Wright Center of Innovation in Biomedical Imaging
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

The Impact of QC in Multicenter Clinical Trials - The IROC Experience for NCTN Focusing on MRI

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References:
- 1) Ellingson BE, Bendszus M, Baxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

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Quality Assurance: An Indispensable Necessity

In recent years, there has been an increased use of MRI as the preferred modality in multi-center clinical trials. Developing neuroimaging standards / best practices as well as the increased use and need for quantification techniques necessitate consistent as well as sufficient quality image acquisitions specifically for response assessment to therapies.

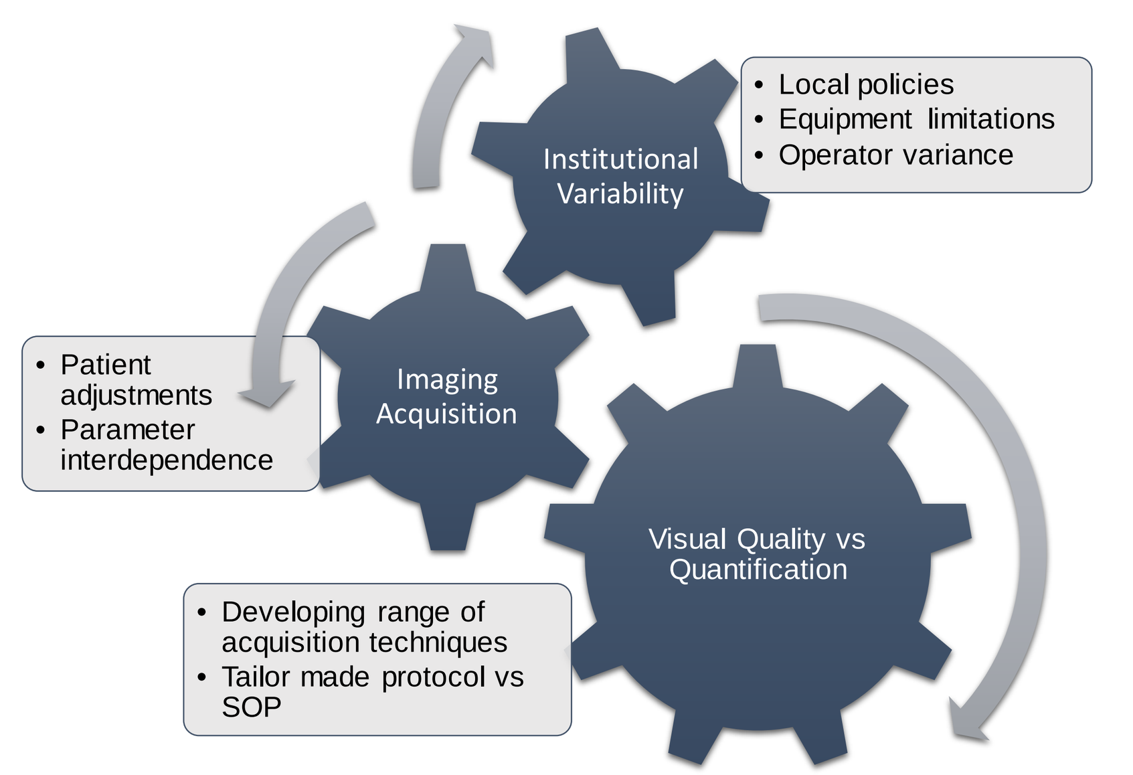
Institutional Variability
Local policies
Equipment limitations
Operator variance
Imaging Acquisition
Patient adjustments
Parameter interdependence
Visual Quality vs Quantification
Developing range of acquisition techniques
Tailor made protocol vs SOP

Figure 1. All the gears in motion that influence MR image acquisition are detailed here. While local policies must be standardized within a site, sometime inter-departmental differences exist in a larger institution. Equipment limitations and variations (1.5T to 3T) from baseline to follow-up exams add additional burden on the reviewers. System operators / technologists can influence a given acquisition, whether it is by individual preferences or patient driven adjustments due to the parameter interdependence in MRI. In the absence of a specialized local protocol, a more inclusive protocol is then used to change the field of view or add sequences. These tweaks might not necessarily alter the visual quality due to recent advancements in scanning protocols, while they may influence quantification. Specialized quality assurance techniques are thus essential to ensure the optimal acquisition for clinical assessment and quantification.

