Standards for Imaging Endpoints in Clinical Trials: Standardization and Optimization of Image Acquisitions: Magnetic Resonance

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Why Use MR Measures as Imaging Biomarkers?

- Exquisite soft tissue imaging with multiple contrast mechanisms
  - Lesion size / volume assessment
  - Good spatial resolution
  - "Multispectral" data for image segmentation (T_1, T_2, post-Gd T_1, *etc*.)
- No ionizing radiation
- Functional imaging assessments
  - Dynamic Contrast Enhanced MRI (DCE-MRI)
    - Microvascular volume, flow, permeability measures
  - Diffusion MRI
    - Cell density/volume measures
  - MR Spectroscopy
    - Biochemical measures
  - Others, including blood oxygen level dependent (BOLD) MR (hypoxia)

OK, so what are the challenges?

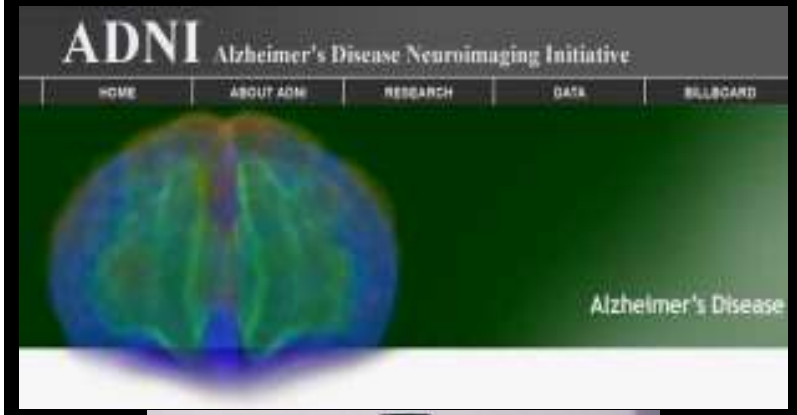
- General MR quantification challenges
  - Lack of standards (acquisition, data processing, and reporting)
    - Varying measurement results across vendors and centers
  - Lack of support from imaging equipment vendors
    - Competitive advantage in diagnostic radiology, not quantitative imaging
    - Varying measurement results across vendors
    - Varying measurement results across time for any particular vendor
  - Highly variable quality control procedures
    - Varying measurement results across centers

General Challenges in MR Quantification

Arbitrary (and spatially- / temporally-dependent) signal intensity units

- Magnitude and homogeneity of the main magnetic field (B_o)
  - Higher B_0 better signal-to-noise; homogeneity impacts image uniformity and spatial accuracy
- Magnetic field gradient nonlinearity and/or miscalibration
  - Spatial accuracy depends strongly on gradient subsystem characteristics
- Radiofrequency (RF) coil dependency: RF coil type, sensitivity profiles, subject positioning within the coil
  - Image signal uniformity; impact on longitudinal signal intensity measures
- Slice profile variations (with RF pulse shape, flip angle, *etc*.)
  - Slice thickness depends on pulse sequence and RF pulse shape; prescribed thickness and measured thickness differ, especially for fast imaging techniques
- System stability issues (RF & gradient subsystems, B_o, RF coils, *etc*.)
  - Quality control programs are critical for reproducible measures!

Difficult? Perhaps, but it can be done!



Sphere ID	Color	Number of Spheres	Grams of Copper Sulfate Penta Hydrate per liter	Target T1 (ms)
1.0cm	none	158	0.820	
1.5cm	none	2	0.820	
3.0cm	green	1	0.220	900
3.0cm	yellow	1	0.295	750
3.0cm	red	1	0.430	600
3.0cm	orange	1	0.590	450
6.0cm	none	1	0.820	

- Multicenter, multivendor study
- Optimized pulse sequence / acquisition parameters for each platform
- MagPhan/ADNI phantom scan at each measurement point
- Access to vendor gradient correction parameters
- With full correction for gradient nonlinearities and optimized acquisition strategies, spatial accuracies of ~0.3 mm can be obtained over a ~180 mm diameter spherical volume

http://www.loni.ucla.edu/ADNI/

Raising the bar – Functional MR Measures

- General MR quantification challenges
  - Lack of standards (acquisition, data processing, and reporting)
    - Varying measurement results across vendors and centers
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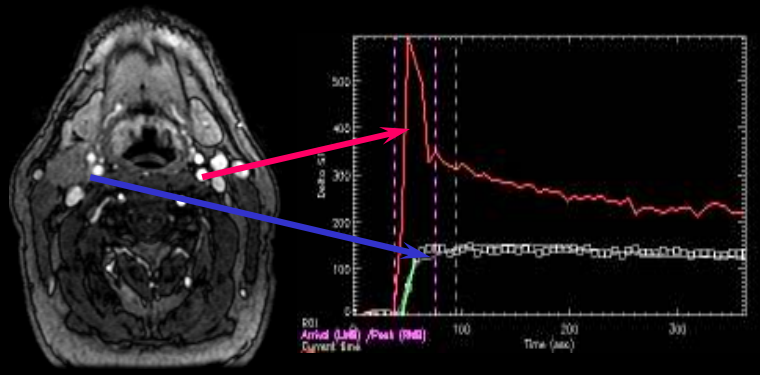
    - Competitive advantage in diagnostic radiology, not quantitative imaging
    - Varying measurement results across vendors
    - Varying measurement results across time for any particular vendor
  - Highly variable quality control procedures
    - Varying measurement results across centers
- Raising the bar: From morphological to functional MR biomarkers
  - DCE-MRI
  - Diffusion MRI
  - MR Spectroscopy
  - BOLD MRI

