measures similar to MTF curves used for CT scanners in other modalities.
3. Standardization of parameters based on phantoms followed by some guidelines on the protocols that the actual scanner settings should be determined in a predefined way rather than arbitrarily.
4. Open source tools for validation should be developed.
5. Standardized protocols will aid in obtaining reproducible results.
6. Develop methods/tools for monitoring image systems to detect and correct drift.

The following needs were identified on Day 1:

1. A workshop for development of standards for patient preparation and imaging protocols (near term).
2. Large public datasets with data, imaging parameters and protocols in standard format
3. Phantoms for characterization of systems and tools.
4. Human phantoms (rescan of patient, may be hard to do).
5. Methods/tools for monitoring systems (imaging equipment) to detect, correct drift and detect study flaws.

The single key subtopic discussed in more detail on day 2 is described below.

*Subtopic 1: Large public datasets with data, imaging parameters and protocols in standard format*

Customer needs: A proper infrastructure for collecting/sharing clinical trial, academic and normal clinical data is a prerequisite to large scale data collection and management. This data needs to be annotated, which would aid in image analysis and interpretation. Within this infrastructure, we also need methods for improved image analysis techniques and for performance benchmarking of these techniques. Appropriate training and test paradigms should be developed. This will result in reduced software tool development/validation costs and reduced need for controls in some trials, which will drive down cost of clinical trials

Current problems and measurement issues:

1. Lack of infrastructure for collecting/sharing clinical trial, academic and normal clinical data.
2. Need to establish/unify measures of response.
3. Lack of truthing/annotating data.
4. Lack of implementation to collect necessary “raw” data.
5. Need for different data for different diseases.
6. Continuous effort to acquire data;.
7. Where/how/cost to host data?
8. Lack of support from patient, health insurance companies.
9. Lack of metrics for comparing different systems.

Proposed solutions:

1. Develop a generic kernel to represent “raw” data.
2. Develop metrics for comparing systems (needs directed discussion for individual applications).
3. Develop new statistical ideas for imaging in clinical trials.
4. Put in place training of readers with tools.

Suggested government roles:

1. Develop correct task-specific validation methods.
2. Promote consensus process for these methods.
3. Recognize standards.
4. Enhance data sharing.
5. Maintain data (along with industry).

**3.6 Breakout Session 6: Data Archival and Access Methods**

Chair: Michael Vannier, MD, Co-chairs: David Clunie, MD, Mike Hehenberger, PhD, and Richard Cloase, PhD, NIST support: Wo Chang, MS, and Eswaran Suubrahmanian, PhD

Seven subtopics were discussed in this session concerning:

1. Research PACS (Picture Acquisition and Communication Systems) for (more than just) clinical trials.
2. Legacy PACS for clinical research
3. Data structure and model for data exchange – 21CFR11
4. Metadata harmonization (DICOM, ISO 11179, CDISC)
5. Imaging biomarker validation: Integration of images and non-image data with quality control.
6. Database discovery: Hypothesis generation and testing
7. Capture image-guided treatment plans

*Subtopic 1: Research PACS (Picture Acquisition and Communication Systems) for (more than just) clinical trials.*

Customer needs: Current PACS<sup>5</sup> are closed systems and do not facilitate research use of images obtained by clinical trials. Images developed during research are not entered in clinical PACS. Appropriate extensions and interfaces are needed for seamless storage and access of research and clinical trial images. Fred Prior's thoughtful presentation entitled *Imaging Data Management in a Multi-Center Medical Research Environment* at the IBM Summit in June 2006 discusses the needs for research PACS in considerable depth. (URL for various IBM summits: <http://www-03.ibm.com/industries/healthcare/doc/content/landing/974017105.html#imaging>)

Current problems and measurement issues:

1. Current PACS are closed expensive systems and vendors are not motivated to provide flexible integration of clinical trials data for research and other associated purposes.
2. PACS do not support the FDA reading paradigm (21 CFR Part 11).
3. User identity management is weak.
4. Inadequate interfaces with EMRs (Electronic Medical Records).
5. Lack of standards.

Proposed solutions:

1. Develop PACS aimed at research.
2. Develop methods to integrate clinical trial images into legacy PACS (these can be used for research later on), including appropriate de-identification mechanisms.
3. Develop external standardized interfaces.
4. Provide extensions so that PACS support FDA reading paradigm.

Suggested government roles:

1. Support/host test beds, specifications, requirements analysis, standards.
2. Develop policy issues related to data access.
3. Provide hosting for various databases and tools (use NCBI Entrez as a model).

*Subtopic 2: Legacy PACS for clinical research*

Customer needs: Legacy PACS, which are used extensively in clinical practice, are not currently designed for doing clinical research. Researchers can benefit considerably if these PACS had capability for supporting various research activities.

Current problems and measurement issues:

1. Lack of proper data exchange standards.
2. Firewalls are an impediment (need to ensure security and privacy, but allow access to clinical images for research).
3. Lack of ability to modify PACS.

Proposed solutions:

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<sup>5</sup> PACS (Picture Acquisition and Communication Systems) are a network of dedicated computers (and associated software) which deal with all aspects of image storage, retrieval, and distribution.

1. Engage PACS vendors and demonstrate the utility of these functions.
2. Develop interfaces for data export, along with appropriate security measures.