Phantom based device quality assessments, while important for instrumentation calibration, do not ensure quality image acquisition due to inter-operator, intra-institutional protocol variability and patient induced artefacts (**Figure 1**). As our team serves as IROC for the NCI-NCTN, we have embarked upon developing an imaging based MRI quality assurance methodology that can also be used for local quality management.

Imaging Radiation and Oncology Core (IROC)

The Imaging and Radiation Oncology Core (IROC) cooperative was formed with the reorganization of the NCTN and started to provide network wide services in March 2014. IROC Ohio is one of six imaging core laboratories within the cooperative and focuses on supporting and managing NCTN trials for the Alliance and SWOG network groups.

Our broad spectrum of services, a selection of which is listed below, puts us in prime position to analyze, educate and standardize acquisition even in a multi-center clinical trial environment.

- Protocol development support
- Site credentialing (equipment validation, test patient data assessment)
- Site personnel training & education
- Data quality assurance, banking and case management.
- Real time as well as end point data analysis and review.

DICOM in the Age of Big Data

General Parameters	
Field Strength	[0018,0087]
Vendor Make	[0008,0070]
Vendor Model	[0008,1090]
Contrast / pharmacologic agents used	[0018,0010]
Receiving Coil	[0018,1250]
Sequence Specific Parameters	
No. of Slices [N]	[0025, 1007]
Imaging Sequence	[0018, 0020]
Imaging Plane	[0020, 0037]
Acquisition Matrix	[0018,1310]
TR (ms)	[0018,0080]
TE (ms)	[0018,0081]
Flip Angle (degrees)	[0018,1314]
Echo Train Length	[0018,0091]
Number of Excitations (NEX)	[0018,0083]
Bandwidth (Hz)	[0018,0095] x [0018, 1310]
Slice Thickness (mm)	[0018,0050]
Gap (mm)	[0018,0088] - [0018, 0050]
FOV_Frequency Direction (mm)	Max([0028,0010], [0028,0020]) x [0028, 0030]
Temporal Resolution	[0020,0110]
B-values used for DWI	[0019,900c]

DICOM metadata is comprised of numerous tags that can be separated into public or private and their purpose is documented in the vendors' DICOM conformance statement. **Table 1** gives an example of relevant MR acquisition parameters with their associated DICOM tags, which are embedded in every image and can be readily accessed.

Table 1: List of DICOM tags representing some key MRI acquisition parameters. This data, when compiled, could be used as a "blue print", thereby providing an insight into local imaging practices. In addition, it allows for a comprehensive analysis of any variations between the established local standards to their implementation in reality.

Standard of care MRI based on local practices are often recommended in the protocol language in a multi-center clinical trial setting. Analysis of DICOM metadata exposes the range of variability across different institutions. Traditionally MRI has been driven based on visual assessment of imaging quality, which can be achieved using a range of different acquisition approaches. In this assessment, we are demonstrating the use of data extracted from DICOM metadata for a quantitative analysis and standardization of MRI acquisition protocols.

DICOM Driven Methodology

We had previously developed a DICOM driven quality assurance methodology modeled for PET/CT exams and have extended it to some of the more specialized MRI acquisitions. As shown in **Figure 2**, the two key starting points are the imaging and/or clinical expectations of the protocol and the information obtained from previous site questionnaires that reported local practices (**A**). The DICOM metadata (**B**) is extracted and compiled using an adapted in-house software. This compilation when parsed using the criteria set, allowed us to "push the boundaries" in specifying parameter ranges (**C**). The desired expected parameter range is defined (**Green**) as well as the additional ranges that would be classified as not desirable, but still acceptable (**Yellow**) and those that are not acceptable (**Red**). This heat-mapping spectrum helps with the development of an assessment matrix. A highly standardized and parameter driven semi-automated quality assurance approach (**D**) is then used to a QC reporting feedback loop (**E**).