Dynamic Contrast Enhanced (DCE) MRI



Plasma Flow

Endothelium

K^{trans}

Plasma
C_P, v_P

EES
C_{EES}, v_e

k_{ep}

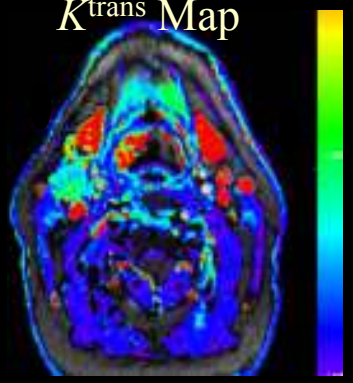
Measured

Measured

$$C_L(t) = v_P C_P(t) + v_e C_{EES}(t)$$

$$C_{EES}(t) = K^{trans} \int_0^t C_P(t') \; e^{-k_{ep}(t-t')} \; dt'$$

K^{trans} Map



C_P = [Gd] in plasma (mM) = C_b / (1-Hct)

C_{EES} = [Gd] in extravascular, extracellular space (mM)

K^{trans} = endothelial transfer constant (min^{-1})

k_{ep} = reflux rate (min^{-1})

v_P = fractional plasma volume, v_e = fractional EES volume (= K^{trans} / k_{ep})

Standardized parameters as proposed by Tofts *et al.*, *J Magn Reson Imaging*, 10:223-232, 1999.

DCE-MRI Data Acquisition Challenges

- Pulse sequence
  - Contrast response must be well characterized and maintained for duration of study (or a process for compensation for changes must be developed)
- Temporal resolution
  - Must match choice of pharmacokinetic model and parameters of interest
    - Must be rapid (≤~4-6 s) for generalized kinetic model with estimation of v_p
    - Recommended to be ≤15 s for any pharmacokinetic model
- T1 measurements
  - Required if contrast agent concentration is used in modeling
  - Must be obtained in reasonable scan time
  - Must be robust as uncertainties in T1 estimates propagate to output measures

DCE-MRI Data Acquisition Challenges

- Spatial resolution
  - Must be adequate for target lesion size and application
- Anatomic coverage
  - Should fully cover target lesion(s) & include appropriate vascular structure
- Motion
  - Effects should be mitigated prospectively during acquisition and/or retrospectively, *e.g.*, rigid body or deformable registration

DCE-MRI Data Analysis Challenges

Many choices to be made:

- Vascular input selection
  - Manual ROI vs. automated identification of vascular structure pixels
  - Reproducibility
- Lesion ROI(s)
  - Definition criteria
  - Reproducibility
- Fits of single averaged pixel uptake curve or pixel-by-pixel fits
- Modeling of: gadolinium concentration (requiring T1 mapping) or simple change in signal intensity data
- Reporting of results (structured reporting)

Single-Vendor, Single-Site Studies

Major challenges:

- Acquisition protocol optimization
  - Pulse sequence and acquisition parameter optimization for:
    - contrast response
    - temporal resolution (for dynamic imaging)
    - spatial resolution
    - anatomic coverage
  - Application specific phantom needed for initial validation scans and ongoing quality control
    - phantom acquisition and data analysis protocols
    - established frequency of assessment and data reporting
- Mechanism for detecting and addressing changes in measured response due to system upgrades (Quality Control)
  - Vendors focused on "competitive advantage" in radiology, not on quantitative imaging applications; no focus on maintaining signal response characteristics over time

From Single- to Multi-Vendor Studies

Major challenges:

- Acquisition protocol harmonization
  - Pulse sequence and acquisition parameter selection for matched:
    - contrast response
    - temporal resolution (for dynamic imaging)
    - spatial resolution
    - anatomic coverage
  - Application specific phantom needed for initial validation scans and ongoing quality control
    - phantom acquisition and data analysis protocols
    - established frequency of assessment and data reporting
  - Can be achieved, but requires effort at start up and, subsequently, constant monitoring for changes in hardware/software (need for ongoing quality control)
- Vendors focused on "competitive advantage" in radiology, not on quantitative imaging applications

From Single- to Multi-Center Studies

Major challenges:

- Acquisition protocols
  - Harmonization across centers and vendors
  - Distribution and activation of protocols
    - Distribute/load electronically (ADNI)
    - Provide expert training and initial protocol load/test
    - Develop / utilize local expertise
  - Compliance with protocol
    - Local radiologists, technologists
- Widely varying quality control
  - Ranging from specific for a given imaging biomarker, to ACR accreditation, to none
  - Even if QC program is in place, it may not test parameters relevant to the study
- "Scanner upgrade dilemma"
- Data management and reporting

How can we move forward?