Suggested government roles:

1. Develop guidelines for dealing with the Office for Human Research Protections Department of Health and Human Services.
2. Simplify HIPAA compliance.
3. Simplify IRB approval processes.
4. Define security standards that are universally applicable (NIST can advise on this).
5. Remove liability constraints.
6. Define best practices and templates.
7. Provide test beds for research.
8. Attend to international harmonization.

*Subtopic 3: Data structure and model for data exchange – 21 CFR 11 Electronic Records; Electronic Signatures*

Customer needs: Since FDA accepts data compliant with 21 CFR 11,<sup>6</sup> providing appropriate enhancements (e.g., audit trails) to image databases arising out of clinical trials would result in faster acceptance by FDA. This will result in considerable savings in drug development, as it would allow companies to test new algorithms, CAD, and image analysis tools. It is very difficult to become 21 CFR 11 compliant after the databases are created.

Current problems and measurement issues:

1. DICOM, which is a widely used standard for image representation, does not support audit trails needed for 21 CFR 11 compliance.
2. Lack of appropriate annotations of image data.

Proposed solutions:

1. Develop statistically robust and validated imaging database solutions that are in compliance with FDA regulations.
2. Enhance DICOM to support 21 CFR 11 rules.

Suggested government roles:

1. Need standards and guidance that users can follow to assemble and submit image collections.

*Subtopic 4: Metadata harmonization (DICOM, ISO 11179, CDISC)*

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<sup>6</sup> Title 21 Code of Federal Regulations Part 11 is an FDA document that provides guidance for the acceptance of electronic records, electronic signatures, and handwritten signatures (scanned into electronic records) by the pharmaceutical and other related industries ([http://www.fda.gov/ora/compliance\\_ref/part11/](http://www.fda.gov/ora/compliance_ref/part11/)).

Customer needs: DICOM, ISO 11179,<sup>7</sup> and CDISC<sup>8</sup> deal with different aspects of image databases. While ISO 11179 deals with metadata, DICOM is concerned about image representation (mostly syntactic). CDISC has support from FDA. Each of these standards has its own support base. It would be useful to harmonize various common elements.

Current problem and measurement issues: Two primary issues were identified:

1. Disparate metadata standards, not all of which can use generic software tools and modeling infrastructure.
2. Mapping DICOM to ISO 11179 is verbose, complex, and tedious.

Proposed solutions:

1. Harmonization and development of mappings between commonly used established and supported metadata.

Suggested government roles:

1. Facilitate the harmonization process.
2. Utilize the metadata expertise at NIST with generic tools and ISO standards, as this is nonexistent in most healthcare organizations

*Subtopic 5: Imaging biomarker validation: Integration of images and non-image data with quality control.*

Customer needs: An individual may be subject to various imaging modalities (e.g., PET, MRI, etc.) over time. Recent advances in genomics will likely provide additional genetic data, including potential genetic changes over time. There are several issues that need to be addressed here:

1. Establish imaging as a surrogate marker for clinical outcomes.
2. Define measures of image quality with appropriate metrics.
3. Validate image biomarkers with other data (doing so will lead to better image validation techniques, thus ensuring quality control).

Current problems and measurement issues:

1. Lack of integration of multi-temporal datasets on individuals linked to outcomes.
2. Paucity of expertise in the intrinsics of imaging physics, in particular on ability to measure quality.
3. Inadequate standards for exchange of quality control information from centrally monitoring imaging instruments

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<sup>7</sup> DICOM (Digital Imaging and Communication), was developed by the American College of Radiology - National Electronics Manufacturers Association committee (ACR-NEMA), to exchange radiology imaging information. ISO 11179 (<http://metadata-standards.org/>) is an international standard for representing metadata about an organization/database in a metadata registry.

<sup>8</sup> According to <http://www.cdisc.org> “CDISC (Clinical Data Interchange Standards Consortium) is an open, multidisciplinary, non-profit organization that has established worldwide industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and biopharmaceutical product development.” CDISC has several standards that relate to healthcare.

Proposed solutions:

1. Design and test phantoms with measurement software that provides quantitative centrally reviewed quality results that can be used to assess day-to-day variations from site to site and scanner to scanner (including use of mixed modalities).

Suggested government roles:

1. Define quality standards/benchmarks.

*Subtopic 6: Database discovery: Hypothesis generation and testing*

Customer need: Large amounts of data – image and non-image --- are collected during various clinical trials. Mining the data to discover new knowledge will lead to innovations in drug design. Novel validated analysis techniques will be needed to accomplish such a task.

Current problems and measurement issues:

1. Incompatible data formats in various databases.
2. Lack of open source software tools.
3. Inability to integrate data across databases, which contain data in different modalities.
4. Missing data and poor quality data.
5. Inadequate application program interfaces (APIs) for data manipulation.

Proposed solutions:

1. Provide methods and policies for data migration from legacy database(s) to a data warehouse or federated data archive with data cleaning and mining tools.
2. Develop tools and techniques for integrating heterogeneous databases.
3. Generate tools for cleaning data.

Suggested government roles:

1. Long term data retention, i.e., archiving of clinical datasets after closure.
2. Define access rights and policies.

*Subtopic 7: Capture image-guided treatment plans*

Customer needs: Tools and standards are needed for the seamless integration and fusion of heterogeneous multimodality imaging information and the interoperability of image-guided intervention treatment tools, yielding true plug-and-play capability.

Current problems and measurement issues: The following issues were identified:

1. Target and day-to-day changes in morphology not defined.
2. Lack of standards for treatment plans.

3. No standards for integrating datasets from different modalities
4. Interfaces between imaging data and intervention tools are not standardized.

