

## **Title: Metrology for advanced materials in quantitative MRI**

### **Abstract**

Quantitative MRI (qMRI) has the potential for use in both the diagnosis and monitoring of many pathologies such as cancer, dementia, stroke and heart disease. Recent work in quantitative MRI (qMRI) metrology has enabled SI traceable test objects (phantoms) for key measurands and a metrological framework to support them. However, a common criticism from qMRI practitioners is that the materials are too simple and do not reflect the properties of human tissue closely enough. This is particularly true for two commonly used quantitative MRI biomarkers; Proton Density Fat Fraction (PDFF), used in liver and muscle imaging, and diffusion imaging, used in neuroimaging. Providing SI traceability to more advanced materials would support medical imaging and the uptake of these approaches in clinical trials.

### **Keywords**

Quantitative MRI, qMRI, traceable medical imaging, clinical quantitative MRI, clinical qMRI, tissue mimicking materials, phantoms, biomarkers, diagnostics, patient monitoring

### **Background to the Metrological Challenges**

Quantitative MRI (qMRI) techniques offer a potential revolution in imaging and have potential applications in both the diagnosis and monitoring of patients for many pathologies including cancer, dementia, stroke and heart disease. These techniques can provide highly detailed information on tissue structure, morphology, and composition non-invasively from individual patients without exposing them to ionising radiation. However, uptake into clinical applications is limited mainly because of challenges with reproducibility and perceived technical difficulty as well as a lack of any available international standards. Recent progress in MRI metrology has led to new capability in qMRI, including traceable reference materials, benchmarked protocols, and uncertainty quantification. As a consequence, the ability of current MRI scanners to produce consistent measurements has been demonstrated using fully SI-traceable references for a small set of quantitative parameters in relatively simple materials.

As highlighted at a recent meeting of the International Society for Magnetic Resonance in Medicine's (ISMRM) Quantitative Imaging Study Group concentrating on metrology for quantitative MRI, a common criticism of some current SI-traceable phantoms for qMRI is that they do not fully represent the complexity of patient tissue. EMPIR project 20NRM05 iMet-MRI established SI traceability underpinning the characterisation of scanner performance, but existing SI-traceable test objects are not sophisticated enough to allow for calibration or benchmarking of clinical measurement. For example, current SI-traceable fat phantoms, used in liver and muscle imaging, use simple fatty compounds such as t-butanol which exhibit very simple characteristics that fail to reproduce the complexity of the nuclear magnetic resonance (NMR) spectrum of fatty acids in human adipose tissue. Similarly, current SI-traceable diffusion phantoms, used in neuroimaging, typically make use of polyvinylpyrrolidone (PVP) solutions. Varying the PVP concentration in solution provides a well-controlled way to provide a reference for diffusion processes, but in tissue there is a strong interaction between diffusion and tissue microstructure which leads to additional dependences in the observed diffusion attenuation in the magnetic resonance (MR) signal which PVP solutions are not able to capture. More advanced materials are needed but there is currently no available SI-traceable metrological capability which captures the uncertainty and biases, and this severely limits the application of available phantoms.

Modern implementations of the relevant MRI pulse sequences and associated post-processing make this issue even more important. In both cases the effects are unavoidable in clinical applications. In fact, there are reliable

experimental findings which can be used to inform the engineering and improve the perceived quality of images produced on the scanner. Commercial MRI scanner hardware and software are highly optimised to deliver high quality images in clinical applications, however vendor implementations have diverged due to lack of standardisation. Manufacturers make detailed assumptions about image and signal analysis based on what would be typical for human tissues. These assumptions are very different to the simple responses of current SI-traceable phantom materials and imaging test objects with overly simple materials can lead to unexpected biases and performance which are not representative of typical clinical MRI applications. Accordingly, they are not always a fair test of how a scanner will perform when measuring a patient. Conversely, there are important biases present in clinical imaging applications in tissue which are not captured by current SI-traceable test objects and cannot be effectively characterised.

The emergence of AI approaches also presents a risk here. AI is increasingly used in MRI image reconstruction and parameter estimation, where it has great potential for accelerating image acquisition and analysis. Without effective reference metrology there is a risk that AI-based reconstruction could introduce additional biases, and that such biases could vary in an uncontrolled way as algorithms develop. There is a very real and immediate need for metrology to support reference materials which reflect the measurements made in patients.

## Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The proposal shall focus on the SI traceable measurement and characterisation of advanced tissue mimicking phantom materials in quantitative MRI.

The specific objectives are

1. To develop advanced, SI-traceable material characterisation and analysis methods suitable for advanced tissue mimicking phantom materials for two commonly used quantitative MRI biomarkers: Proton Density Fat Fraction and Diffusion imaging.
2. To characterise the uncertainties and biases in advanced tissue mimicking phantom materials including SI traceability of the relevant MRI-based measurements using both clinically available and state of the art metrological approaches.
3. To develop approaches to characterise and quantify the variability and biases of the advanced tissue mimicking phantom materials in quantitative MRI across different scanners through use in an international multi-site trial. This will consider different models, vendors, and MRI scanner specifications and include vendor-neutral pulse sequence implementations as well as vendor product sequences where available.
4. To develop methods to quantify the performance of individual measurement pipelines on a representative range of clinical scanners and benchmark to available metrological primary standards using advanced phantoms. The suitability of these methods will be demonstrated during the multi-site trial in Objective 3, and will be supported by the approaches developed in objectives 1 and 2.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain, standards developing organisations, end users (e.g. clinical stakeholders, phantom manufacturers) and other stakeholders. In addition, to develop a good practice guide for characterising advanced tissue-mimicking materials in fat fraction and diffusion imaging, including approaches for bias correction where feasible. This will be done in consultation with commercial phantom manufacturers to specifically support their priority materials

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development. Where relevant, proposals are encouraged to build on, or seek collaboration with, existing projects and develop synergies with other relevant European, national or regional initiatives and funding programmes. In particular, links are encouraged with (i) the projects funded under earlier relevant topics of the Horizon Europe programme; or (ii) other relevant European Partnerships.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this. In particular, proposers should outline the achievements of the EMPIR project 20NRM05 iMet-MRI and how their proposal will build on those.]

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 2.1 M€ and has defined an upper limit of 2.6 M€ for this proposal.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

## Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the 'end user' community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the "end user" community (e.g. letters of support) is also encouraged.

You should detail how your proposal's results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Facilitate improved industrial capability, or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the medical sector.

You should detail other impacts of your proposed JRP as specified in the document "Guide 4: Writing Joint Research Projects (JRPs)"

You should also detail how your approach to realising the objectives will further the aim of the Metrology Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

## Timescale

The project should be of up to 3 years duration.