Publishable Summary for 17IND01 MIMAS
Procedures allowing medical implant manufacturers to demonstrate compliance with MRI safety regulations

Overview

Medical implants represent a multi-billion market across Europe. A majority of the 50 million EU citizens carrying a medical implant will likely need a magnetic resonance imaging (MRI) scan during the lifetime of their device. However, the powerful electromagnetic fields of MRI systems in these cases represent a unique hazard for patient safety. Therefore, it is vital for both patient wellbeing and the success of a medical implant on the market that implant manufacturers can demonstrate safety compliance for their device in an MRI environment. This project will improve the competitiveness of European implant manufacturers by providing innovative, metrologically sound and legally safe methods to demonstrate the compatibility of their products with MRI safety regulations.

Need

With more than 30 million MRI scans per year across European countries, safety for patients with medical implants is an ongoing concern with some carriers having suffered fatal accidents due to the interference of their device with the electromagnetic fields (EMF) from the MRI scanner. MRI compatibility of an implant thus represents a key factor for the competitiveness of a manufacturer. This was exemplified in 2011 when Medtronic Inc. achieved the first ever MRI approval for a cardiac pacemaker and within a few years virtually all non-compatible devices disappeared from the market. However, the currently applied procedures to demonstrate MRI compatibility are either outdated (ASTM F2182) or incomplete (ISO/IEC TS10974). Additionally, large producers of high-end active implantable medical devices are facing technological challenges to demonstrate MRI compatibility, and SMEs manufacturing passive medical implants are overburdened by the necessity to demonstrate MRI safety for each new size and shape of a particular device, therefore limiting their innovation potential.

The established state of the art technique is currently the numerical modelling of field distributions in human subjects. However, even though this technique has been used to include the presence of metallic implants, an experimental verification of the results was limited as mostly generic or simplified implants with non-detailed features were modelled. Parallel-transmit (pTx) radiofrequency systems can be used to steer, within certain limits, the electromagnetic field in MRI scanners as well as temperature distributions in and around the implant. The use of pTx for risk mitigation has an enormous potential to ensure safety for a wide range of different implants and boundary conditions. These systems can be combined with sensor-equipped implants to provide real-time feedback. However, this concept is still in an early stage of development and further work is needed to prove its use.

The EMRP project ‘HLT06 MRI safety’ discovered that heating of metallic implants due to switched magnetic-field gradients is an underestimated hazard in MRI. As some normative documents ignore this effect completely, whilst others mention the possibility of such effects only in the context of protecting the device rather than the patient, it is now essential that the risks are subjected to further investigation.

Objectives

To enable manufacturers of medical implants to demonstrate that patients carrying their products can safely undergo an MRI scan, the project aims to achieve the following objectives:

1. To develop **anatomical models of human subjects with realistic medical implants** and millimetre resolution. The models to be sufficiently detailed for use with *in silico* medicine concepts, with resolution to be determined according to image analysis needs.

2. To dev5elop validated computational tools for the **numerical simulation of electromagnetic fields (EMF) and temperature distributions** in a virtual human subject **during MRI exposure**. The computational tools should be able to process high-resolution anatomical models.

3. To develop validated methods and sensor-equipped reference implants for quantifying real-time implant-induced hazards during MRI exposure. This should include an assessment of parallel transmit (pTx) radiofrequency (RF) systems in MRI with real-time feedback and the **development of appropriate mitigation strategies**.

4. To investigate numerically and experimentally the hazards associated with **the interaction between bulk metallic implants and switched magnetic fields** in the kilohertz regime. In addition, to develop a reference set-up for testing metallic implant heating, using switched magnetic-field gradients of a few mT/m with a target gradient uncertainty below 5 %.

5. To develop and apply a **suitable statistical method to demonstrate MRI compliance** for small (< 10 cm) orthopaedic implants without extensive testing or numerical modelling, by determining an upper limit for the hazard associated with the new implant by comparison with a similar surrogate implant, which has already been fully assessed, thus enabling small manufacturers of a large variety of similar small metallic implants to dramatically reduce their costs for compliance demonstration.

6. To **interact closely with manufacturers of implants, MRI and test equipment and with standards developing organisations** (e.g. ISO/TS 10974, IEC TC/SC 62B and ASTM Subcommittee F04.15 on Material Test Methods) to align the project and facilitate the take up of the technology and measurement infrastructure developed in the project.