To move MR imaging biomarkers from exploratory / secondary endpoints to primary endpoints:

- To quote George Mills: “Precision is the goal”. We should not assume anything but should “discover and adjust for differences”.
- There exists a need for standardized acquisition pulse sequences and analysis techniques for MR imaging biomarker studies.
- Vetted phantoms should be available to quantitatively characterize vendor-specific acquisition techniques for a particular MR biomarker (lesion morphology, perfusion, diffusion, MR spectroscopy, *etc*.).
- Application specific phantoms should be used in the site validation phase for every clinical trial and periodically during the longitudinal study.
- Vetted test data need to be publically available to users in order to test new releases of analysis software.

How can we move forward?

To move MR imaging biomarkers from exploratory / secondary endpoints to primary endpoints:

- Repeatability (test/retest) studies are needed for any new MR-based imaging biomarker.
- Additional imaging biomarker to tissue-based and outcome measure comparisons are needed.

What are we doing to get there?

Quantitative MR Imaging Initiatives

- NCI: RIDER and Academic Center Contracts
- NCI: Imaging Response Assessment Team (IRAT) / MR Committee
- RSNA: Quantitative Imaging Biomarker Alliance MR Committee
- ISMRM: *Ad Hoc* Committee on Standards for Quantitative MR
- AAPM: Quantitative Imaging Initiative / Working Group for Standards for Quantitative MR Measures
- NCI: Quantitative Imaging Initiative (QIN)

NCI RIDER

NCI Cancer Imaging Program **RIDER**

- Reference Image Database to Evaluate Response*

  Collaborative project for development and implementation of a caBIG public resource

  Data and meta analyses made publicly available through NBIA (phantom and anonymized human subject data, including DCE-MRI and diffusion MRI)

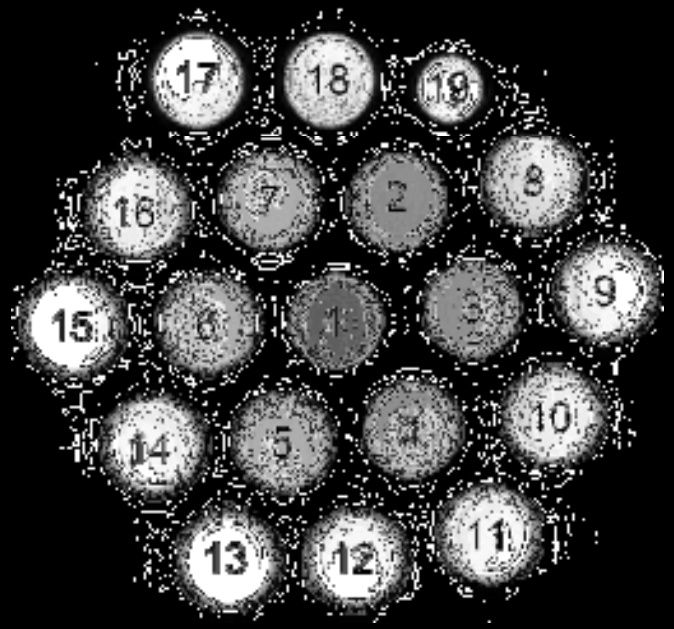
  Series of manuscripts in *Translational Oncology* in Dec 2009

https://wiki.nci.nih.gov/display/CIP/RIDER

NCI RIDER DCE-MRI Phantom Data

Gel-filled compartments with varying T1 relaxation times

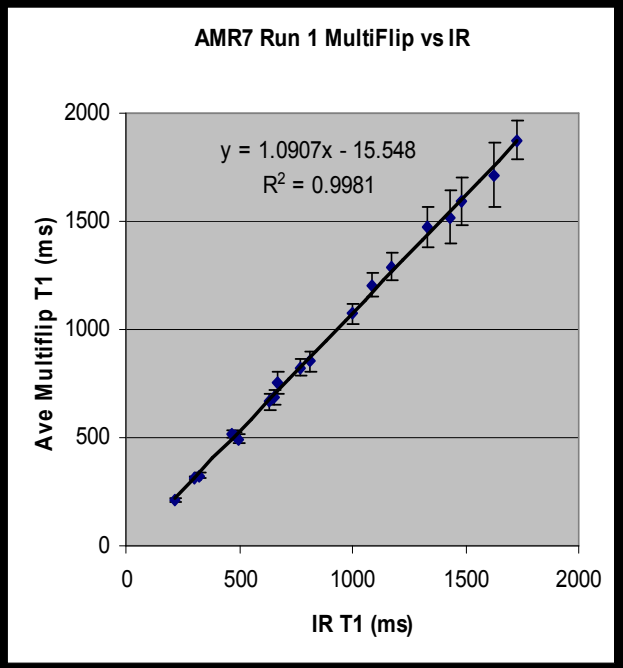
Eurospin TO5 – DiagnosticSonar, Ltd.

