Publishable Summary for 20NRM05 iMet-MRI
Improved metrology for quantitative MRI

Overview

Magnetic Resonance Imaging (MRI) used in routine clinical practice produces images designed for single use, to be looked at by individual human experts. Although a powerful tool, it lacks consistency when comparing images acquired on different scanners or at different times. MRI scanners are capable of producing images known as quantitative MRI (qMRI), which can provide additional consistency and clinical specificity but these measures need metrological support. This project will develop test objects, procedures, analysis tools, and best practice guidance for various qMRI techniques and demonstrate them in an international multi-site trial.

Need

Cancers, heart disease, dementia, and stroke can all be detected and monitored using MRI, and European health services maintain thousands of MRI scanners from different manufacturers, with various ages, field strengths and pulse sequence implementations. Conventional MR images are qualitative, showing relative contrast between tissue types which varies greatly from one scanner to another. This means that images produced at different sites using different scanners are not directly comparable which is challenging in large-scale clinical trials using MRI. qMRI forms images by making measurements of physical quantities, creating the possibility to calibrate different scanners and directly compare their performance. This reduces data variability, and hence the sample size required to observe a clear effect, and has the potential to reveal new, clinically useful information not present in conventional scans. qMRI has patient benefits including diagnosing and treating liver disease, muscular dystrophy, heart failure and ischemic stroke. However, it is necessary to be able to evaluate scanner capabilities using well characterised test objects and measurement protocols.

All major scanner manufacturers now offer qMRI as an option in their products, and third-party solutions such as FerriScan for imaging iron fraction in tissue have obtained FDA approval. To realise the potential of qMRI methods and their benefits to patients, there is an urgent need to ensure that scanners are calibrated to a common standard and to develop guidance for quality assurance procedures for routine clinical use. At present, normative standards covering MRI either do not address quantitative measurements (IEC EN 62464-1) or exempt MRI from measurement requirements (IEC EN 60601-2-33). To increase uptake of qMRI, standardised guidelines are needed to enable harmonisation of image analysis between clinical centres and ensure consistency in measurements made between sites and allow effective calibration and benchmarking of quantitative MRI approaches.

Objectives

The overall aim of this project is to support the clinical uptake of qMRI methods by providing a metrological foundation that enables independent validation of qMRI measurements and the provision of improved normative standard documentation which is compatible with existing quantitative approaches. The project additionally aims to achieve uptake of the new qMRI and associated metrological approaches with interested MRI user groups such as clinical trial providers and MRI professional bodies.

The specific objectives are:

1. To develop traceable novel material measurement and manufacturing methods for phantoms (with a focus on concentration agents), for use in the quantitative assessment of qMRI on individual scanners with a specific focus on T1, T2, fat fraction, iron content, diffusion, and dimensional metrology for features. In addition to develop reference methods to provide traceability to these materials.
2. To develop robust standardised measurement procedures and User Guides using both experimental and digital methods, for data analysis and uncertainty quantification of qMRI measurand maps, and to

apply these methods to specific qMRI image measurements such as T1, T2, fat fraction, iron content and diffusion.

3. To demonstrate the reproducibility, harmonisation and calibration of the traceable methods developed for relaxometry, fat fraction, iron content, and diffusion parameters within phantoms and the standardised measurement procedures for qMRI acquisition in a large-scale multi-site study of at least 5 sites, including an investigation of the feasibility for the translation of these into human studies at multiple field strengths.
4. To publish methods and at least two best practice guides based on the results from Objective 2. In addition, to develop guidelines on the harmonisation of qMRI data from a large-scale multi-site study from Objective 3. The guidelines will be suitable for dissemination to standards developing organisations and to organisers of clinical trials.
5. To collaborate with the technical committees IEC TC62/SC62A and BSI CH/62/2, and the users of the standards they develop to ensure that the outputs of the project are aligned with their needs, including the provision of a report on qMRI calibration, the deployment of phantoms that are important for the assessment and comparison of MRI image quality, and recommendations for the incorporation of this information into future standards at the earliest opportunity.

Progress beyond the state of the art

Very few traceable phantoms and processes exist for use in qMRI, with only NIST in the US able to provide traceable characterisation of phantom T1 and T2 values. iMet-MRI has defined routes to traceability for all measurements outlined in Objective 1: T1, T2, Fat Fraction and Iron Content, as well as synthesising several sets of well-characterised samples which are now being scanned in the multi-site trial. The project has also identified a proposing additional material for use in fat fraction imaging which is a closer mimic of the NMR spectrum of human subcutaneous fat than other existing approaches. This material is also being scanned using trial protocols and we are exploring additional funding routes to develop it further.

A simulated MR system based on the Bloch equations has been developed to produce synthetic MR images for relaxometry and iron to support delivery of Objective 2. Digital models of the phantoms developed as part of Objective 1 have also been developed and used to generate relevant synthetic data. Numerical experiments which use these models to perform a sensitivity analysis on results generated are also underway. Software has been developed for the analysis of both synthetic and experimental results in the investigation of all measurands of interest in the project and is now being used to analyse multi-site trial and sensitivity analysis data. These software packages are also being used to investigate the uncertainties present in the measurement techniques used in iMet MRI.

