Steps on the Path to Clinical Translation: A workshop by the British and Irish Chapter of the ISMRM

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Abstract

The British and Irish Chapter of the International Society for Magnetic Resonance in Medicine (BIC-ISMRM) held a workshop entitled "Steps on the path to clinical translation" in Cardiff, UK, on 7th September 2022. The aim of the workshop was to promote discussion within the MR community about the problems and potential solutions for translating quantitative MR (qMR) imaging and spectroscopic biomarkers into clinical application and drug studies. Invited speakers presented the perspectives of radiologists, radiographers, clinical physicists, vendors, imaging Contract/Clinical Research Organizations (CROs), open science networks, metrologists, imaging networks, and those developing consensus methods. A round-table discussion was held in which workshop participants discussed a range of questions pertinent to clinical translation of qMR imaging and spectroscopic biomarkers. Each group summarized their findings via three main conclusions and three further questions. These questions were used as the basis of an online survey of the broader UK MR community.

KEYWORDS

clinical translation, consensus, Imaging biomarkers, quantitative MRI, survey

1 | INTRODUCTION

Quantitative MR (qMR) imaging and spectroscopic biomarkers can probe a multitude of biophysical properties in patients with a wide range of disease. They offer great potential for advancing our understanding of pathology as well as improving diagnosis, prognosis, and prediction of response to therapy. Too often, this potential has not translated into widespread clinical adoption, with a low number of qMR imaging or spectroscopic methods used in clinical decision making.[1,2] On 7th September 2022, the British and Irish Chapter of the

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International Society for Magnetic Resonance in Medicine (BIC-ISMRM) held a workshop entitled "Steps on the path to clinical translation" in Cardiff (UK). The aim was to highlight to the BIC-ISMRM community the difficulties in translating qMR imaging and spectroscopic biomarkers, developed in academia, into clinical application and to discuss some possible solutions to improve successful translation.

1.1 | Problems

In the morning session, we focused on problems associated with the clinical translation of qMR imaging biomarkers. Speakers presented the perspectives of a radiologist (Shonit Punwani – University College London), a radiographer (Rebecca Mills – University of Oxford), and two clinical physicists (Maria Yanez Lopez – Swansea Bay University Health Board and Matthew Grech-Sollars – University College London and University College London Hospitals NHS Foundation Trust).

A. Radiologist's perspective: Shonit Punwani (S.P.) opened the workshop by expressing his opinion that the clinical community is aware of more sensitive imaging biomarkers being developed but that there is not an established pathway to move imaging biomarkers into the clinic. He suggested that we need to link up the translational pathway by providing supportive infrastructure for the essential translational work that takes place in between the initial development of a novel qMR imaging biomarker and the final clinical application. The infrastructure developed by the National Cancer Imaging Translational Accelerator[3] is such an example. He also suggested that there should be suitable academic recognition for clinical translation such as high impact journals publishing more reproducibility studies and more research grant funding focussed on clinical translation. S.P. described his personal experience of taking multi-parametric MRI for prostate cancer from a single centre implementation to a clinically relevant tool,[4] a process that took over 10 y. SP highlighted the need for strong technical and biological validation and multi-centre evaluation, explaining how not all steps along the pathway need to be performed by one group of researchers. To progress along the radiological research pathway a research group or community needs to:
   1. establish that there is an unmet clinical need,
   2. find the resources to support the necessary studies to provide an evidence base,
   3. understand the regulations involved in the anticipated change in clinical practice,
   4. test the repeatability and reproducibility of the proposed measure,
   5. evaluate the risk to patients of the change,
   6. assess the relative performance of the novel methodology compared with the established methods,
   7. calculate the real cost to the healthcare system of implementing the change in clinical practice, and
   8. have resolve!

B. Radiographer's perspective: Rebecca Mills (R.M.) stated that a novel qMR method should begin with the clinical application in mind. A lack of incentives, high costs, and time-intensive demands in image analysis or interpretation may contribute to barriers in translating research to clinical practice. R.M. described how, by having suitable research ethics permissions and accompanying governance structures in place, a department allows the development of research methods alongside clinical scanning, speeding up implementation and testing a range of possible use cases. R.M. used the development of the Shortened MOLLI (ShMOLLI)[5] for clinical myocardial T1-mapping as an example of the steps required and challenges in moving a research idea to clinical product. In over 10 y of development, ShMOLLI has amassed a large published clinical evidence base, which supports its use for clinical applications.[6,7] Industry partner support is vital for clinical translation of MR methods borne out of research development. Radiographers are at the coalface of data acquisition and perform initial quality assurance on the data. Therefore, the need for quick, easy to interpret inline analysis and quality testing is important.