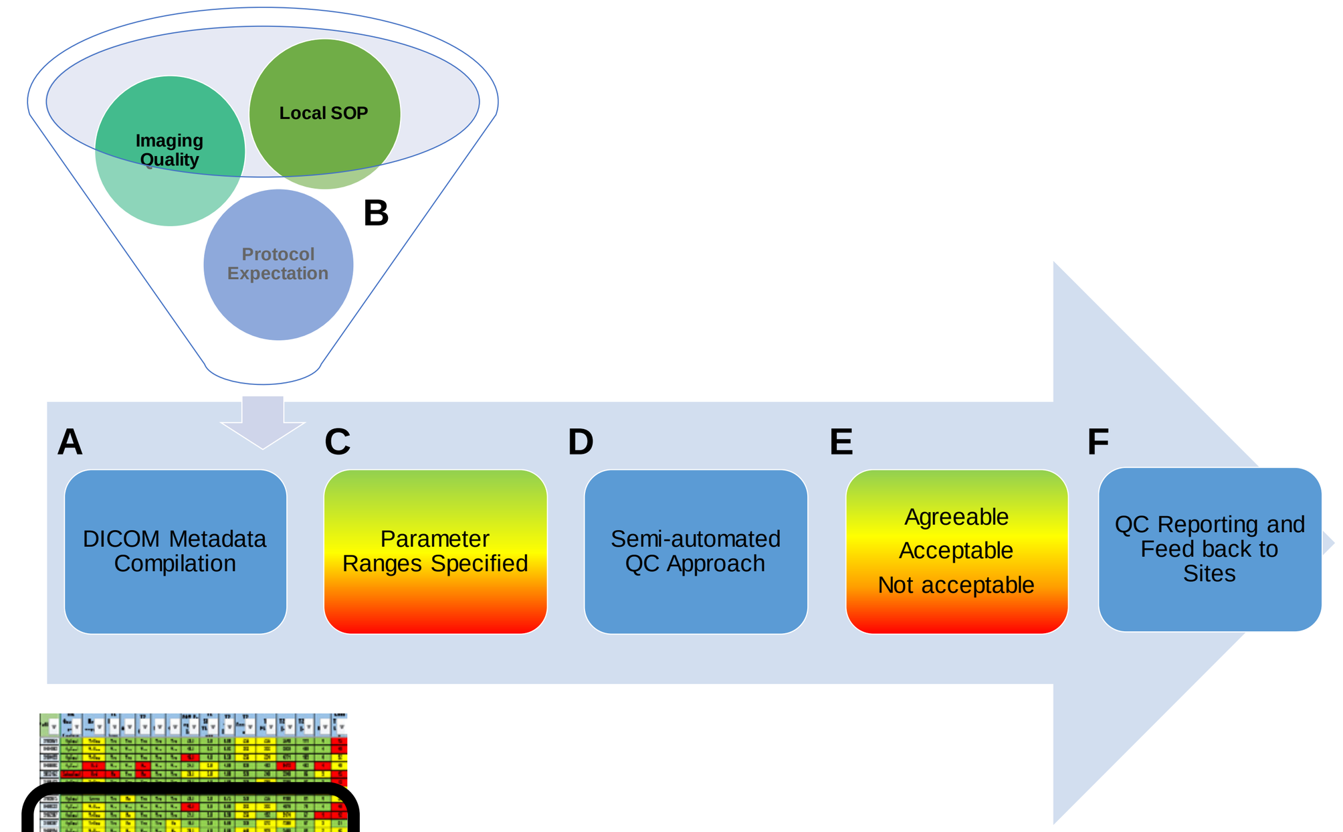

Figure 2. This figure highlights the workflow of IROC quality assurance methodology. DICOM Metadata compilation (**A**) when analyzed through input from the protocol imaging committee, and considering the local SOP as well as its effect on imaging quality (**B**), we were able to generate a parameter heat-mapping distribution (**C**). This then allows us to implement a semi-automated QC reporting approach (**D**) to assess images using a weighted parametric rating (**E**). Communication with sites in a feedback loop mechanism (**F**) has resulted in an increased rate of imaging compliance over the lifetime of the clinical trial.