Suggestions to address the above problems:

1. Develop standards for treatment plans (oncology).
2. Provide standard interfaces for moving data from image databases to image guided intervention treatment tools.
3. Develop tools for integrating data from different modalities.

## 4 Summary and Action Items

Michael Vannier, MD, provided an excellent summary of the workshop proceedings on the final day. His summary, along with a list of action items, is provided below.

### 4.1 Michael Vannier's Summary

This workshop is notable for the fact that all the major stakeholders from the industry (medical imaging, clinics, pharmaceutical, contract research organizations), the academia, professional societies (RSNA, ACR, ISMRM, SPIE, AAPM, SNM, NEMA, NISS) and the government (NIH, FDA, NIST, CMS) came together to discuss an important topic: use of biomedical imaging for providing early indication of drug response. Medical images are frequently acquired and evaluated in clinical trials of drugs and devices. However, lack of standardization (for collecting and managing images) increases costs and introduces development and regulatory approval delays.

There were perspectives from various professional societies: American Society of Physicists in Medicine, Society of Nuclear Medicine, and Radiological Society of North America. PhRMA, FDA, Contract Research Organizations, and the Software Industry also provided their views. Several successful precedents for conducting multi-center trials were presented: ADNI, OAI, ACRIN, RIDER, and ATC.

PhRMA felt the need for consensus and partnership toward developing industry standards, regulatory and clinical guidelines for *harmonizing* (old ones) and *standardizing* (new ones) imaging in clinical trials to *manage quality, cost and time*. Considerable emphasis was made on the content of both information standards for data collection, data exchange, image post-processing, data management and archival, quality, control, and hardware standards, such as phantoms, standard reference materials. An important point made is that industry should drive the process, with neutral agencies providing supporting roles.

Six breakout sessions were organized to address the following four key questions:

1. Why do we need standards? (e.g. impact on quality, cost, and speed)
2. When do we need standardization vs. harmonization?
3. What is a priority list of areas that guidelines are required?
4. Who are the key partners and what are their expected roles?

Key summary points regarding imaging as a biomarker are as follows:

- Clinical trials involve multi-center trials. The variability in the multi-center trials that use imaging is too high.
- Standards developed for clinical medicine (care of individual patients) are insufficient to pool data from multiple sites (different instruments, locally varied acquisition protocols, etc.).
- Sharing of imaging data in clinical trials is rare.
- Medical imaging systems, PACS, workstations, and interfaces are not designed to support various activities required by FDA.
- Processes to distribute, update, track clinical trials and image data are absent in most hospitals and clinics.
- There is a need for comprehensive databases, which adhere to standards methods of data representation, storage, and access, to develop and validate image biomarkers.
- Validation of software tools and data are essential.
- There is a need for proper documentation.

- Ensure cross-site consistency.
- Standard reference phantoms are essential for validation.
- The medical imaging industry does not have the incentive to develop standards.

The proposed roles for various stakeholders were identified by speakers and in breakout discussions as follows.

PhRMA (and CROs), should: seize the initiative and take the lead; state the problem clearly, set priorities and engage FDA early; and link CDISC with DICOM.

Professional societies should: recognize and endorse *imaging biomarkers*; publicize the issue to their memberships, empanel domain experts that perform clinical trials, and engage them with PhRMA and government; act as a facilitator; define quality of clinical trials in their domain; define and disseminate best practices for clinical trials in their domain; and develop case studies.

Medical imaging systems manufacturers should: respond to *imaging biomarkers* initiatives; attend and participate in “DICOM” meeting that address imaging biomarker needs; link DICOM to CDISC; recognize the advantage of imaging clinical trials in the future success of their products; cross license software technology; and educate users.

Academia should: include “clinical trials” infrastructure in procurements of new systems (imaging scanners, PACS, etc.); integrate clinical records with images (and genomic data) in single center studies; share results and recognize sharing as important; engage radiologists/medical physicists/nuclear medicine physicians/MRI experts in the design of new trials; and enhance the role of clinician-scientists with imaging expertise that conduct human-oriented research.

Government should: ensure inter-agency communication and collaboration; support a whitepaper on imaging biomarkers; sponsor test beds; support an “Imaging Physics Center”; facilitate data sharing (by sponsoring an open standards-based archive); develop standard phantoms; provide a framework to address gaps for standardization.

In summary, there is a critical and immediate need to establish and implement standards for medical imaging in clinical trials. On completion, a standardization initiative would benefit patients by accelerating availability, and “outcomes based” use of new drugs and devices to treat their conditions. The government, the payers, and the public would also greatly benefit from this.

## 4.2 Closing Panel

The workshop concluded with a panel consisting of the following members: Nick Petrick (FDA), Bill Ott (NIST), Ed Jackson (representing AAPM), Jeffrey Evelhoch (representing ISMRM), Paul Kinahan (representing SNM), Darrick Fu (PhRMA), Larry Clarke (NCI). All of the panel members indicated the interest and commitment of their organizations to continue work on the workshop theme. A summary of their comments is provided below:

- Quantitation in imaging, especially in biomarkers, is critically important. If we don’t get an handle on the problem then it won’t help either the imaging industry or PhRMA.
- Validation of software will play an increasing important role in imaging.
- We need to focus on the patient, i.e., we need to concentrate on a patient-centric approach rather than a industry-centered approach.

- Collaborations between various stakeholders is important. We need a “conductor” who would help orchestrate the very large variety of moving parts in many different organizations that would be necessary to translate imaging from a promising cottage tool to medical/diagnostic reality of the mainstream. AAPM indicated its interest in playing such a role.