C. Clinical physicist's perspective: The morning session concluded with Maria Yanez Lopez (M.Y.L.) and Matthew Grech-Sollars (M.G.S). They stated that the problems faced by MR physicists are primarily those of time, staff resources, training, hardware and software requirements, offline analysis, clinical evaluation, and legal requirements. They reinforced that the development of new hardware and software for clinical application requires a research agreement to be in place with the scanner manufacturers and in-depth knowledge of the regulatory issues involved in implementation. M.Y.L. and M.G.S. highlighted the upcoming changes in the United Kingdom 'Guidance for health institutions on in-house manufacture and use of medical devices, including software',[8] which will revert the current exemption for many research applications, adding extra requirements, as well as improved quality management practices, to the development of medical devices. M.Y.L. and M.G.S. described that clinical physicists support many aspects of qMR biomarker translation including sequence installation, protocol

setup, image acquisition and reconstruction, image analysis and reporting. They concluded that good communication across all disciplines and stakeholders is key to a successful outcome and that clinical physicists play a central role in this.

1.2 | Solutions

In the afternoon session, we focused on solutions. Speakers discussed the perspectives of a vendor (Fabrizio Fasano – Siemens Healthineers), an Imaging Contract/Clinical Research Organization (CRO) (John Waterton – Bioxydyn Ltd), an open science initiative (Michael Thrippleton – ISMRM Open Science Initiative for Perfusion Imaging (OSIPI)), and a metrologist (Matt Hall, National Physical Laboratory). To conclude, insights from imaging networks and the use of consensus papers to improve the standardization and harmonization of qMR imaging were provided (Penny Hubbard Cristinacce, National Cancer Imaging Translational Accelerator (NCITA)).

A. Vendor's perspective: The session opened with Fabrizio Fasano (F.F.), quoting Zoellner and Porter in stating that 'Translational research is a bidirectional process that involves multidisciplinary integration among basic, clinical, practice, population, and policy-based research. The goal of translational research is to speed up scientific discovery into patient and community benefit'.[9] F.F. described the research agreements that assist provide researchers' access to pulse sequences beyond the standard imaging protocols:

a. academia-led, locally tested protocols that use Consumer-to-Producer (C2P) software prototyping

b. industry-led protocols that use Work-in-Progress (WIP) software packages which are documented and can be distributed to other researchers and scanners

c. WIPs that undergo regulatory assessment are CE marked and released as product.

Each of these steps can contribute to different extents to the quality of the result, with the intent of delivering to the market a reliable product. Reliability is an essential aspect of the "prototype-to-market process". In fact, it minimizes the time spent on later product revisions. Every small modification in hardware or software components translates into a new CE marking process, which is a costly effort, both in time and resources (both technical and legal). The necessity to consider the intellectual property aspects of an implementation, as it moves through initial research and validation, was also discussed.

B. Imaging CRO perspective: John Waterton (J.W.) highlighted the role of industry collaboration. He described how an imaging CRO can deliver imaging biomarkers to clinical trial sponsors and develop imaging biomarkers suitable for multicentre trial use, often in a multi-national setting. The roles of software engineer, quality manager and project manager are added to the typical science-focussed roles typical of academia. J.W. emphasized how, working together with academia and clinicians, an imaging CRO can advance an imaging biomarker along the translational pathway. He cited an example of such collaboration in a dynamic contrast-enhanced MR study in rheumatoid arthritis.[10] J.W. emphasized how an imaging CRO can provide advanced MR capabilities that the clinical trial sponsor lacks and that are not currently incentivized in academia. These include: impartial advice on feasibility, logistics and risks; implementation of valid MR protocols to provide comparable data for all MR vendors, coils and field strengths used in the trial; site inclusion/exclusion; training and support for all sites especially non-expert sites; ongoing quality assurance; responding to aberrant phantom data; prompt review and triage of incoming data including prompt requests for rescanning as appropriate; analyses in compliance with sponsors' and regulators' requirements including ICH GCP[11] and ISO9001[12] in most jurisdictions plus 21CFR Part 11[13] in the United States; and data export in the form required by sponsors' statisticians.