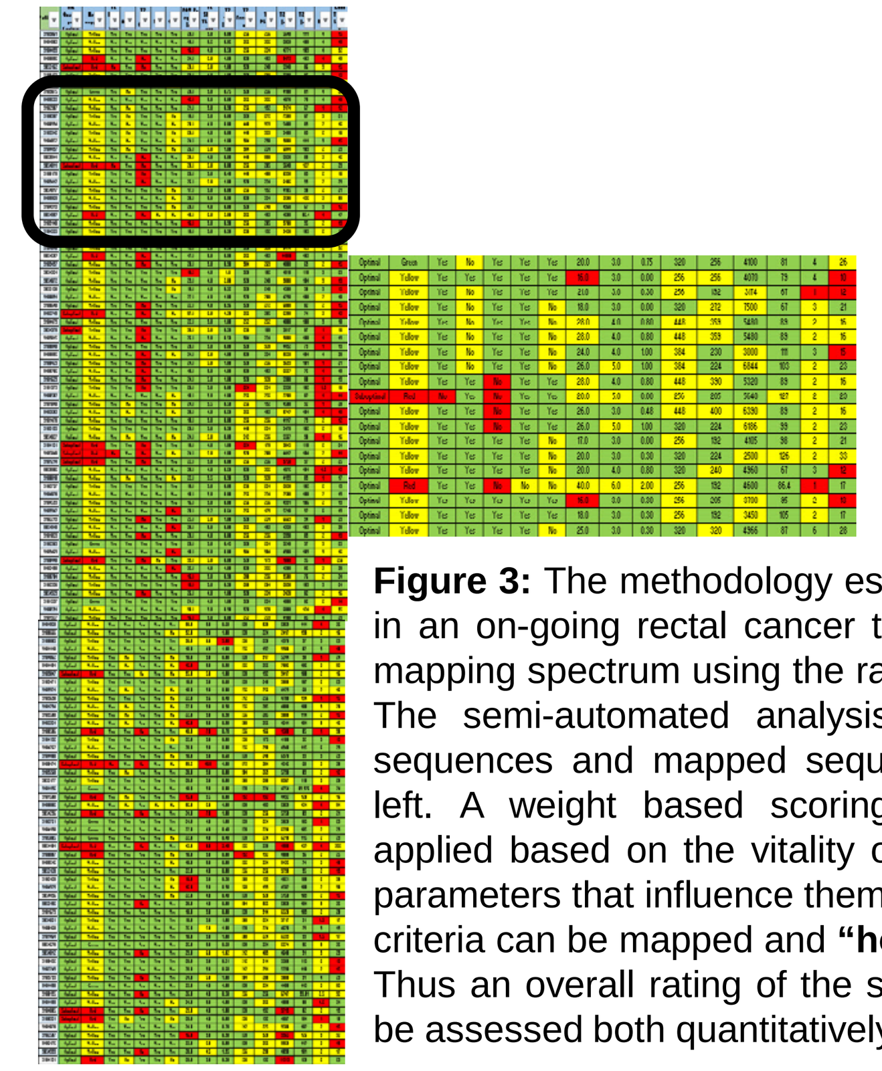

Figure 3: The methodology established above was used in an on-going rectal cancer trial to generate this heat-mapping spectrum using the ranges specified in **Table 2**. The semi-automated analysis is color-coded for MR sequences and mapped sequentially as shown on the left. A weight based scoring system could then be applied based on the vitality of sequences and the key parameters that influence them. By setting filters, specific criteria can be mapped and "**hot spots**" (Red) identified. Thus an overall rating of the submitted examination can be assessed both quantitatively and qualitatively.

Table 2: The range of parameters set based on imaging requirements, either as set in the protocol or based on clinical goal, along with input from imaging readers. These ranges are then used to produce a heat-mapping spectrum starting at the parameter level to the entire exam based on a weighted score assessment.

		Green	Yellow	Red
Primary Sequence		Axial T2 Oblique	Axial T2, Coronal T2 Oblique	Fat Saturated Axial T2
TR (ms)		4000-6000	2000-4000, 6000-9000	<2000, >9000
TE (ms)		80-120	60-80, 120-140	<60, >140
Slice Thickness (mm)		≤ 4	4-6	>6
Gap (mm)		≤ 1	1-2	>2
Field of View (cm)		18-26	>26	<18
Frequency Steps		300-340	250-300, >340	<250
Phase Steps	1.5 T	180-220	>220, 160-180	<160
	3.0 T	200-256	>256, 180-200	<180

Such heat-mapping (**Figure 3**) based on the parameter ranges specified (**Table 2**) enables visualization of parameter performance that can be zoomed in to a specific sequence and zoomed out to assess at the level of an examination, a patient, an institution or the overall trial performance. This adaptive visual display is an efficient quality assurance tool as many clinical sites do not even realize the variability of protocol implementations and adherence to the protocol within a clinical trial. This helps to generate a detailed quality check report identifying problem areas from patient preparation to imaging parameters, which could then be communicated back to sites. Such a feedback loop helps to bring imaging acquisitions from the Red/Yellow ranges to Green, thereby not only improving quality of an ongoing clinical trial, but also raises the standards of the current local practice for future clinical trial participation and clinical care.