### **4.3 Action Items**

The following is a list of action items that are based on the breakout sessions and other deliberations:

1. Define the physical performance of different imaging platforms required to measure change analysis.
2. Design phantoms that may better characterize the time related physical performance of imaging systems, and the performance for specific functional and molecular based measurements.
3. Develop and share open source tools to analyze phantom or simulated data.
4. Develop and share open source tools for validation and image mark up of clinical data, including statistical methods.
5. Develop public resources to help optimize and validate imaging methods prior to their implementation in drug trials.
6. Develop comprehensive standards for acceptable variation, auditable records keeping, and linkage to ancillary clinical data.
7. Develop industry standard, regulatory and clinical guidelines for harmonizing and standardizing imaging in clinical trials to manage quality, cost and time.
8. Develop scalable resources to archive de-identified image and metadata.

### **Acknowledgments**

As the General Coordinator, Linda Beth Schilling played a very significant role in organizing the workshop. Without her persistence and drive this workshop could not have been such a success. We would also like to thank all the speakers and participants for their valuable contributions. Our final thanks to the NIST WERB readers for all their editorial help.

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## Appendix A: Device Industry Panel Session

The panel members were:

Jonathan Allis (JA): (GE Healthcare, Moderator),  
David Rollo (DR): (Philips Medical Systems), and  
Heinrich Kolem (HK): (Siemens Medical Systems).  
Chair: Andrew Whitman (AW) (VP NEMA Medical).

In the following discussions, we use their initials. We use AM to connote an audience member, unless otherwise specified.<sup>9</sup>

**AM:** Thank you for the excellent presentations. Dr. Rollo, you talked about licensing technologies to the other vendors. I think, you said cost-free. Is that a realistic sort of approach to solving standardization problems?

**DR:** That is correct. This is a suggestion. I think many of you are aware that our companies have cross-licensing agreements in various categories. The software side of it is, however, is new. One of the approaches that we were suggesting is that we will be willing to cross licensing the technology to the other manufacturers to save the cost of development. But, since the software is clinically validated by the original company, it saves an enormous amount of time to prove that the technology does in fact work.

**HK:** I think it is an interesting concept and we will look forward to this. But, it also has to be a process that is established over time. When we do this for medical imaging equipment, it is relatively easy. If you look at the MR (magnetic resonance) system, it probably contains about 1500 patents, and they are distributed, mostly, between the 3 lead manufacturers. So, it does not really make sense to charge each other for each patent. Every 5 years, we come up to the table and say okay, we require so many patents in between and then we extend the cross licensing. If we want to do this for software, I think we just have to make sure that the portfolio is equal. Otherwise, it does not make sense economically. But, I think in time, this will come. But, it will take time, and you should be aware of this.

**JA:** From the perspective of a company making diagnostic imaging agents, it is obviously attractive to have the software broadly available anyway. So, I do not know exactly what it would look like, but I think, it is in everybody's interest to have analysis software broadly available on all platforms.

### Panel was now open to the audience:

**AM** (Larry Clarke, NCI): I have a comment and also have a request to the audience. Our industry colleagues, I believe have provided a very unique presentation here to all of us in terms of their rising to the challenge of looking this standardization issue. Within their list of challenges they stated that there is a critical need for the imaging societies to get engaged to identify and provide some of the science behind what we need for standardization for image data collection and analysis. So, I am actually coming to the microphone to encourage others from the scientific societies to actually get up and direct questions to the industry presenters because this is a unique forum for your input. I would again challenge my colleagues from the academic societies to really do pose questions and state their interest in becoming engaged.

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<sup>9</sup> Please note: The text below was edited by NCI and NIST staff without changing the context of the questions and responses by industry.

**AM Comment:** With regard to cross-licensing, I wanted to make a point that there is actually another approach for having customized, agent-oriented software running on all imaging platforms in the same way. For example, the work of two DICOM groups that is currently ongoing. DICOM Working Group 23 is developing a standard for software interoperability, and it is called application hosting. Also, NCI's caBIG has developed an effort called XIP (eXtensible Imaging Platform) that has been mentioned in Dr. David Clunie's talk yesterday, and that is developing a software development framework that will enable everybody to author these types of plug-in interoperable solutions that DICOM is specifying. In addition to the cross-licensing approach, these approaches are also available.

**AM (Orhan Suleiman, FDA):** I want to compliment the mention of SPECT. I think it is the chemistry that drives the imaging, and so within this forum, we have to be modality-independent and select the most appropriate technology for imaging. I thank the organizers for this NIST-inter agency symposium. I think a lot of things have already been developed. It is just the case of getting all the different groups speaking with each other, and not reinventing the wheel. The question I pose to the vendors is: "would it be appropriate --I have heard different levels of effort -- to ensure that the equipment is performing in a consistent way, to do periodic audits during multi-centered clinical trials, testing with phantoms or whatever to just ensure that minimum performance is consistent across modalities?" I come away with the feeling that some facilities are doing things right, but there are lot of other facilities that are not doing things properly. The imaging drift, or change over time, that George Mills was mentioning yesterday may, in fact, occur. That is going to mask any real changes that may be actually happening as a result of the therapy treatment.

**JA:** We would support this approach from the medical diagnostics business with GE healthcare because we require that our own clinical development people do that, and so the answer is yes.