Scan protocols for all measurands have been developed and tested at core scanning sites. The protocols are now in use at all scanning sites for the multi-site trial of Objective 3. These have also been used to verify the suitability of phantom materials developed under Objective 1 for use in the work.

The iMet MRI project has also completed a review exercise of existing standards and national regulatory guidelines worldwide covering the subject of quantitative MRI, as part of the background to Objective 4, and have formed the basis for a submission to a joint meeting of BSI CH62 and its subcommittees (including CH62/2 as per Objective 5), which will take place in September 2023.

Results

<u>Objective 1: Development of traceable novel material measurement and manufacturing methods for phantoms and reference methods to provide traceability to these materials</u>

The sourcing and synthesis of test materials, as well as routes to traceability, for a range of clinically relevant T1 and T2 relaxation time values has been completed, using a 60MHz desktop NMR system with traceability ultimately to the TUBITAK rubidium atomic clock. A further set of 10 traceable T1 and T2 measurements at 125MHz has been ordered from NIST to provide a fully traceable reference at 3 Tesla in addition to the current set at 1.5 Tesla. The consortium has synthesised and characterised all samples needed for the multi-site trial and distributed to all scanning partners along with validated phantom holders for all sites. A more complex fat mimic has also been identified and synthesised and is included in the multi-site trial scanning as far as the number of available samples allows. A further set of samples is currently going through testing for long term stability alongside the other test materials.

Objective 2**:** Development of robust standardised measurement procedures and User Guides using both experimental and digital methods.

A full Bloch equation simulator, including all aspects of the imaging sequence and readout has been implemented and a draft for publication in an open access journal being prepared. A digital version of the physical phantom designed for the multi-site trial has been built, and simulations of the acquisition for all measurands run on it. It is also being used for the sensitivity analysis. Images from both simulated and live scanning have been used with postprocessing software to develop the analysis approaches as part of the multi-site trial. The digital version provides a known ground truth against which we can compare the results of the measurand map analyses.

Objective 3: Demonstration of the reproducibility, harmonisation and calibration of developed traceable methods and the standardised measurement procedures for qMRI acquisition in a large-scale multi-site study.

To ensure that all multi-site trial protocols and procedures were practical and achievable on the clinical MRI systems being studies, we first performed a scoping study on a subset of systems. The enabled us to iron out any difficulties in the procedure and optimise image quality. These initial acquisitions were performed using commercially available product sequences available at typical hospital MRI facilities, and used the materials developed in Objective 1. This study enabled us to refine our procedures to make sure they could be implemented by all partners, and also provided a “live” test of the materials developed as well as providing an assessment of the time that our procedures would take to acquire all images. This is important because time on busy clinical MRI systems is often as a premium. The scoping study also enabled us to compare the differences and similarities in the DICOM image meta-data from different manufacturers – this is similar in many places but different in others according to each manufacturers implementation of the imaging standard. The scoping study thus laid important groundwork for the design and implementation of the multi-site trial and enabled us to make sure all analysis software was fit for purpose.

Having made refinements according to these lessons-learnt, the full multi-site trial is now underway, with increased confidence that acquisitions, materials, procedures, and analyses are as good as we can make them. The scan protocols for all measurands have been written and tested. These include protocols for maximising measurement quality and a second set which perform measurements in a clinically feasible timescale using commercially available sequences. Scanning for the full trial in now underway and we expect to scan at all sites by Q3 2023. Data is being analysed as it comes it. We also anticipate being able to scan at addition sites to increase the size of the dataset, and we are exploring options to make the complete dataset available open-source.

Objective 4: Publication of methods and best practice guides and the development of guidelines for the harmonisation of qMRI data from a large-scale multi-site study suitable for dissemination to standards developing organisations and to organisers of clinical trials

The review of standards and guidelines is complete and confirmed that there is a significant gap in current standards as they pertain to qMRI. In addition, best practice documents for MRI only cover some aspects of quantitative approaches and there is a significant need for improved guidance around qMRI QA. This has been shared with the Chief Stakeholder and has been presented to the stakeholder committee and at to the wider user community at project stakeholder meetings. It has been summarised into a briefing document for the BSI technical committees and subcommittees and will be discussed at an upcoming joint meeting. This review has also aided in the planning of the Good Practice Guide deliverable, which will contain recommendations on qMRI QA and best practice based on experience gained in delivering this project.

Impact

To promote the uptake of project results and to share insights generated throughout the project, results have been shared with a diverse user community. Presentations have been given to RSNA QIBA (The Radiological Society of North America’s Quantitative Imaging Biomarkers Alliance, a major international effort aiming at standardisation and best practice across all modalities of quantitative medical imaging) and EIBALL (the European Imaging Biomarkers Alliance, a parallel European-led effort) as well as to NIST in the US. We have also given numerous invited talks and conference presentations, including a dedicated special session on iMet-MRI at the recent Mathematical and Statistical Methods for Metrology 2023 (MSMM) conference in Turin. We have also given presentations at the 4th European Congress on Medical Physics (ECMP) to approximately 100 people, and to the annual meeting of the British and Irish Chapter of the International

Society for Magnetic Resonance in Medicine (BIC-ISMRM), and invited talks at the National Institute of Standards in Boulder Colorado (audience of approximately 40), and the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility at the US National High Field Research Facility in Gainsville, Florida (approx. 40 live, plus streaming nationally across the US to about 100 more).