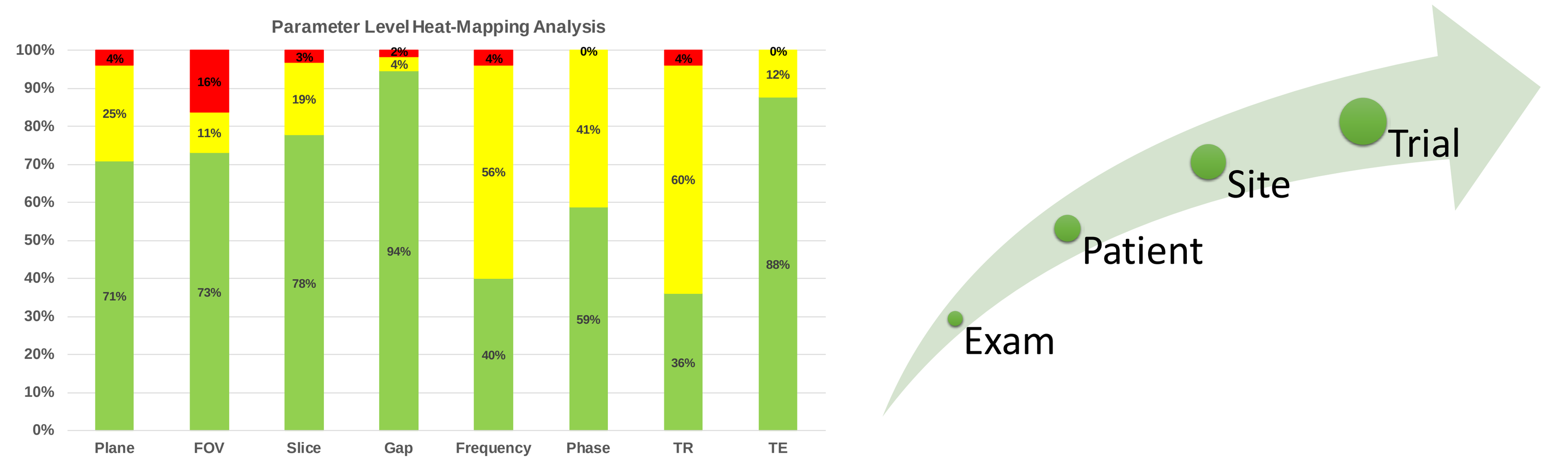

Figure 4: This chart is a pictorial adaptation of the heat-mapping spectrum (**Figure 3**) generated earlier for rectal cancer trial. Such a display can be zoomed into a detailed parametric assessment and zoomed out to identify performance roadblocks at a patient level (baseline to follow-up exams), institutional or an overall trial level accrual expectations. This adaptive visual display is an efficient quality assurance tool and can also be used to provide feedback to the trial leadership for any possible updates to the protocol language.

Standard of Care MRI: Does One Size Fit All?

Clinical trials with MRI as the preferred imaging modality frequently recommend Standard of Care imaging. This approach by the clinical trial community appears to be driven by the need to meet accrual goals without discouraging trial participation due to the perceived complexity in enforcing adherence of MRI standards matching clinical goals. Our DICOM driven methodology as shown above exposes the extensive range of variability in such a clinical trial setting, making the use of Standard of Care MRI a classic case of "trying to fit a square peg in a round hole".

- Perception of complexity and the subsequent difficulty in enforcing protocol standards
- Fear of discouraging trial participation
- Lack of awareness of the inherent variability in such a multi-center setting

While standard of care MRI may be sufficient when supplemented with clinical pathology and blood work results for local treatment decisions, this present some challenges for end point data analysis towards the primary or secondary objectives of a clinical trial.

For example, in the rectal cancer trial mentioned earlier, more than half of the participating institutions have an existing pelvic MRI scanning protocol and adapt it for rectal screening. We observed two key areas of difficulty with such examinations. Primarily, fat saturated sequences (**Figure 5**) that help with pelvic tumor screening tend to suppress signal from a majority of rectal mass. Either contrast enhancement is required as a corrective measure in such cases or the patient ends up having another imaging examination. Secondly, an oblique angled T2 sequence is critical to assess the localization of the tumor in terms of resectability. Without meeting these criteria, either an undue burden is placed upon imaging readers performing blinded independent reviews and/or there's a possibility excluding such cases from the analysis.