Progress beyond the state of the art

Safety testing of metallic implants for MRI is today largely based on unreliable phantom measurements. The project will improve this unsatisfactory state of the art by applying more meaningful numerical modelling of realistic virtual models. High precision numerical models will be developed and subsequently used as an input to electromagnetic field (EMF) simulations. While the utilisation of EMF modelling in this context is becoming more and more accepted as the adequate approach to the problem in the scientific community, it has still not fully arrived at the level of small manufacturers and test houses. Still unique to this project is the use of calibrated sensor measurements to validate those simulation results with metrological rigour.

The project will go even further by exploring technical means to actively mitigate metallic-implant related hazards in MRI. This will be achieved by steering the RF electric field (E-field) away from the implant by using pTx technology, an approach with a high potential for ensuring safety for a wide range of implants and scan conditions. In contrast to some recently published work, where this E-field steering approach has been pursued using the regular RF transmit coil (“body coil”) driven as a two-channel coil, the present project aims to exploit the much larger parameter space of true parallel transmission with at least eight independent channels.

Compared to RF heating, the potential heating of an implant by the switched gradient fields of an MRI scanner is a largely unexplored field. While preliminary results convincingly demonstrated the existence of the problem, this project will be the first ever to systematically investigate this issue. Up to now, this young field is still driven by the work from the project consortium.

Finally, a procedure to demonstrate MRI safety compliance will be developed allowing the manufacturers of small implants, e.g. screws, clips, or fixation devices, to reduce their costs by simplified safety assessments. Instead of performing numerical simulations and heating experiments for each and every new item, as it is the present state of the art, simple scaling laws can be applied to infer a valid safety assessment for their new product from previous, extensive investigations of similar devices.

Results

Objective 1

The project is developing virtual models of human subjects carrying a metallic implant. For the first time, precision planning tools from a virtual surgery will be applied to position the implants with sub-mm accuracy.

Data on main orthopaedic implants, one-dimensional implants and small stand-alone implants has been sourced and analysed. Implant types, implant materials, most relevant locations in the body and human types have been defined. Components of the Virtual Population (ViP) family of anatomical models, licensed by ZMT, have been chosen for the best match with the real population carrying the different types of implant. All the

anatomical models have been fully documented regarding the physical properties of the tissues. Implant samples for experimental validation, and the related CAD models for virtual surgery have been collected. Negotiations with implant manufacturers to contribute to the collection are progressing. Most representative cases of orthopaedic surgery (hip and shoulder) have already been simulated on the ViP family of anatomical models.

Objective 2

Until recently, electromagnetic field simulations for the assessment of implant safety in MRI have been performed only on selected cases. In the project, however, a large selection of different body types, implant positions and RF transmit coils is being investigated via the development of validated computational tools. Thus, general conclusions are being derived from a systematic exploration of the parameter space for implant related RF hazards in MRI. The project output will underpin the ambitious concepts of the new ISO/TS 10974 standard with specific and validated procedures and thus contribute to advancing this document from its present state (a *Technical Specification)* to a full standard.

Existing methods to assess MRI safety of metallic implants have been adjusted, enhanced, and tailored for the specific needs of this project. The induced electric field maps for newly developed anatomical human models have been computed, which will allow adequate evaluations to be performed for the investigated implant categories. The joint effort in identifying and categorising relevant medical implants allows all relevant safety assessments at and beyond the state of the art to be performed. Methods for simplified and accurate estimations have been developed, including an iso-electric exposure scenario within tissues of different relative permittivity (e.g. water-like, fatty, bone) and on their interface (e.g. orthopaedic implants on the bone-muscle interface).

Objective 3

The concept of using *E*-field steering by pTx to mitigate implant-related risks in MRI is only in a fledgling state. Promising first results exist, but only at research level. Their translation into clinical routine can be attempted only after a much deeper investigation. Potentially hazardous thermal effects of RF E-fields from the MRI scanner will be evaluated by validated simulations to ensure robust and reliable results. Sensor-equipped reference implants will be developed for this purpose.

The key parameter to quantify the risk associated with RF-induced heating of one-dimensional implants (e.g. the electrode of a cardiac pacemaker) is the so-called ‘tip-SAR’ (SAR = Specific Absorption Rate), the locally deposited RF power per unit mass at the most critical point, the tip of the implant. A reference implant with a tiny *E*-field probe at its tip was developed and the tip-SAR was determined for a variety of parameters, resulting in more than one hundred reference configurations. This data is now available to evaluate pTx-based mitigation strategies.