A project stakeholder committee of 5 core members has been formed, with each member representing the interests of a group of stakeholders: clinical users, scanner manufacturers, MR physicists, metrology/QA, and standards. Two of three major stakeholder workshops targeted at all the groups named above plus other interested practitioners have been successfully held. The workshops covered the latest project developments split by work package, and covering chemical metrology and materials development, simulation and analysis code developments, scoping study and multi-site trial findings and developments, and the review of the standards landscape for qMRI. The most recent was an online event in June 2023 with 85 attendees. Our workshops have received excellent attendance from a broad range of stakeholder groups and have enabled valuable discussions and feedback in response to project result updates.

Impact on industrial and other user communities

Deployable and verifiable quantitative MRI will have impact on clinical trials, where improved image standardisation will mean reduced study cohort sizes and reduced costs and complexity, so reducing time to market for new therapies by allowing MRI-based assessment of their performance with known and quantifiable uncertainties as well as potentially reducing lengthy set-up and harmonisation activities at the start of trials. Currently MRI harmonisation is difficult to achieve and uncertainties associated with MRI images highly challenging to quantify. This is a significant barrier to using MRI in the development of new therapies. Quantitation allows metrological assessment of images in a way that is not possible with qualitative techniques. Likewise, it also provides a mechanism for assessing new and emerging imaging techniques, supporting translation into clinical application. This project is taking steps to provide a metrologically sound set of references and procedures to support effective qMRI QA and reproducibility.

Impact on the metrology and scientific communities

MRI is extremely diverse. Images can be acquired in literally hundreds of different ways, revealing different contrasts due to differences in the underlying physics of the acquisition technique. Different MRI preparations can reveal not just magnetic response parameters but also, for example, information about iron or fat content, water diffusion, or magnetic susceptibility of tissues. Each of these provides a unique, non-invasive window into tissue and cellularity and the changes wrought on them by various pathologies. The metrology of MRI, however, is relatively under-developed, with most work concentrating only on T1, T2, and diffusion imaging. This project establishes traceable and metrologically quantified measurements of clinically applied quantitative MR contrasts and will allow the independent assessment and calibration of different scanners, products, and services. This would place these services on a similar metrological footing to other medical imaging modalities such as CT or PET, where the use of ionising radiation has meant that metrological considerations are more developed than in MRI.

Impact on relevant standards

The outputs of this project are building the case for improved international standards for qMRI. The standards review has verified that there is a gap in current standards and enabled us to make a compelling case to take to the standards community. This is also timely. By working closely with the Chief Stakeholder, we have been able to get involved with a current effort to redraft IEC 60601, which presents a unique opportunity to improve the standard for qMRI. This will be an ongoing process beyond the lifetime of the project, but without the iMet-MRI project grasping this opportunity would have been extremely difficult. A summary report has been developed as a briefing document for the UK mirror of IEC TC62 (BSI TC62 and its subcommittees). This has been reviewed by the consortium, chief stakeholder, and colleagues at NIST, and will be presented to the committee at the next meeting.

Longer-term economic, social and environmental impacts

A situation whereby qMRI products are available and approved for clinical use but without a requirement for metrological assessment of the outputs is a dangerous one as without a robust metrological framework and a requirement to use it in current standards, there is obvious potential for a race to the bottom in measurement performance. Following the end of this project and the fruition of its activities internationally, it is expected that the future outputs of qMRI products will be externally verifiable, and users will be better able to trust the vendors that these products have been manufactured correctly and tested rigorously.

Similarly, improved calibration of imaging systems are a necessary pre-requisite for deploying AI expertise into medical imaging. In most major economies, the number of MRI scans is increasing but the number of radiologists is broadly flat or in some countries decreasing. This means it is vital to make the most effective use of specialist radiological expertise. Allowing AI to perform repetitive and time-consuming work such as drawing regions of interest in patient scans would free up radiologists to spend more time on patient-critical assessment. Patients would therefore benefit from reduced waiting times and more reliable radiological expertise.

List of publications

-

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

Project start date and duration:	01 June 2021, 36 months	
Coordinator: Matt G Hall, NPL Tel: +44 20 8943 6750 E-mail: matt.hall@npl.co.uk Project website address: http://empir.npl.co.uk/imet-mri/		
Chief Stakeholder Organisation: International Electrochemical Commission	Chief Stakeholder Contact: Richard Scott	
Internal Funded Partners: 1. NPL, UK 2. IMBiH, Bosnia and Herzegovina 3. INRIM, Italy 4. LGC, UK 5. TUBITAK, Turkey	External Funded Partners: 6. AOUC, Italy 7. BHSCT, UK 8. UCL, UK 9. UHBW, UK 10. VERLAB, Bosnia and Herzegovina	Unfunded Partners:
RMG: -		