**HK:** It probably makes sense, but one should be aware that it will not solve all the problems. If you basically ask every clinical site or every institution to do certain quality testing in a regular way, it will definitely help because if it is not done in a widespread manner. It is very clear, it will definitely help, but will not solve all problems. We should be just aware of that.

**AM (Sandy McEwan, President of the Society of Nuclear Medicine):** Again, I thought that they were 3 great presentations. Thank you. I reiterate the comments that I made yesterday about the society's commitment to actually developing and moving forward the standardization process. The question for Dr. Allis is that your talk was primarily about the front-end radiotracers that we are looking at. There has not been a successful radiotracer that has been licensed since 1996. The cost of the traditional development of a radiotracer is something about 400 – 500 million dollars. Most of the molecular imaging tracers that are going to move forward are probably going to be in these niche markets where we are either supporting a clinical trial, supporting a very innovative therapy, or in clinical practice where there will be small number of patients. It seems to me that the traditional method of developing these radiotracers is actually, financially nonviable in the model you described. Have you, in industry, thought of any innovative ways of addressing this issue because if molecular imaging is going to work without the new radiotracers, we can do all the standardization at the acquisition and processing end, but actually there is going to be nothing to acquire a process.

**JA:** Yes. We talk about this regularly, and I have been to very interesting meetings at various locations to address this subject. There have obviously been a number of presentations about this topic over the last few years. We are thinking of that in a few ways. One way is the reason why most trials have failed is through quality. Once you are through the basic efficacy in the early stage, the reason the trials have failed is through quality. So, we are doing lots of things to improve quality, and that will go some way to reduce the cost or at least increase the potential for success. So, that is one side. The other factor that quality addressed is it reduces the number of patients you need. The number of patients you need goes

with a variance. So, as we get better at doing these things, they will get cheaper to do. So that ‘maybe’ gives us a factor of 2 in your argument of improvement. The other approach that we are looking at is, as we have done before, we can pay more for R&D (research and development) and that would help. So we would encourage everybody to feel that paying more would be good. But, assuming that that is not acceptable, the other thing we are doing is a lot of partnership work together with therapeutic companies, because many of the molecular agents certainly can be used to steering direct therapies. We are looking at sharing costs with therapeutic companies. And, potentially if they become linked to the use of the therapeutics that does grow those markets and makes them more cost-effective as well. The last thing is around platforms that actually you could say you don’t get a molecule approved, you get a platform approved. So, you have a standard framework and then you have relatively small amounts of studies which are just that the thing binding to the linker and the isotope. That is more difficult. From a regulatory perspective, that is something that we have not made a lot of progress on that. That would be ideal, but I think it will be difficult.

**AM** (Brad Wyman, Pfizer): This is a great opportunity to have all the major equipment manufacturers here, talking about change detection. One of the questions I have is that as we look at doing clinical trials, our requirements and standards are a little bit different than those that would be required for diagnostic imaging. One of the disadvantages we have is that pharmaceutical companies and biotech companies generally don’t buy equipment, and so, what is the economic incentive to help move you towards these more standardized methods for change detection.

**DR:** One of the incentives that Philips has for becoming involved in clinical trials is, as I suggested in my presentation, there are number of agents that do what they are supposed to do as we begin to look at the preclinical study. So, as we try to image them, you can in fact not identify clearly where the area of activity is, and that requires not only the addition of the CT to the system, but also the development of the unique software that is integrated with the CT system. So, Philips is creating collaborative relationships with the drug discovery groups with a “pay and park” for some of the clinical trials to split the cost in exchange for the data and the licensing rights for the software that goes with that. This is a value to the company that provides the agents, but it is also a value to Philips and that they can have unique software that allows that particular agent to have value in the long term. To point back to Dr. McEwan earlier comment, what we have found is that the majority of the molecular imaging agents of the SPECT type are not being developed by the pharmaceutical companies, but rather by organizations within academic institutions that have NIH money to take their ideas of peptides and proteins and molecular antibodies to develop an agent. They go through the preclinical studies; all supported by government funding and then typically, the academic institution creates a spin-off. By the time they spun off their technology, it is already proven technology that has already had the cost absorbed by the government as opposed to the company developing the process. So, when we begin to look at opportunities for collaboration, for every ten that we look at, there are 1 or 2 that we think have value, but the value we are looking for is potential of a therapy agent for that particular product. As most of you know, now the molecular imaging agents are reimbursed by CMS at about \$2000 for the diagnostic side, and \$20000 to \$25000 for the therapy side. So the end point of real value is on the therapy side, but our investment in these companies allows us to get the software, but also right of first refusal to invest in our company.

**JA:** Just one point about how to make sure that early stage pharmaceutical development benefits by standardization. We, as I mentioned earlier, I talked and worked with most of the large PhRMA companies. And, it is always a brilliant experience until we come to the point of money because it is a competitive-based technology. I do not mean to be fictitious here, but to be honest, the benefits to PhRMA for really putting some money into establishing standards and making sure it will work well is, I think, huge. And the thing that has always been difficult for us is that it is quite difficult to make money out of these relationships, which at some point we have to find a way to do. So, I think it is great to explore, but we would encourage PhRMA or the association in PhRMA, to get together and talk about

how much money should go into these pre-competitive technologies, because then I think you would find people very interested to establish standards and work together to make that happen. I do not mean to be fictitious about this suggestion.