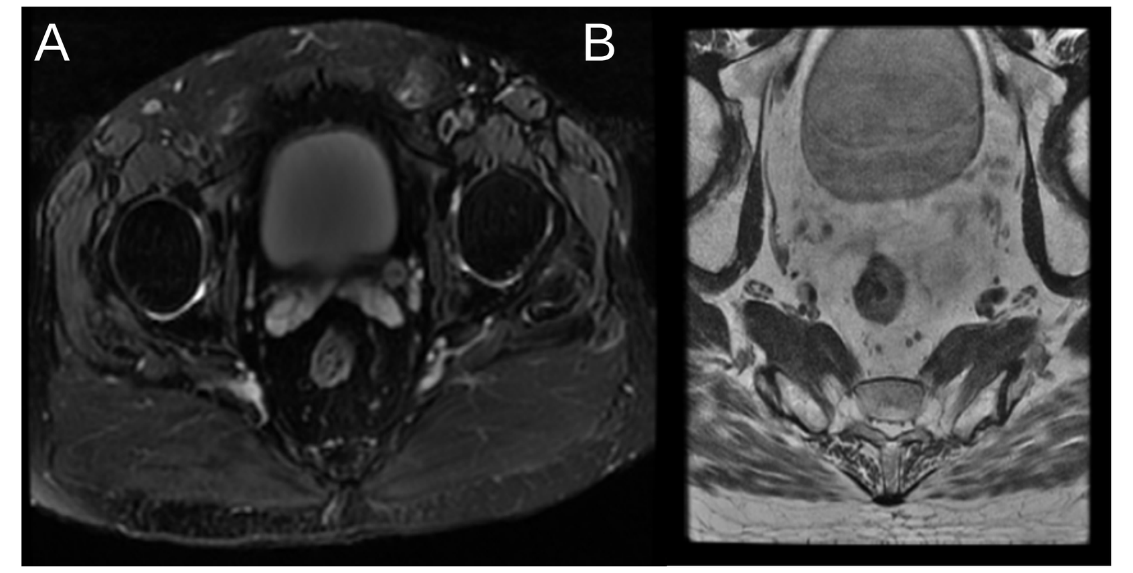

Figure 5: Comparison of a fat saturated non-oblique T2 sequence (**A**) to small FOV T2 acquired an oblique angle to the primary tumor (**B**). Fat saturation suppresses signal from a majority of rectal tumors and angular information is critical to determine resectability. This is an example of some of the challenges in trying to fit an existing standard scanning protocol (pelvis) to protocol specifications (rectum). Without the help of supplemental information (pathology, blood work, etc.), it is nearly impossible for an independent imaging reader from the trial committee to stage disease or assess response.

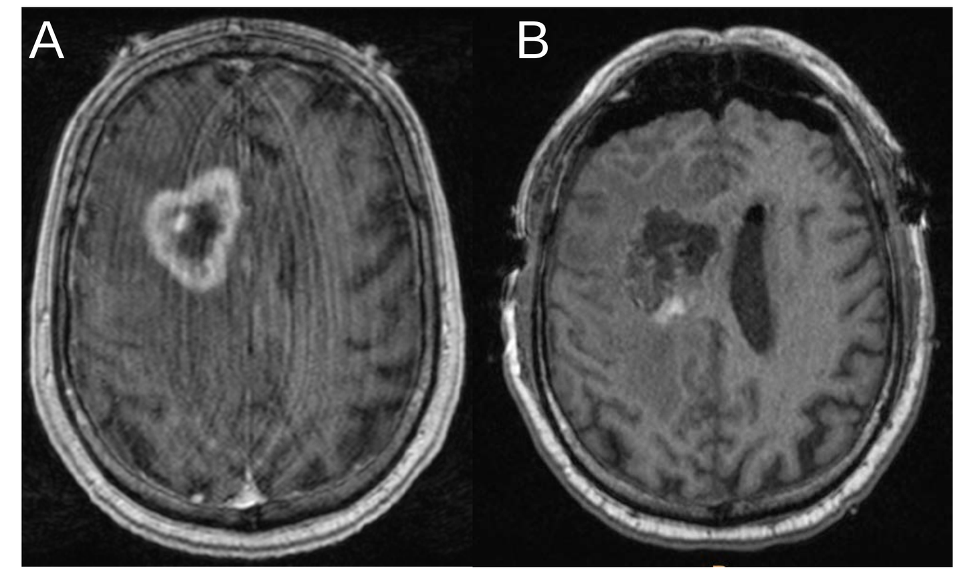

Figure 6: This compares the acquisition of pre-operative (**A**) and post-operative (**B**) T1 weighted sequences of brain MRI for a patient enrolled in a gliobastoma trial. The site appeared to have had difficulty positioning the patient for their pre-operative scan as noticed by ringing artefacts caused due to being too close to the magnetic bore. Though this was corrected in the post-operative scan, it makes comparative response assessment and quantification very challenging.