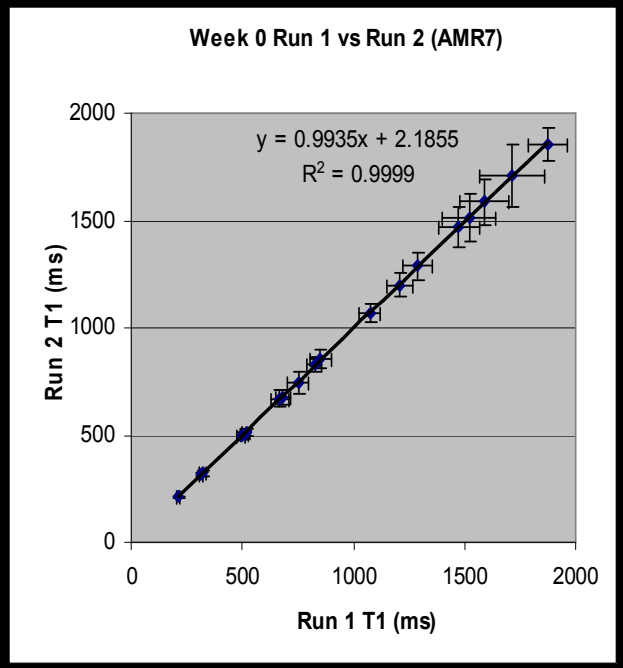


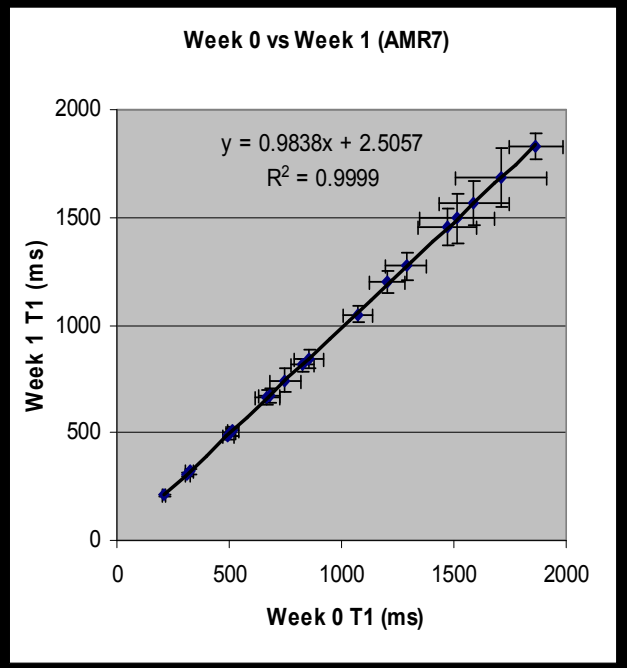
Compartment #	T1 IR (ms)
1	215.25
2	320.18
3	303.80
4	493.36
5	484.81
6	471.17
7	656.59
8	634.46
9	809.73
10	768.12
11	1001.02
12	1728.28
13	1086.39
14	1173.85
15	1331.32
16	1479.87
17	1432.01
18	1624.85
19	669.70

Funded by NCI Contract N01-CO-12400 and 27XS112

RIDER – Single Vendor / Multiple Time Points







Run 1 = baseline

Run 2 = 2 hrs post baseline

Week 1 = 1 week post baseline

Bosca & Jackson, AAPM 2009; Jackson *et al*., *Trans Oncol*, Dec 2009

Funded by NCI Contract N01-CO-12400 and 27XS112

RSNA Quantitative Imaging Biomarker Alliance

RSNA QIBA: DCE-MRI Technical Committee

- Multiple subcommittees:
  - Phantom development / selection
  - Scan protocol / data analysis
  - Synthetic DCE-MRI test data
- MR phantom based on the Imaging Response Assessment Team (IRAT) DCE-MRI phantom
- Acquisition and phantom designed to mimic typical Phase I / II applications to liver using phased array receive coils
- Phantoms distributed to multiple sites to obtain multicenter (N=6), multivendor (N=3) data

http://qibawiki.rsna.org/index.php?title=DCE-MRI

Phantom purchase funded by NCI Contract \27XS112

RSNA QIBA – Multiple Vendors / Three Time Points

RSNA QIBA: DCE-MRI Technical Committee

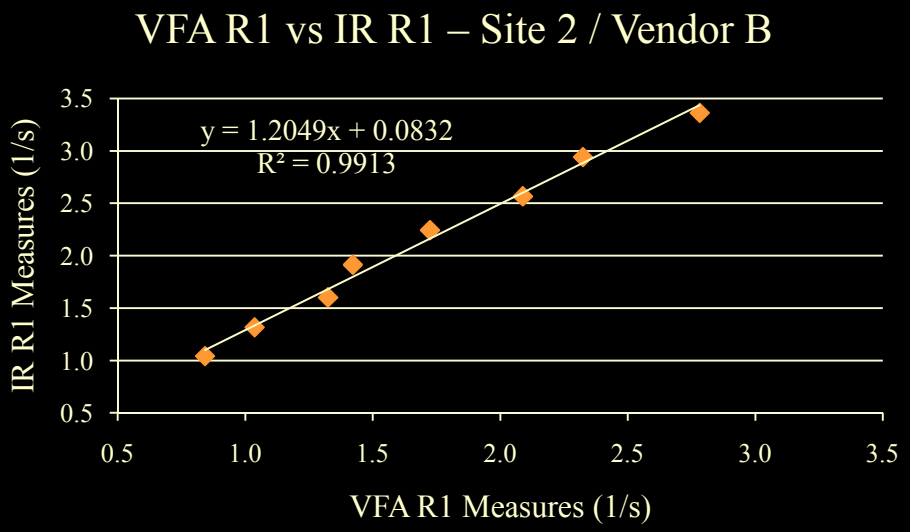
- Phantom measurements:
  - Phased array acquisition
  - Body coil acquisition
  - SNR acquisition
  - Variable flip angle T1 measurement acquisition
  - DCE acquisition