**HK:** There is no natural reason why we should not standardize from the very beginning. But, as I mentioned in the long run, there is an interest, especially from the public, to make sure that there are certain standardizations implemented. So we can wait until this happens, which may be very far out, or we can work together and use basically the interest of the PhRMA company to make it work. It would require a little bit of money, and I think let us just get together on a certain committee and use especially NEMA and other people to make sure this kind of facility is created. We probably need to do that, but it will cost a little bit because there is no direct economical value.

**AM** (Cecil Charles, Duke University): The gentleman from Pfizer pointed out that there is a disconnect between radiolabel therapeutics and the more conventional non-radiolabel therapeutics. But, I think there is another disconnect here, namely between the way the imaging equipment is currently qualified versus the kinds of things you gentlemen have talked about the qualifications of new therapeutic agents. The majority of the imaging equipment does not really go through a clinical trial status anymore. It goes through a very nice process for approval that everyone that makes these kinds of equipment is very happy about. But, within that process, I wonder, is this one of the sources for lack of standardization across manufacturers. Similarly, when you go into the field and look at the same equipment at 50 sites that are from the same product line, supposedly from the same “manufacturing badge,” that one sees large variations in the equipment. The latter is one of the things that we were talking about in some of the breakout sessions. How do we minimize that variance, and that gets to the point that Dr. Allis you raised and that is ...what you want to squeeze is that coefficient of variation in the image acquisition because you cannot do anything about the biology. I just wonder in the context of the FDA 510(k),<sup>10</sup> how we address that.

**HK:** I am not quite sure of the context of the point you mentioned, but, I think there are two issues. One is that if we try to implement a really clinical validation process for many of the innovative techniques, it would just take too long. It will take too long until they are in clinical practice, and so we have to find a way that we are able to introduce new techniques to the field without going to a different process than the current 510K we have. But, in order to make sure we can get revolutionary results, I think the idea is to get together and also make sure what you want to implement. I think some kind of standardized phantom. These are possibilities to go that way. I think that is something we can work out.

**JA:** Just to respond to this question as well. The current imaging systems are mostly about pictures, and they obviously work okay for routine diagnostic radiology. I think once we move to quantitative imaging, we are saying the systems may not be specified right. But obviously they are specified okay for doing clinical imaging which is the vast majority of what is done. But, you are right. Once you get the imaging system, you want it to be incredibly reproducible for quantitative imaging. It may well be that things have to change. We still like 510(k), though.

**DR:** I think that the basic devices from each of the manufacturers have pretty much equivalent performances was pointed out yesterday. But, it is in the software that the differences will be made apparent, primarily from looking at quantification, reconstruction, and the other areas we talked about. That is where the organizations like NEMA, the development of standards, the ability to have databases

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<sup>10</sup> According to the FDA website, “A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA.”

available to test and validate that we are getting equivalent answers or if there is a difference, there may be multiplying factors that allows the numbers to become the same.

**AM** (Michael Knopp, representing Ohio State and ISMRM): There are two areas that I would like to bring up for discussion. One is kind of looking at what are the obstacles. One of the obstacles, from my perspective having been involved in many trials, is actually some of the regulatory issues. For example, the challenges we have is of off-label application. Let me give a couple of examples quickly. For example, perfusion imaging, a vendor was put on notice that the vendor was advertising while there were no approved uses of contrast agents for perfusion imaging. So, from my perspective, what would be very helpful from the manufacturer side, especially from the hardware side, when we go with the integration of research sequences? When we go with the integration of bringing the device together with the diagnostic agent, “what from your perspective are issues that the community and the agencies need to be tackling to help along those lines?” Another example just to give that in a lot of trials it has been established, for example, to develop RF pulse sequences, and to then implement those sequences within the trial. There is lot of regulatory and a lot of legal concerns. I am at least involved with the manufacturer side, and what is something that is really important, I think is a day-to-day obstacle. If we could find a technical solution, what should be or could be done within the regulatory environment and the federal environment to help facilitate these issues.

**HK:** I can comment a little bit on the first part. As I mentioned, this off-label use is really a problem, but I could also understand why you are in this critical situation. It is from the safety perspective—no risk at all, because if the same contrast agent is used for a similar problem. So, the patients are getting this for everything. On the other hand, there is no broad clinical study implemented to show them that there is high efficiency, and that is why I can understand why the regulatory agencies have problems to just say go ahead especially because of people assuming it will increase cost. On the other hand, there is personal experience of many clinicians; it helps and they have to come to shorter and better diagnoses very quickly and they are allowed to do off-label use. So, I think there is no easy way out of this. Maybe at the best, there should be a discussion between FDA and NEMA to find a way to solve this.

**AM** (Michael Knopp, representing Ohio State and ISMIM): Would this help industry if the issue is being addressed more within the agencies to tackle this question? From your industry perspective, are you pumping into these regulatory and legal issues that I think would help you if these issues are being addressed?

**HK:** It would be definitely better if you would have a clearer process, especially with new things coming in. If you make sure the scientific community could somehow directly be involved, that would help. That is definitely clear. But, still I think it is a very complicated topic. It is not easy to solve.