For clinical trial response assessment, maintaining consistency between baseline and subsequent follow-up examinations for a patient is both valuable and essential. Any variations in patient preparation or acquisition technique could alter the parameters in a way that makes quantification difficult. For clinical protocols, proper communication between the treating physicians office (clinical research coordinator) to the MRI technicians is required to maintain the same scanning protocols. Absent which, each examination is performed as a stand-alone acquisition. **Figure 6** demonstrates an instance of a pre-operative scan having a patient/operator induced artefact, which did not occur during the post-operative scan. However, the response assessment and patient eligibility in trial participation is determined by an independent imaging review, which is challenged when major artefacts impact quality. Providing QC feedback from a Core like IROC not only serves to perform detailed quality assurance, but the feedback provided appears to be educational to produce consistent image quality and this also raises the local imaging standards.

Methodology Adaptation and Validation

So far, we were able to demonstrate that a DICOM based heat-mapping approach can be readily implemented and semi-automatically performed, once DICOM tag criteria are established. Using the color-coded tag system, a mosaic of the exam, case, institution and overall clinical trial can be generated and readily visualized. "Hot spotting" can then quickly identify deviations and trends.

For this quality storyboard, we have identified two neuro-imaging clinical trials with standard of care imaging recommendations in the protocol language. Over 200 examinations from 60 different institutions were analyzed using an adaptation this DICOM driven methodology based on neuro-oncology consensus recommendations[1]. Both of these trials have a clinical goal of response assessment to treatment performance and/or progression of disease confirmation, as applicable.

A combined 60% of baseline MRI examinations for both trials has at least one Red category, while 69% of the follow-up exams were inconsistent when compared to baseline. It is therefore critical for the baseline acquisition to be protocol conformant as this scan acts as the benchmark for clinical assessments. Surprisingly, there were a number of instances of exclusion of sequences (6%). Apart from that, the main parameters that caused these MRI scans to have a Red color tag were slice thickness, slice gap and inconsistent acquisitions (**Figure 7**). Inconsistencies exist both within a given imaging study, such as pre-contrast and post-contrast T1 weighted sequences, also extending to follow-up examinations. With the clinical goal of progression assessment, it is critical to identify these factors causing inconsistencies with given imaging submission and educates site on how to keep those at a minimum.