  } Ratio map correction for RF coil sensitivity characteristics

- Each of the above acquisitions repeated with phantom rotated by 90, 180, 270, and 360^{o}
- All acquisitions repeated one week later
- Version 2 phantom in initial testing

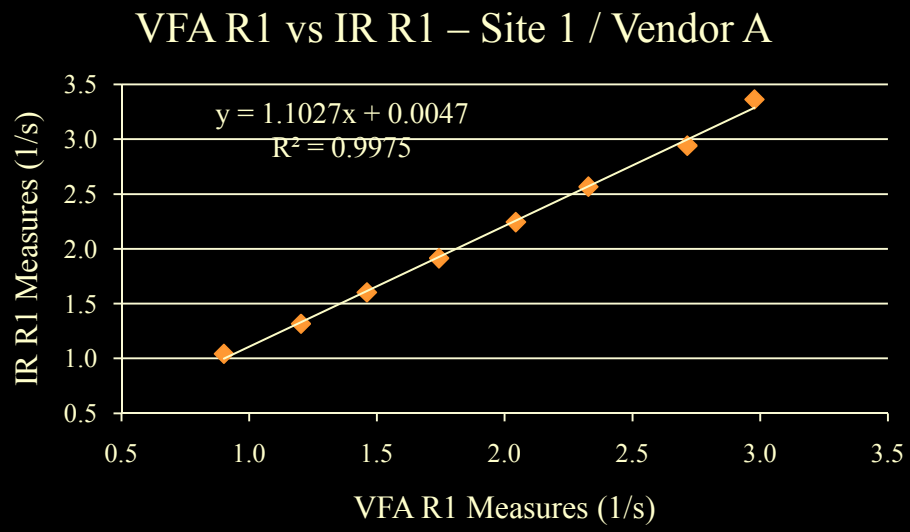
Phantom purchase funded by NCI Contract \27XS112

RSNA QIBA – Multiple Vendors / Three Time Points



Variable flip angle relaxation rates vs IR (gold standard) values (Site 2 / Vendor B)

IR measures acquired on Vendor A at Site 1

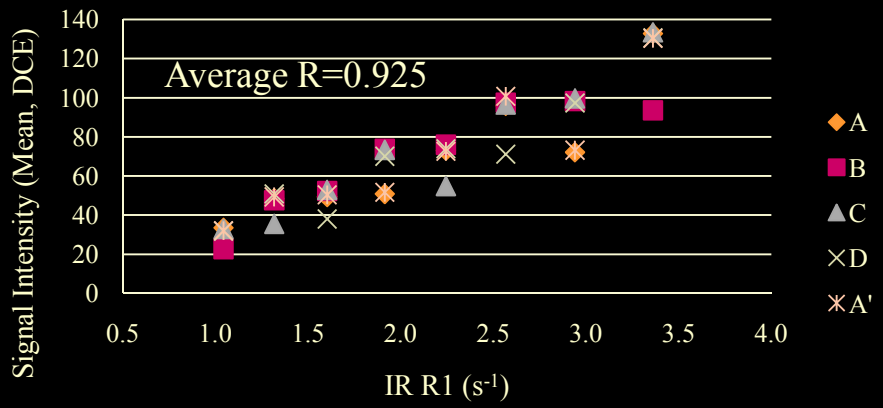


Variable flip angle relaxation rates vs IR (gold standard) values (Site 1 / Vendor A)

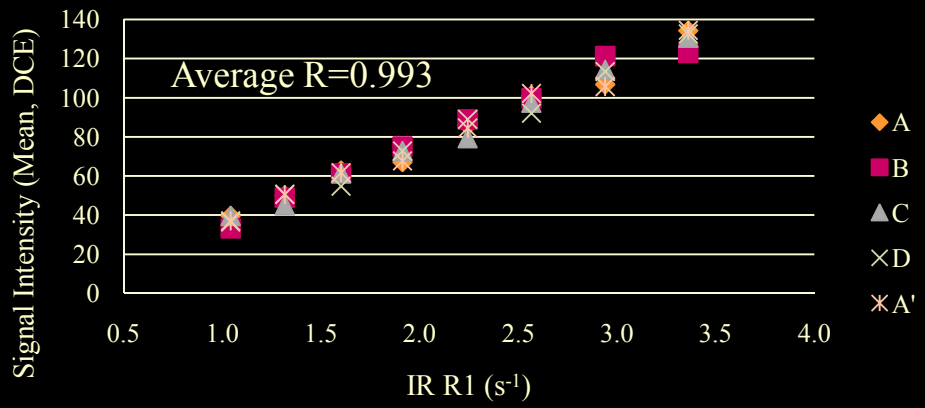
Phantom purchase funded by NCI Contract \27XS112