A procedure was subsequently developed and tested, using pTx to optimise the distribution of the RF *B*-field, which determines the image quality, while keeping the maximum tip-SAR below a predefined limit. Compared to the standard method used in most clinical scanners today, the optimised approach produces 2.5 times higher RF B-field without any compromise in tip-SAR or image homogeneity. This is significant progress that underlines the power of the pTx approach to mitigate implant-related risks in MRI.

For a systematic exploration of this concept, a comprehensive ‘Parallel Transmission Implant Safety Testbed’ was developed, a compact setup allowing to investigate different sensor feedback methods, perform validation measurements and assess the safety of a variety of implants for a wide range of MR settings (from 1.5 T to 7 T). A manuscript with a detailed description of this setup and first experimental results has already been submitted to a peer-reviewed scientific journal. The test-stand was developed as open source project, all construction details and operating software will be made publicly available, duplication is explicitly encouraged.

Objective 4

For a long time, the possible heating of an implant by the switched gradient fields in MRI was overlooked as a safety issue. For a systematic investigation of this problem this research project combines modelling results with validating measurements. Real-life implants, e.g. hip prostheses, are being investigated in a clinical MRI scanner under real-life imaging conditions, but simultaneously a test stand has been built and is being utilised for systematic experiments in a precisely controlled environment.

A wide database containing the magnetic field distributions from different gradient-coil designs has been built. Seven gradient designs were considered, adopted for different types of MRI scanners, ranging from

conventional clinical scanners to special-purpose designs. This database has been used to select the potentially most hazardous positions in the scanner, for a patient carrying a knee/hip/shoulder metallic implant. In parallel with the hardware analysis, an extensive examination of clinical sequences has been performed, to select the most relevant cases for a subsequent investigation. This refers to sequences which are in widespread clinical use and/or are expected to be very 'aggressive', in terms of gradient heating, because of a high duty cycle of rapid gradient switching.

A new laboratory with a gradient test-stand, in conventional clinical design, was built. It will specifically be used to investigate thermal effects of gradient coils on real metallic implants, under controlled conditions. In addition, first gradient-heating experiments in a regular, clinical MRI scanner have already been performed and will soon be extended to open-bore scanners. To this end, a Non-Disclosure Agreement (NDA) has been signed with stakeholder Esaote spa (Genova). This manufacturer of special-purpose MRI scanners has already provided the hardware design and the pulse sequences of the open and extremity scanners for the aforementioned databases. Esaote will also provide access to an open scanner for the planned heating experiments.

New computational tools designed to simulate the exposure to MRI gradient fields of a patient carrying a prosthesis have been implemented. These tools can calculate the instantaneous power developed by the magnetic field inside the implant, following the time-behaviour of each single gradient signal. This data is fed to a transient thermal solver, to compute the temperature increase in phantoms or human body models. When the temperature distribution in human body models is computed, the solver allows to include thermoregulation effects in blood perfusion and metabolic heat terms. The computational tools for the simulation of gradient-induced heating have been validated, for the first time, against experimental data available in the literature, obtaining an excellent agreement. Further validations will be performed by comparison with new measurements to be carried out later in this project. Simulations of implants embedded in virtual human models or phantoms, and exposed to realistic or simplified gradient fields are currently underway. First results were compared with corresponding dosimetric analyses of MRI typical RF exposures, with the aim to explore the feasibility of developing a *joint* assessment procedure for the exposure to all MRI fields.

Objective 5

A statistical approach is being employed to assess the MRI safety for small metallic implants like stents or screws or fixation parts; groups of devices with a large variety of sizes and shapes within each group. Very few reference implants of a given type are being investigated in detail and scaling laws will then be derived to transfer this knowledge, including its uncertainties, to a whole class of similar devices.

The most common small implants in current use have been determined as i) Nails, ii) Screws, iii) Plates, iv) Staples, v) Surgical Anchors. These are typically made from stainless steel or either of two titanium alloys. Materials are widely available, and the procurement of physical samples and CAD models has begun. Sizes are also standardised, and ranges from 10 cm downwards are being considered. It has been agreed to use the same set of body models for small implant experiments as for other, larger implant investigations.

Mathematical models of parameterised implants have been used to explore how shape factors, field strength scan sequence, and orientation affect the heating of implants during scanning. An extensive series of simulations of simplified versions of orthopaedic implants in gradient fields have shown that there is a strong correlation between maximum temperature rise and deposited power per unit surface area, and a parametric model has been developed to describe this and other correlations. A set of parameterised models of screws demonstrated that the most important geometric factor affecting the heating was screw length, with screw radius being the next most significant.