**AM** (Gil Jost: President, RSNA): I think everyone in this room feels the ultimate goal is worthwhile, and yet the question I ask myself is how do we get started? If we try to leap to a final solution immediately, we may never get out of the starting blocks. If you think back to the start of the DICOM demonstrations, we took a very tiny step initially, but procedures were put in place for companies to work together that led to real successes in the long run. The IHE initiative is another good example where industrial competitors found ways to work cooperatively and effectively together. But there are some real challenges to overcome. One challenge is gaining the support of the user community. Radiologists in this room understand the importance of biomarkers for drug development, but there are only a handful of radiologists in this room, and getting the average radiologist on board may be challenging. On the imaging equipment manufacturing side, as many of you have pointed out, we face a challenge in that the number of scanners that will be used in clinical trials may not provide enough of a profit motive to justify a significant investment of resources on the part of the imaging vendors. I have confidence that we at least have a methodology in place for the imaging manufacturers to participate, because each of the major

imaging companies participated actively and successfully in the IHE and the DICOM projects. IHE is an example where imaging companies and IT companies came together and figured out ways for competitors to work together in a collegial fashion to achieve an important common goal. So the imaging community has a track record and a methodology to allow competitors to work cooperatively together. With IHE, it took years to convince the IT companies that it was in their best interest to relinquish their proprietary solutions in favor of a common cooperative approach. Yet they succeeded. And the question I have for the pharmaceutical industry is “Are you ready to take that kind of a step? Are you ready to give up proprietary solutions and agree on common industry-wide standard methodologies for the quantitative measurement of biomarkers to evaluate the effectiveness of treatment?”

**DR:** In response to the question, I think in my experience over the last several years of being on this side of the industry, as opposed to being a user and a buyer, I felt that the several years that I chaired the NEMA nuclear section, which was really an amazing experience, for all the manufacturers came together, we took off our hats (with label to who we belong to) and had very open discussions about what we needed to do in the industry in order to move imaging forward, more recently on the PET side and the molecular imaging side. The initiative, for example, for the phantoms on the PET side and now phantoms being considered for the SPECT side came out of those meetings, where people sat down, discussed openly what we needed, agreed to developing the standards, the phantoms, and issues that come along with that. More recently, we have had the ACRIN group come forward. Now, all of the companies have agreed to participate in that program because we thought that was the other place where we had the third party that could help us with the organization, the conduct, and the standardization of the clinical trial. The Society of Nuclear Medicine had the bench-to-bed side program. We also were invested in that initiative because that was another opportunity for us to work together with our hats off to do what was really right for the patient and right for the overall industry. The biggest concern I have is the point that we just raised. We, as the device industry, now have that definition, but there used to be a time when the FDA said that a device can be an agent or an instrument. When we talk about the industries now, pharmaceuticals are not considered part of our industry. We need some kind of an organization that combines the two groups so that they can sit down as we have in NEMA to discuss what we really need to do in order to move molecular imaging forward. Because, I believe very strongly and believe others do as well that it is an agent and a device that the combination of the two integrated with the software that will make this technology move forward. And, if we can have open discussions about how we can coordinate and cooperate. I think this whole thing will continue to move in parallel paths and could come in together as an industry initiative.

**AM (Darrick Fu, PhRMA):** I have some comments to make. First, it strikes me that we are in the same boat as the industry group in that from the perspective from what we are here for and what we are trying to do that is driven basically by patients, by delivering something that is good to those patients. We both are basically in the same boat and we face the same kind of challenges long, difficult, development time, costly, and the need to prove that they bring value in today’s society and then all of the pressures that there are. And, that is just an observation and I think there is more in common than we want to believe when we think of it in terms of what we are about and put this in the perspective of driving that, not to our customers, but to the ultimate customer -the patients. From the perspective of PhRMA, we have done two things and we are prepared to engage in all of these kinds of discussions and I just wanted to highlight two of them briefly. In terms of imaging standardization and the use of imaging in clinical trials, we have organized a group of cross companies that are multifunctional, that are multidisciplinary – with representation that includes imagers, radiologists, clinical practitioners, statisticians, and regulatory people. The leaders of all of those groups and subgroups, working groups, I think, are here in this conference still, and we are prepared to engage all of the other communities and that is why this is such an important conference. Mostafa (Pfizer) has already been mentioned as one of the co-leads of the group and David Mozley (Merck) is the other co-leader of that group. So that is one thing. The second thing is regarding what are we prepared to share, what are the intellectual property issues, and other kind of

things, and how do we progress with these developments? The other thing that we have been driving is the formation of a public-private partnership -- a consortium that has been mentioned before at the conference to work on the biomarkers. It does turn out that many of the industry's interests do happen to be along the lines of developing imaging-related biomarkers. That is [not] a consortium, however. It is not intended to be solely imaging related. There are many other ideas coming from other partners, genomic-related biomarkers, proteomic-related biomarkers and our commitment -- this is not our commitment as a trade association--but it is a reflection of the commitment of our members to drive our policy. In order to address these challenges, we need to find pre-competitive space and mechanisms to work on them together. One thing in our minds in setting up that consortia was in fact to provide a forum where pharmaceutical companies and diagnostic companies will come together and work on those things that we have basically of common interest in doing. I am very confident, as confident as I am to say, that that is the intention. I am also confident that we probably have not totally achieved everything that is probably going to be necessary for that and part of the reason that I wanted to just standup is that we could know who we each other are now and continue this dialogue, sort of offline.

**AM** (Mostafa Analoui, Pfizer): Gill Jost posed a specific question and I just want to add this comment. I think it is an important question. Darrick mentioned about the general strategy that PhRMA has here and you have heard from many of us in the past that we can no longer operate without having some harmonization and standardization around these issues. Our business has not stopped because there are elements that are not in place. We are moving forward and the cost of moving forward with the current strategy versus developing industry standards is much higher moving in this direction, so it would be more cost-effective for the industry to have this strategy in place. That is one rationale why we are looking at that. So, there is incentive to make sure this moves forward. The second thing is that when you look at what are the elements needed to drive this initiative forward, I would say that the budget is only a small portion of what is needed. The collective wisdom and the decision by multiple partners and active engagement is more important element of this. It is not going to get accomplished until we have this common understanding that we had here over the past two days in this place. And, I see this as a primary issue that will drive this process forward.