RSNA QIBA – Multiple Vendors / Three Time Points

Uncorrected – Site 2 / Vendor B

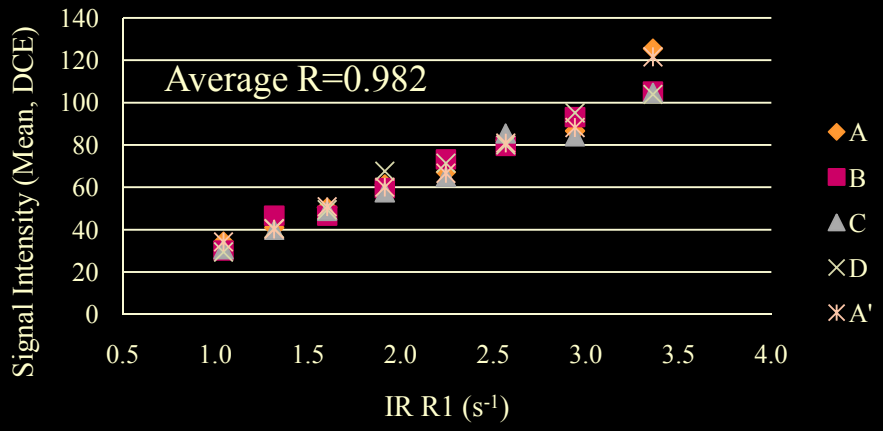


Corrected – Site 2 / Vendor B

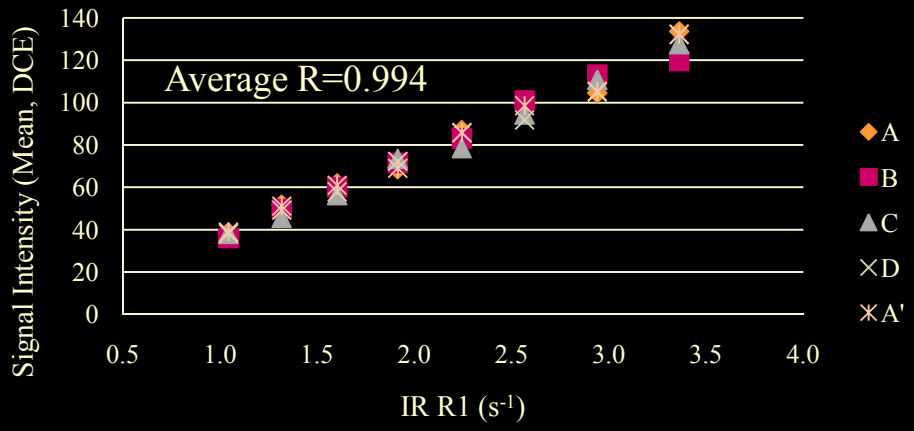


Comparison of Signal Intensity Change vs Relaxation Rate

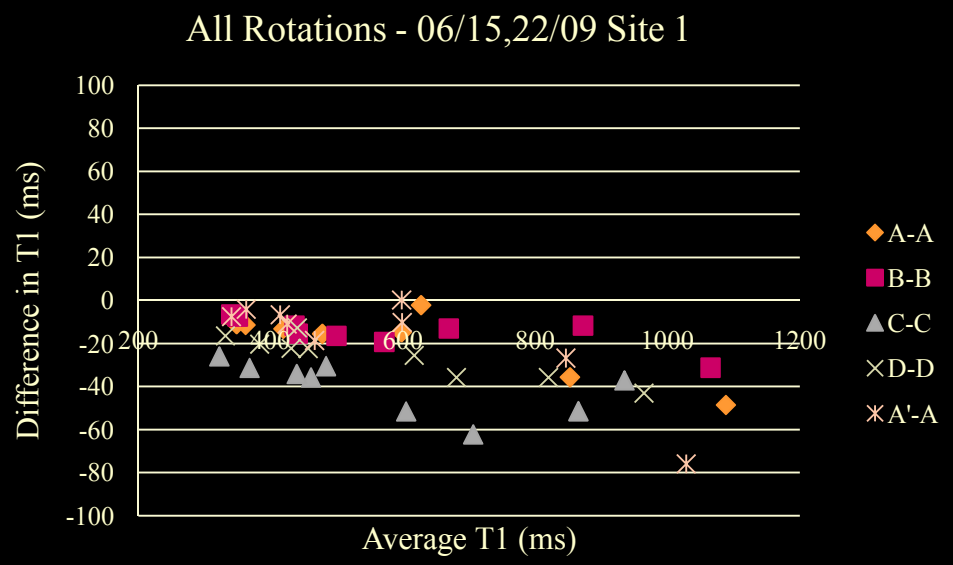
Uncorrected – Site 1 / Vendor A



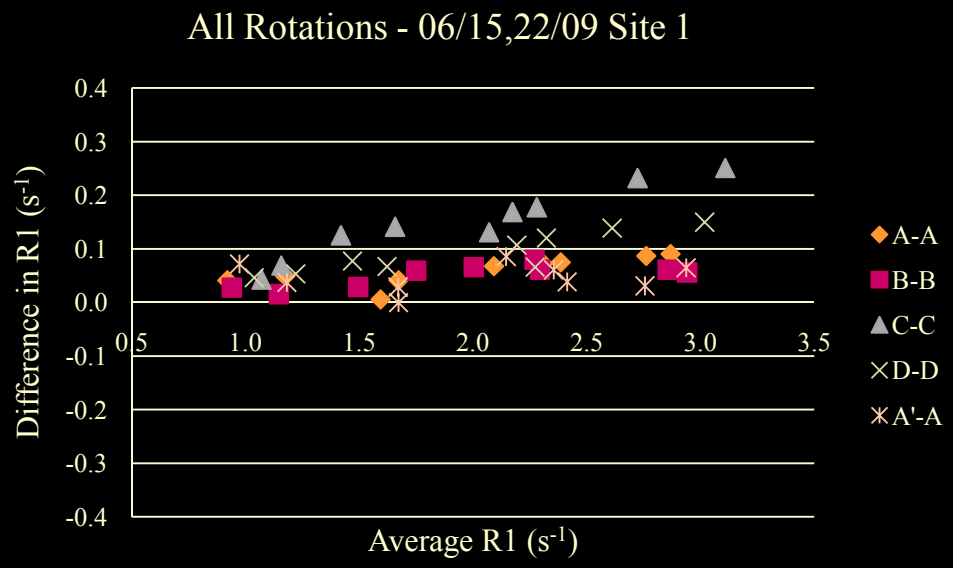
Corrected – Site 1 / Vendor A



RSNA QIBA – Multiple Vendors / Three Time Points



Difference in T1 from each contrast sphere, week 1 minus week 0.



Difference in R1 from each contrast sphere, week 1 minus week 0.

Phantom purchase funded by NCI Contract \27XS112

