Project Acronym:

SOUNDPET (INTEGRATED/0918/0008)

MRI-guided focused ultraSOUND system for cancer in pets (dogs and cats)

Deliverable number: 1.1

Title: Interim report

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Date: 15/12/2021

Ευρωπαϊκή Ένωση
Ευρωπαϊκά Διαρθρωτικά και Επενδυτικά Ταμεία

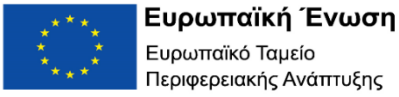
Κυπριακή Δημοκρατία

Διαρθρωτικά Ταμεία της Ευρωπαϊκής Ένωσης στην Κύπρο

PROGRESS REPORT

RESTART 2016-2020 Programme for Research, Technological Development and Innovation

RESEARCH AND INNOVATION FOUNDATION



A.1. GENERAL PROJECT INFORMATION	
Project Protocol Number:	INTEGRATED/0918/0008
ESIF Number:	-
Project Title:	MRI-guided focused ultraSOUND system for cancer in pets (dogs and cats)
Project Title in Greek:	Ρομποτικό σύστημα εστιασμένων υπερήχων υπό την καθοδήγηση μαγνητικής τομογραφίας για καρκίνο σε κατοικίδια (σκύλους και γάτους)
Host Organisation:	Cyprus University of Technology (CUT)

A.2. DESCRIPTION OF THE WORK CARRIED OUT BY ALL BENEFICIARIES DURING THIS REPORTING PERIOD. *(Maximum Recommended 3 pages)*

Please provide an overview of the progress towards the project objectives, justifying the differences between work described under Annex I of the Contract and work actually performed, if any.

The coordinators managed all scientific, financial, and legal issues of the program and monitored all the activates to ensure the quality of results generated, as described in Word package (WP) 1, without any significant issues arising. There was only some delay in the recruitment of staff due to engagement in other programs. Finally, two well-qualified researchers were recruited in November 2021. Overall, ALL the deliverables were completed according to the timeline and objectives set in the contract. Full completion of hardware allowed initiation of the evaluation process earlier. Thereby, three more deliverables intended to be submitted by month 27 (D6.1 and D6.2) and month 36 (D6.4) of the project, were completed in the first reporting period and are delivered earlier. Accordingly, the German Oncology Center (GOC) was involved in the project sooner than initially predicted. Totally, 14 deliverables out of the 28 are submitted. It should be noted that in the effort to convince pet owners to give us the green light for treating their pets, the rabbit experiments (WP6) began earlier to obtain proof of safety. Since we managed to recruit some pets, system's evaluation in pets (n=3) also began earlier. The safety and efficacy of the system and therapeutic protocol will be further assessed in pets and the relevant deliverable will be submitted by the end of the project.

The activities of WP2 began from the beginning of the project with the organization of an opening event aimed to generate awareness about the project to key stakeholders, including researchers, physicians, academics, and potential end users. A dynamic website was created early on to ensure dissemination of project activities to the wider public. Three (3) newsletters were written for communicating on project progress and uploaded on the website. A brochure was created to be used in future campaigns for informing stakeholders. The project was also promoted in Facebook, and the technology was showcased in local events (2). Regarding dissemination of scientific data, we have reached the number of two published papers in topic-related scientific journals of high circulation, whereas one paper was delivered by oral presentation at a scientific conference. Regarding exploitation activities, a patent application relating to the developed MRgFUS robotic system was prepared based on a freedom to operate (FTO) analysis and will be submitted upon receiving the necessary funding.

In the framework of WP3, the design of all hardware was finalized. Three robotic devices (versions 1, 2, and 3) featuring motion in three linear and one angular axis were developed. Each axis motion is actuated by a piezoelectric motor and monitored by a set of optical encoders. Jackscrew and speed reduction gear mechanisms were employed to increase the power output of the positioning mechanism and provide a smooth and highly accurate motion. Other techniques were also implemented for increasing robustness and rigidity, thus improving the overall system performance.

The first two versions were designed to be integrated in the Magnetic Resonance Imaging (MRI) table for a bottom to top delivery of therapy to patients placed in the prone position. The positioning mechanism of the second version was significantly improved in terms of robustness and accuracy by incorporating larger piezoelectric motors capable of producing ten times higher torque than the previous ones. The incorporation of larger motors allowed the creation of a mechanism with significantly tighter tolerances, thereby enhancing the performance of the positioning stages. Accordingly, design improvements were made to arrange the larger motors in an enclosure of the same size as the first version.

The tasks were extended beyond the proposed ones with the development of a third version of the system to enable a top to bottom ultrasonic delivery to the target, and thereby, supine placement

of the subject, given that the prone position is very uncomfortable during long treatment sessions. The device is mounted on the MRI table with a set of four C-shaped arms, which connects to a height adjustment mechanism for changing the height of the device depending on the patient's size.