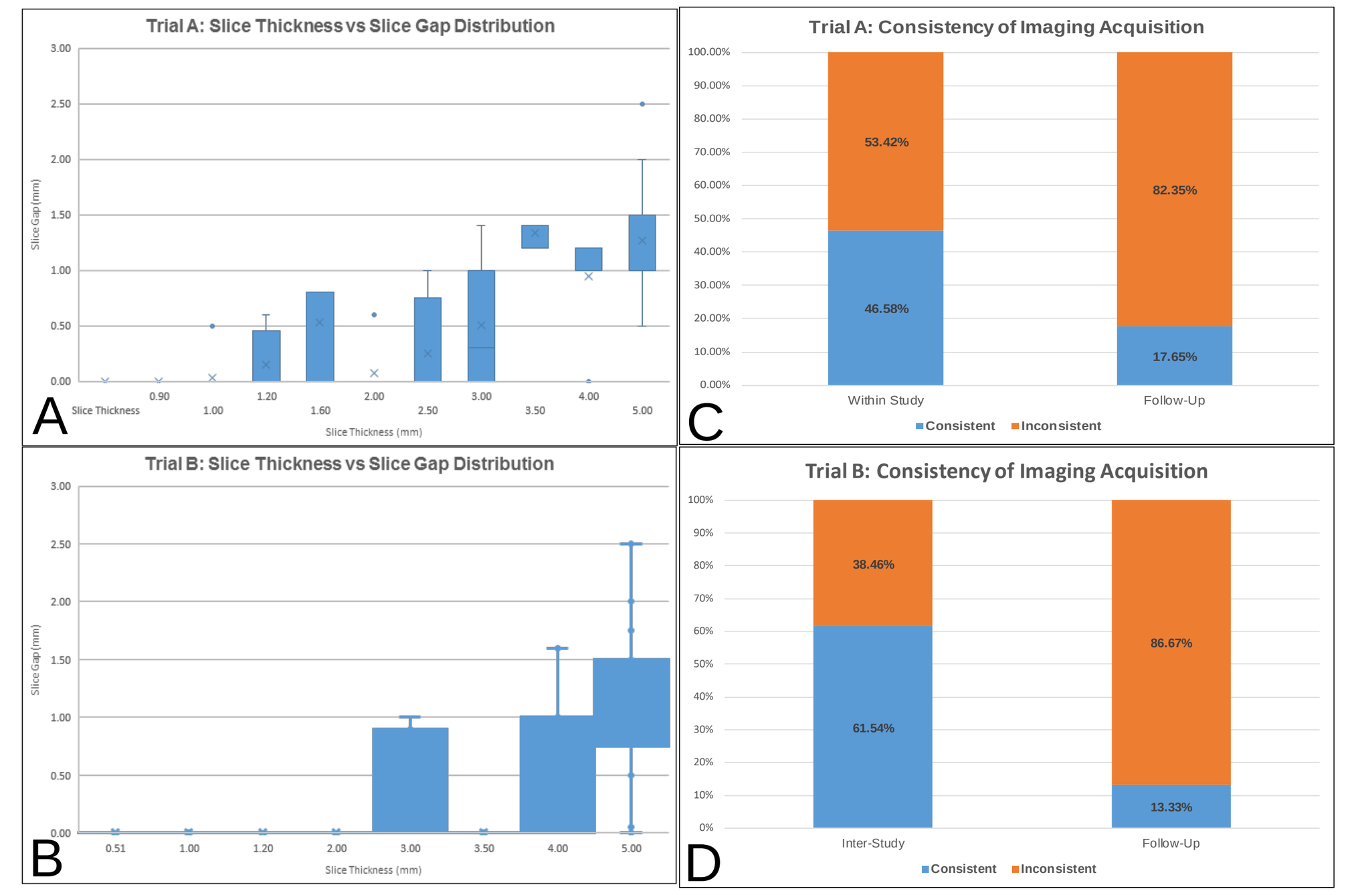

Figure 7: Thinner slices (4mm) with no gaps are increasingly recommended in developing neuro-imaging protocol standards. A distribution of these parameters is laid out for Trial A (**A**) and Trial B (**B**). For most examinations, these are problem areas that could swing the spectrum from Red/Yellow to Green. Consistency of acquisition, both within a study (e.g. before and after contrast administration), and between baseline and follow-up is critical for quantification and response assessments. As seen here, there is a fairly high rate of inconsistency in both trials (**C, D**). This methodology should encourage real time quality assurance and feedback through communication to improve imaging performance for a trial.

Highlighting just some of the acquisition deviations from the protocol expectations indicate that we have to re-educate primarily the MRI technologists as well as protocoling clinicians and demonstrate that these variations are at a minimum burdensome to efficient response assessment and increasingly jeopardize the effective use of software tools to analyze and quantify MRI. From prior experiences on other modalities such as PET, we know that awareness of these issues and feedback to encourage improvements are effective tools to improve image quality performance.

Conclusion and Discussion

- The reliable collection of DICOM tag based metadata can be readily achieved in clinical trials. The developed quality assurance methodology facilitates a semi-automated, highly structured approach that can deal with the complexity of clinical care based MRI within multi-center trials.
- While the commonly used phantom based performance assessment characterizes the ability of the MRI system to meet industry or expected clinical trial system standards, the most extensive and quality impacting variability occurs in the MRI acquisition and post-processing parameters which are commonly not readily analyzed and their adherence mapped.
- Heat-mapping is an effective assessment tool for protocol compliance in clinical trials. We were surprised with the large amount of variability that is occurring in broad based multi-center clinical trials. This obviously has impacted the ability for consistent response assessment and has caused the under utilization of MRI within such settings.
- Standard of care MRI recommendations in protocol verbiage can co-exist with protocol expectations as long as proper considerations are given to the key areas of variability introduced to the inherent parameter interdependence of the MR imaging modality.
- We believe that raising awareness to this predominantly unnecessary variability by readily visualizing the deviations from desired parameters is an effective image quality management tool that enables feedback and training / learning opportunities as well as helps to achieve consistent image quality that typically is only achievable in single center trials or highly trained performance sites.