**AM** (Gary Fullerton, AAPM): I detected in all of your excellent talks that there is a great deal of discomfort about the concept of standardization of devices. I see real conflicts between the fundamental design of your instruments which are for qualitative imaging serving the imaging communities and the needs of quantification for measurement and pharmaceutical development. It seems to me that conflict is never going to go away; it costs too much to build an instrument for quantitative measurements. Have you given, as a group, thought to the creation of a separate class of instruments or a special preparation of instruments, including special software of instruments, designed for these purposes of quantitation and drug development? Molecular imaging is also going to demand this type of quantitation. I think there are very different issues from imaging and I do not think that you are ever going to eliminate that conflict from those communities.

**HK**: So, there is no discussion so far about the second class of instruments that has clear standardized measurements with quantifiable outputs. But, I would not agree that, of course, there is a conflict but that would never go away. I think for things which are implemented for a certain point of time and are working in the clinical field for several years we can still talk about standardization. Of course, there is no natural driver to this, but if somebody says everybody or all stakeholders are in agreement, I would feel responsible for this to go forward. I think we would be engaged.

**JA**: We talked about this in the MR breakout yesterday as to whether people will be willing to pay for a higher specified clinical trial application. We talked about this in the context of software, but, it could be an instrument, which would cost more. We chose the best components and measure- the tolerances, etc. I do not think anyone in the industry has talked about doing it.

## List of Acronyms

2D	2-Dimensional
2D RT	2-Dimensional Radiotherapy
21CFR11	The Code of Federal Regulations, Title 21, Part 11
3D CT	3-Dimensional Computed Tomography
8F-FDG	Fluorodeoxyglucose 8
AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
ADNI	Alzheimer's Disease Neuroimaging Initiative
API	Application Programming Interface
ATC	Advanced Technology Consortium
caBIG	cancer Biomedical Informatics Grid
CAD	Computer-Aided Design
CDE	Common Data Element
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CROs	Contract research organizations
CSTL	Chemical Science and Technology Laboratory
CT	Computed Tomography
DCE	Dynamic Contrast Enhanced (imaging)
DICOM	Digital Imaging and Communications in Medicine
DQC	Double Quantum Coherence
EEEL	Electronics and Electrical Engineering Laboratory (NIST)
EMR	Electronic Medical Record
ERBB2	Erythroblastic leukemia viral oncogene homolog 2
FBP	Filtered Back-Projection
FDA	Food and Drug Administration
FDA 510(k)	Section 510(k) of Food and Drug Administration act
FDG PET/CT	Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography or Computed Tomography
FLT	fluorodeoxythymidine
FMISO	fluoromisonidazole
GE	General Electric
HIMSS	Healthcare Information and Management Systems Society
HIPAA	Health Insurance Portability and Accountability Act
IBM	International Business Machines Corporation
IDRI	Imaging Database Resources Initiative
IGRT	Image-Guided Radiation Therapy
IHE	Integrating the Healthcare Enterprise
IMRT	Intensity-Modulated Radiation Therapy
IRB	Institutional Review Board
ISMRM	International Society of Magnetic Resonance in Medicine
ISO	International Organization of Standardization
IT	Information Technology
ITL	Information Technology Laboratory
JNCI	Journal of the National Cancer Institute

kcps	kilocycles per second (otherwise known as kilohertz)
LIDC	Lung Imaging Database Consortium
MEL	Manufacturing Engineering Laboratory
MI	Myocardial Infarction
MIRC	Medical Imaging Resource Center
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSEL	Materials Science and Engineering Laboratory
MTF	Modulation Transfer Function
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NEC	Noise Equivalent Count
NEMA	National Electrical Manufacturers Association
NIA	National Institute of Aging
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIH ICs	National Institutes of Health Institutes and Centers
NISS	National Institute of Statistical Sciences
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
NOVA	National Organization for Victim Assistance
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PACS	Picture Archiving and Communication Systems
PET/CT	Positron-Emission Tomography and Computed Tomography
PCs	Personal Computers
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Principal Investigator
PL	Physics Laboratory
PPP	Public--Private Partnership
PSA	Prostate-Specific Antigen
QA	Quality Assurance
QA/QC	Quality Assurance and Quality Control
QC	Quality Control
R&D	Research and Development
RECIST	Response Evaluation Criteria in Solid Tumors
RPC	Radiological Physics Center
RIDER	Reference Image Database to Evaluate Response
ROI	Region of interest
RSNA	Radiological Society of North America
REMIND	Reliable Extraction and Meaningful Inference from Non-structured Data
RF	Radiofrequency
RIT	Radioisotope Therapy
RPM	Real-Time Position Management
RT	Radiotherapy

Rx	Prescription
SNM	Society of Nuclear Medicine
SNR	Signal-to-Noise Ratio
SPECT	Single Photon Emission Computed Tomography
SPIE	The International Society for Optical Engineering
SUV	Standardized Uptake Value
UPICT	Uniform Protocols for Imaging in Clinical Trials
URL	Uniform Resource Locator
U.S.	United States
USMS	United States Measurement System
XIP	eXtensible Imaging Platform