A detailed statistical study was made of data provided by the U.S. Food and Drug Administration. The data was taken from test reports for RF-induced heating of nearly 100 medical implants of various kinds. The analysis showed large scatter in the residuals of various empirical models fitted to the data, which made it very difficult to draw reliable conclusions. A subgroup analysis was carried out for stents so that variations in geometric detail could be eliminated as a source of scatter, but the scatter remained high. It was concluded that even if further test data became available, it would not be useful as a basis for experimental validation of model-based data obtained by simulation as envisaged in ISO/TS 10974:2018. Thus, it was decided that the use of sound model-based data was the most viable way to proceed.

Impact

To inform the scientific community and the general public about the MIMAS project, its ideas and goals, a press statement and a YouTube interview were released immediately at the start of the project. Consortium members seized the opportunity to advertise and present the project and its first results, but also to interact with stakeholders, at meetings of the International Society of Magnetic Resonance in Medicine (ISMRM) in Paris (June 2018) and Montreal (2019). The consortium received valuable feedback and several stakeholders from industry, standardisation boards, test-houses and academia agreed to support the project as advisory board members. In Montreal, MIMAS results were reported in several oral and poster presentations. The project's commitment to develop sustainable and affordable open-source hardware, as exemplified by the home-built parallel-transmit testbed, was presented and very well received at the ISMRM Workshop on Accessible MRI for the World in New Delhi, India (March 2019).

An oral presentation on the use of "virtual experiments" to investigate the thermal effects of gradient fields without performing invasive measurements in vivo was given at the workshop on Mathematical and Statistical Methods for Metrology – MSMM (Torino, 2019). The new computational scheme for analysing gradient-induced heating was also presented at the next COMPUMAG conference (Paris, 2019), one of the most important conferences for computational electromagnetics, and described in a paper published on Physics in Medicine & Biology [1]. Lectures on gradient-induced heating of implants have been held for PhD students in Engineering (at Politecnico di Torino) and for students of a qualifying course in Health Physics (at University of Torino). Project results were also presented at an international workshop on the Thermal Dose Concept for MRI safety, hosted by MIMAS partner ZMT in Zurich (April 2019). The workshop was organised as an extension to an IEC TC 62/SC 62B MT40 meeting and its discussion and results are expected to be crucial for the future shape of the IEC 60601-2-33 MRI standard.

Project partners participated in and contributed to several international and national standardisation board meetings, e.g. for maintenance and development of the IEC 60601-2-33 (Technical and safety requirements for MRI equipment), ISO/TS 10974 (MRI safety for carriers of active medical implants), or DIN SPEC (PAS) 3105 (Open Source Hardware).

Impact on industrial and other user communities

Currently, regulators accept and approve applications from implant manufacturers about the MRI safety of their devices according to ISO/TS 10974 despite the recognised gaps in its methodology. Project results will close these gaps by providing validated procedures for assessing implant safety. An updated standard will be developed, reducing the legal risks for the manufacturers. This will greatly impact both the European implant industry and regulators with respect to potential liability claims. In addition, the reduction of the uncertainty through the evaluation protocol will reduce manufacturer design costs.

The long-established and close communication of consortium members with European MRI manufacturers will facilitate the longer-term uptake of project results on patient-specific sensor feedback and active hazard mitigation. This will result in a market advantage by providing MRI scanners with improved diagnostic capabilities at lower risk. Negotiations with implant manufacturers are progressing in order to guarantee exchange of information and prosthetic devices and give the stakeholders prior access to the project results. This makes it possible to check, within the project lifetime, the suggested solutions to predict MRI heating on most common orthopaedic prostheses.

The NDA signed with Esaote spa will guarantee exchange of information and give the stakeholder priority access to project results. This allows to check, within the project lifetime, the level of compatibility of some common orthopaedic prostheses with their commercial scanners and operating sequences.

In December 2019, ZMT's in-vivo RF-exposure libraries *MRIxVIP 1.5* and *MRIxVIP 3.0T* and the standardised evaluation tool *IMAnalytics* were approved, as the first computational tool ever, by the U.S. Food and Drug Administration (FDA) as a Medical Device Development Tool (MDDT). This is a major success, since the MDDT label certifies that evaluations of the health risk posed by medical implants to patients undergoing MRI are traceable, easy-to-conduct, and standardised at the most comprehensive level. The combination of *IMAnalytics* and *MRIxViP* data libraries enables the medical device industry to accelerate their approval processes with standardised risk evaluations of approved, high quality.