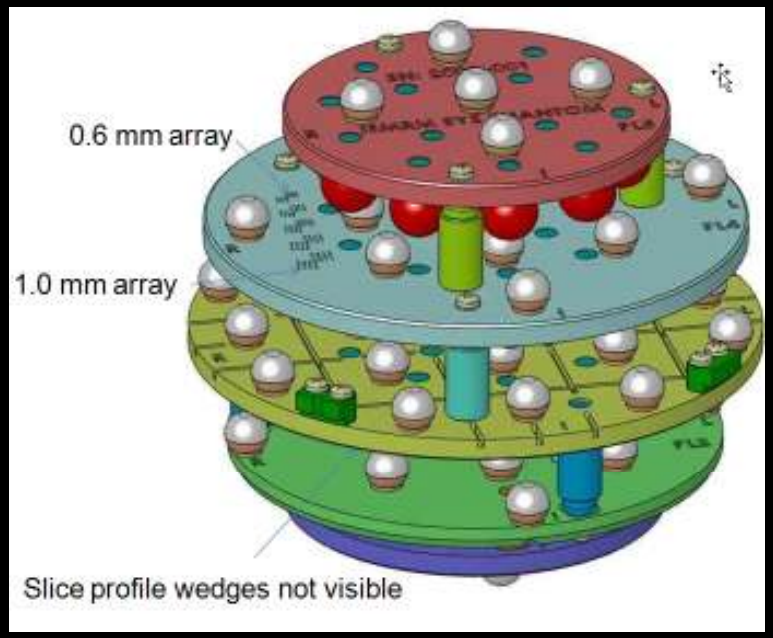
ISMRM Ad Hoc Committee

ISMRM: *Ad Hoc* Committee on Standards for Quantitative MR (SQMR)

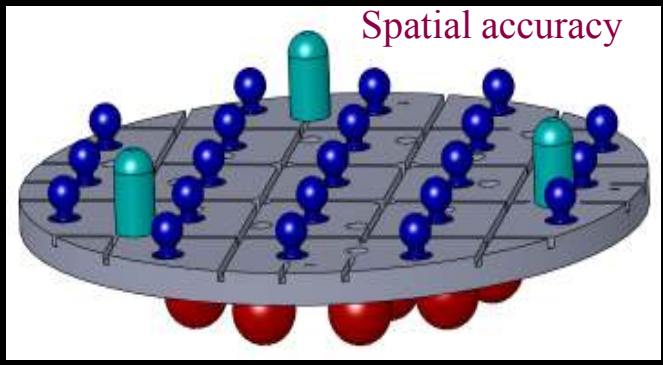
- Membership includes MR physicists, technologists, radiologists, NIST staff, NCI/CIP staff, vendors, and pharma. Expertise in research trials using quantitative MR.
- Current status:
  - White paper on quantitative MR
  - Design specifications & construction of an "open source" MR system phantom (collaboration with and funding by NIST)
  - Initial multicenter / multivendor phantom pilot studies to begin in May 2010.