C. Open science perspective: Michael Thrippleton (M.T.) provided the "Open Science perspective", highlighted the role of open-science working practices in promoting quality, transparency, efficiency, and fairness in science. M.T. stressed that these practices have strong potential to aid clinical translation. For example, transparent reporting ensures that a qMR biomarker is clearly defined and understood by scientists working at different stages within the translational pathway; meanwhile, code and data sharing reduce unnecessary duplication and cost. M.T. is a task force lead for ISMRM OSIPI, which aims to develop centralized open-science resources to make perfusion imaging "better and more accessible." OSIPI[14] is a network of researchers working together to create such resources, including shared code repositories (e.g., https://github.com/OSIPI/DCE-DSC-MRI_CodeCollection),[15] to minimize duplicate development and increase accessibility, and shared lexicons, to standardize terminology and reporting. M.T. concluded that the OSIPI approach could serve as a model for other imaging methods and modalities.

D. Metrologist's perspective: Matt Hall (M.H.) of the National Physical Laboratory explained how qMR

TABLE 1 Conclusions and survey questions generated from the roundtable discussions at the BIC-ISMRM workshop

	Conclusions	Survey questions
What will and will not work in a clinical workflow?	• For diagnostic imaging biomarkers, identify if the biomarker provides a definitive answer or has to be used as a guide alongside other assessments/biomarkers. • Standardized language is important to facilitate clinical adoption. • Understand the practicalities of the workflow, in terms of analysis time and processing power, as they can determine usability.	1. Is an imaging biomarker useful if it does not give a yes/no answer to aid diagnosis? 2. How can we standardize the language we use to aid clinical translation? Should effort be made to develop a consensus paper to standardize terminology to aid clinical translation? 3. Quantitative MR parameter maps often need to be created away from the scanner console. What is the maximum amount of time after acquisition, if an imaging biomarker is to be integrated into the clinical workflow?
How big of an improvement justifies a change in clinical practice?	• Identify and consult with clinical practice policy makers. • Understand the financial benefit of the change. • Understand what resources are necessary to enact the change.	1. With regard to sensitivity and specificity, what percentage of change is significant enough to change practice? How should this be defined? 2. Who should be involved in the decision to change practice? 3. Should change in clinical practice be for all patients or selected cohorts?
How can we improve validation of an imaging biomarker?	• Relevant/appropriate phantoms are necessary and phantom lending libraries would be useful. • Methods transparency. • Well-characterized references and to query precision of our measurements.	1. Does "validation" mean something different to a physicist and a clinician? 2. At what point do you consider something validated? 3. How do we incentivize transparency and reproducibility?
How do we standardize data acquisition and analysis more effectively?	• Consider the role of both bespoke and commercial phantoms and whether they are attractive to vendors for manufacture. • Parameter standardization between vendors is difficult. • More transparency and consensus papers are needed.	1. It is known that vendors will find a method less attractive if a method requires a phantom, so when should we use a phantom? Should we use phantoms to standardize data acquisition for every sequence? 2. Do you agree with a goal-orientated approach to quality? 3. Should we standardize, harmonize or optimize pulse sequences in multi-centre studies?
How do we share data, code, and good practice more effectively?	• Individual institutions and grant-awarding bodies must promote good sharing practices and facilitate code and data sharing between researchers. • Good practice is well served through networks, but contributions to shared code need to be acknowledged suitably. • Consent tracking is necessary for data sharing and robust anonymization processes required to allow personal data to be removed without losing necessary detail to perform the data analysis.	1. At what point should we be sharing code? At what point should we be sharing data? 2. How do we balance the need for the subject's privacy against the value of sharing data? i.e., how much can we anonymise without losing valuable information and how do we get consent for making data public? 3. Techniques generally require buy-in from scanner manufacturers to become part of their product in order to change clinical practice. How do we balance the need for researchers to protect the IP to allow this to happen, against the value of sharing code and data publicly?