Impact on the metrology and scientific communities

The procedures for the in-situ calibration of EMF field-probes to be developed within the project can be adopted by other NMIs. This will expand their measurement capabilities and they can propose corresponding changes

to their Calibration and Measurement Capabilities statements in the Key Comparison Database of the Bureau International des Poids et Mesures.

Implant safety assessments based on validated simulations, following the procedures developed in this project, will become a new service to be offered by calibration and verification offices accredited for dielectric measurements and electro-magnetic field measurements inside materials (for both the low-frequency and the radio-frequency range). The traceability for these services will in turn be provided by the NMIs with their newly expanded measurement capabilities.

The successful cooperation within the MIMAS project and the deeper insight into mutual research interests and capacities led consortium members to join forces in a different research field, too. MIMAS partners were the key drivers in conceiving and procuring a new joint research project on quantitative imaging which will be coordinated by a MIMAS consortium member. Despite its different research subject, the new project will strengthen the scientific exchange within MIMAS as it was born out of its cooperative spirit.

In the longer term, the knowledge obtained by the participating NMIs will be transferred to less experienced NMIs, due to the presence of implant manufacturers in these countries. The competitiveness of EURAMET members will be further increased with respect to NMIs outside Europe, since there are many implant manufacturers with a large market share outside Europe. Consequently, European NMIs will increase their revenue and reduce the expenses of European manufacturers.

The scientific community learns about the newly developed methodologies through high-impact journal publications and conference presentations. For the first time ever, numerical models of tissue and implant heating in MRI, which are already in widespread use in the research community, will be supported by a metrological underpinning.

Impact on relevant standards

The Technical Specification ISO/TS 10974 on MRI safety of active medical implants is still lacking key procedures necessary for progression to a standard. The project is developing specific procedures and validated tools for the safety assessment of implants and provide a metrological underpinning to ensure that ISO/TS 10974 will i) become a full standard and ii) be continuously developed and improved. This will also contribute to the future development of IEC 60601-2-33, the international standard on MRI equipment and safety, since a complementary co-development of the MRI and the implants standard was agreed upon by a joint ISO/IEC working group. IEC 60601-2-33 will further be amended by the project results on the gradient induced heating of bulk metallic implants. The project's goal to assess thermal effects is also called for in the C95.1 IEEE standard on electromagnetic field exposure. Both the IEC 60601-2-33 maintenance team (MT40) and the Joint Working Group developing the ISO/TS 10974 mandated this project. Consortium members are represented on these boards, keep them updated on the project results, and work towards getting those results implemented in future editions of these important standards.

Data on implant heating were successfully procured from the U.S. Food and Drug Administration (FDA) and the consortium has been encouraged by their engagement. The contact at the FDA is supportive of the project efforts and has indicated an interest in the results.

Longer-term economic, social and environmental impacts

Several branches of the European medical technology industry will become more competitive through innovation of products and due to the reduced times and costs for safety assessments:

- European implant manufacturers (€ 3 billion market) will benefit from a faster development of and introduction to market for their innovative products as metrologically approved methods to assess their safety and reduced costs for testing of the MR compatibility will be available (Objective 2).
- Manufacturers of small and diverse implants (screws, clips, etc.), which are predominantly SMEs, will benefit the most from drastically simplified compliance testing (Objective 5).
- Technology leading European MRI manufacturers will benefit from new applications for their innovative developments (e.g., active hazard control by parallel transmission, Objective 3).

Existing safety measures in MRI sacrifice scanner performance by restricting the transmitted RF power. An improved assessment allows removal of *unnecessary* safety margins, resulting in shorter scan times and better image quality. € 320 million p.a. savings in EU health care costs can be projected through reduced MRI scan

times; additional savings of € 400 million p.a. are estimated resulting from reduced times for per-patient safety assessments of implant carriers.

Approximately 32 million MRI patients p.a. in EURAMET countries would benefit from personalised safety assessments based on sound scientific methods. About 50 million implant carriers would gain safe access to a potentially lifesaving imaging modality. Manufacturers and clinicians will have reliable metrics to assess the MRI safety of medical implants and legal certainty about their safety measures. The proposed work will facilitate the inclusion of implant MRI compatibility in future revisions of the EU Medical Device Regulations, enhancing the safety of EU citizens bearing implants.

List of publications

In silico evaluation of the thermal stress induced by MRI switched gradient fields in patients with metallic hip implant. Arduino A, Bottauscio O, Brühl R, Chiampi M, Zilberti L. Phys Med Biol. 2019;64(24):245006. https://doi.org/10.1088/1361-6560/ab5428.

Project start date and duration:	01 June 2018, 36 months	
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RMG: -		