http://wiki.ismrm.org/twiki/bin/view/QuantitativeMR/

ISMRM SQMR System Phantom

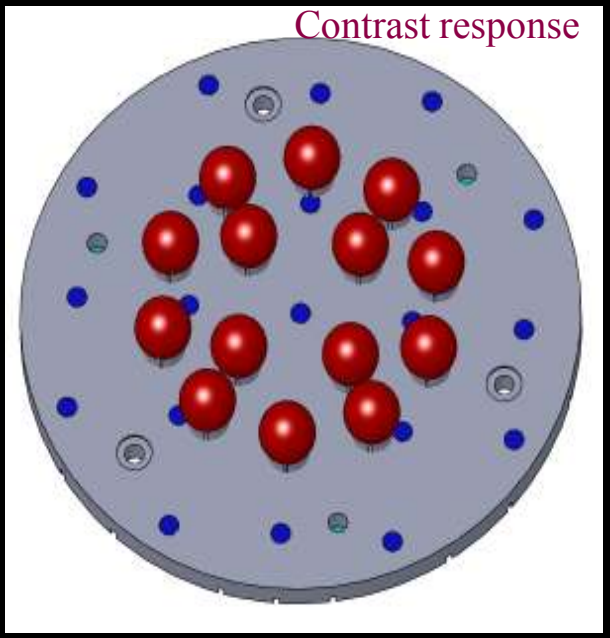


Spatial accuracy



All materials characterized by NIST

Contrast response



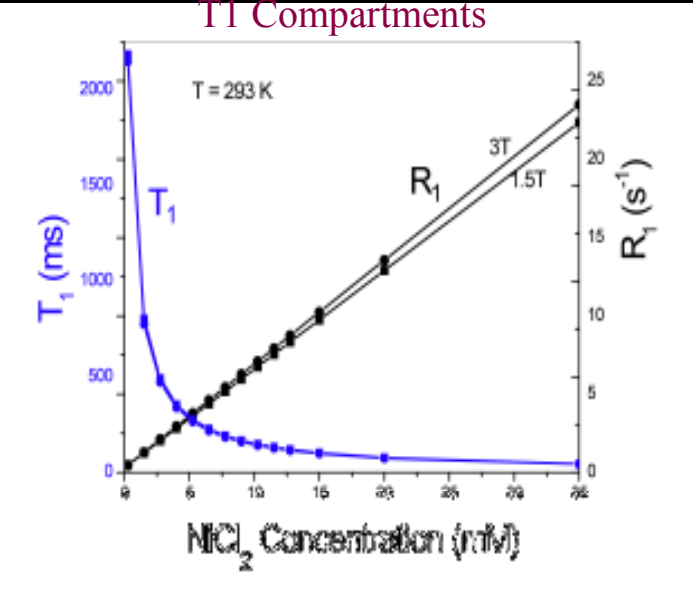
High contrast resolution

0.6 0.7, 0.8, 0.9, 1.0 mm

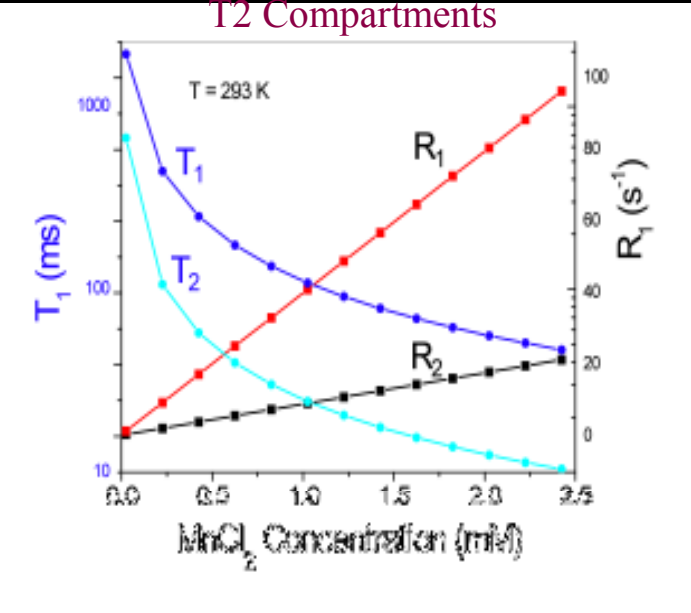
Section thickness

ISMRM SQMR System Phantom

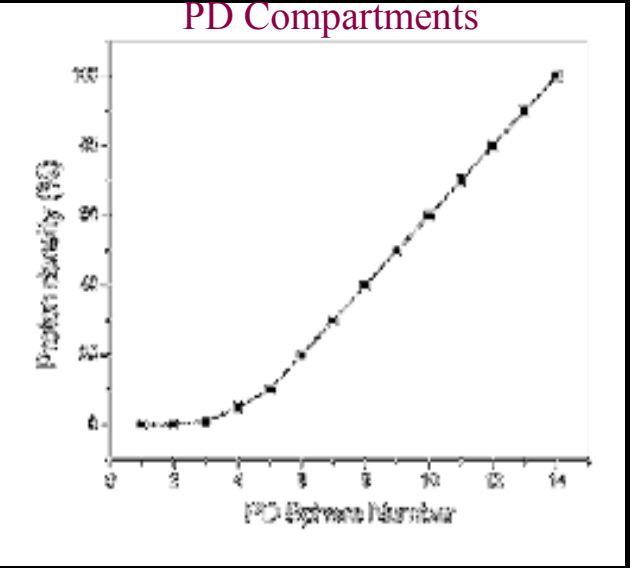
T1 Compartments



T2 Compartments



PD Compartments



Quantitative MR Initiatives