TABLE 1 Continued

	Conclusions	Survey questions
How can we improve quality management of qMR imaging biomarkers?	• Define quality, as quality means different things to different people e.g. vendors, researchers. • The "Quality Management System" should scale with the problem. • In-house expertise and assistance within institutions needed to show researchers what to do and how to do it.	1. Does a Quality Management System (QMS) exist in your place of work? 2. Do you use it? 3. How do we incentivize the use of a QMS?
How can we engage with end users to support clinical translation?	• Understand the challenges and bottlenecks. • Provide good documentation and continuation. • Involve end users sooner.	1. As an early career researcher, what is the best way to contact clinicians? 2. How do we integrate our MR development with PACs systems? 3. How do we find out if a patient group can tolerate the imaging method?

Note: Survey questions were derived from those suggested by each of the seven roundtable discussion groups.

image contrast is not arbitrary and therefore has physical meaning. This allows variability to be quantified and scanners to be compared and calibrated. Metrics such as length, temperature, concentration, dosage, mass, time, and energy are all traceable to international definitions of SI units, and he suggested that this could be the case for qMR parameters. Using phantoms with traceable materials and structures, the principles of metrology can be used to allow scanners to be benchmarked in an application-specific way. For instance, for T_1, T_2, apparent diffusion coefficient, and iron and fat content. M.H. stated that, alongside optimized and consensus-built acquisition methods and open-source and community recommended analysis, a metrological approach to quantification can help us address the challenges of personalized medicine, patient stratification, large and long-term studies, and the integration of artificial intelligence approaches in qMRI.[16–18]

E. Imaging Network's perspective: Penny Hubbard Cristinacce (P.H.C.) concluded the day with some thoughts on Imaging Networks and Consensus Papers. Following discussion with James O'Connor, P.H.C. used biomarkers derived from oxygen-enhanced MRI (OE-MRI) as example of biomarker evolution from early studies of signal feasibility and preclinical validation to first-in-human application in cancer patients.[19] P.H.C. outlined how establishment of the NCITA framework and an associated OE-MRI network in 2019 is now helping develop this technique in multicentre studies. She described how NCITA[3] and other networks (such as Dementias Platform UK, Radnet, and the International Alliance for Cancer Early Detection) bring the imaging research and clinical communities together to develop infrastructure that facilitates translation via complex multicentre studies.

F. Consensus paper perspective: P.H.C. described the consensus work of the UK Renal Imaging Network (UKRIN) and the COST Action PARENCHIMA, using material from Susan Francis. P.H.C. discussed how experts in renal MRI have reported community recommendations on arterial spin labeling, diffusion weighted imaging, BOLD, T_1 and T_2 mapping, and phase contrast MRI.[20–25] These consensus imaging protocols and analysis methods now form the basis of the UKRIN-MAPS multi-parametric renal MRI protocol, paving the way for similar consensus building for other organs and/or disease areas.

2 | CONCLUSIONS AND NEXT STEPS

Following the talks, participants were allocated into small groups to discuss one of seven questions related to the translation of MR imaging biomarkers, such as 'How do we standardize data acquisition and analysis more effectively?' and 'How can we improve quality management of qMR imaging biomarkers?' (Table 1). Participants were asked to provide three main conclusions and three further questions arising from these group-facilitated discussions and presented these at the subsequent panel discussion. Themes of transparency, standardization of language, acquisition, and analysis, and the need for institutional support of code/data sharing and quality management, ran throughout the conclusions.

The questions produced from these discussions were used to form a survey aimed to capture the opinions and

knowledge of the wider MR community (open from 9th September to 17th October 2022). The survey was circulated to the workshop participants and subsequently on the following mailing lists: British and Irish Chapter of the International Society for Magnetic Resonance in Medicine (BIC- ISMRM), MRI-PHYSICS and to gain a clinical perspective, the British Society of Neuroradiologists (BSNR). We received 101 responses with the completion rate varying from 27.7% to 100%. Responses were received from imaging scientists (research (42.6%) and clinical (11.9%)), clinicians (6.9%), others (5%), and 33.7% chose not to disclose. The survey results will be summarized in a future publication and will form the basis of ongoing consensus building. We plan to expand our discussions to include other relevant voices such as, other clinical and preclinical imaging and non-imaging societies, manufacturers of ancillary equipment, National Health Service's National Institute for Health and Care Excellence (NHS NICE), the Medicines and Healthcare products Regulatory Agency (MHRA), the US Food and Drugs Administration (FDA), European Medicines Agency (EMA), and Patient-Public Involvement groups. We also intend to obtain a wider international perspective at ISMRM 2023 by surveying attendees and through the new ISMRM Standardized Measures and Benchmarks committee.

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