Two single-element, spherically focused transducers were specially designed to be incorporated in the SOUNDPET device depending on the target's location. The selection of their structural characteristics was based on high intensity focused ultrasound (HIFU) beam simulations of candidate transducers. A transducer with a central frequency of 2.5 MHz (50 mm diameter and 65 mm radius of curvature) was selected for manufacturing since it offers optimal targeting of shallow tissue. Another transducer with a frequency of 1 MHz (60 mm diameter and 70 mm radius of curvature) was deemed suitable for deeper targets and manufactured. The specific diameters and radiuses of curvature were selected so that good focusing of the ultrasonic field is achieved over a large depth. Notably, a focusing of 7 cm is considered adequate for the chosen application (mammary cancer) in pets. For future use in patients, a larger radius of curvature might be required.

An electronic driving system was developed for controlling the positioning mechanism. Advantageously, an Arduino Uno was incorporated for commanding actuation of the motor drivers, which reduces the robot's operation time and improves the overall performance of the system. Finally, all the electronic components were assembled in a modern, ergonomic medical cart that was designed by adjusting the features of a commercial cart based on the specifications of the SOUNDPET system.

An agar-based phantom was developed to mimic soft tissue in MRI applications in the content of WP4. The most critical acoustic, thermal, and MR properties of soft tissues were replicated to enable accurate Magnetic Resonance guided Focused Ultrasound (MRgFUS) studies in the phantom. A more common recipe containing agar as the gelling agent, silicon dioxide, and evaporated milk was originally proposed. However, a biological material was instead used as the single additive in the agar gel. Specifically, a phantom was prepared using 2 % weight per volume (w/v) agar and 4 % w/v wood powder at a very low cost. Advantageously, this phantom was found to possess an absorption coefficient closer to that of soft tissues compared to other agar-based phantoms doped with various additives. The ability of the developed tissue mimicking material (TMM) to model the formation of thermal lesions above a still unknown temperature threshold was also demonstrated. HIFU sonications leaded to lesion formation in the phantom, without any evidence arising safety concerns regarding the use of wood powder. Temperature changes during the heating and cooling periods were successfully recorded using both thermocouples and MR thermometry, with the results being in good agreement accounting though for the significantly higher sensitivity of the latter method. It is noted that the phantom enabled insertion of thermocouples without losing its structural integrity. These initial testing experiments suggest that the developed phantom could be used for evaluating the effectiveness of thermal exposures using MR thermometry, thereby fulfilling the initial objective of the relevant task.

In the framework of WP5, a software written in C sharp was developed. During the reporting period, the design of the main window of the software that includes all the commands for controlling the therapeutic ultrasound and robotic positioning systems was finalized. The software was interfaced with the MRI system enabling real time transfer and display of DICOM images, and thus the development of MR thermometry tools. More advanced features for therapy planning, including tumour segmentation tools and grid operation along the tumour margins, are currently under development and will be presented in the final report.

Assessment of the system's performance in terms of MRI compatibility and motion accuracy (as described in WP6) began earlier than stated in the contract since the manufacturing of all hardware was finished earlier. The relevant tasks were thus completed during the first reporting period and are herein presented.

The robotic devices and transducers were entirely manufactured from non-magnetic materials to achieve compatibility with the MRI scanner. For MRI compatibility assessment, a homogeneous phantom was scanned using common sequences in a 1.5 T MRI scanner under various activation

conditions of the system. The results suggest that connection of cables and activation of the amplifier and transducer do not significantly affect the overall image quality of the MR phantom when Fast Spin Echo (FSE) and Echo Planar Imaging (EPI) sequences are used, and thus MR thermometry can be performed properly. Furthermore, the robotic system version 2 was assessed for MR compatibility according to the American College of Radiology (ACR) MRI quality assurance guidelines. Several imaging accuracy tests were implemented to evaluate the robot's impact on MRI performance, with the results classifying the system as MR compatible when operated under the specific conditions that were used in the relevant experiments. However, the systems are typically classified as MRI-conditional according to American Society for Testing and Materials (ASTM) standards because the motors, optical encoders and transducers require electrical conductivity during operation.

The motion accuracy of the robotic devices was evaluated using digital calipers, which were integrated on the motion stages with the assistance of specially designed 3D-printed structures. Motion steps of specific distances were commanded through the controlling software and compared to the actual displacements as measured by the incremental distance of the caliper. Overall, the motion error was found to be increasing with increasing motion step for all four axes. For the second version of the system, the mean error of linear motion varied from 0.042 ± 0.032 mm for the 1 mm step in the X axis forward direction to 0.123 ± 0.082 mm for the 10 mm step in the Y axis right direction. Regarding rotational motion, the maximum mean error of angular motion was 0.320 ± 0.225° for the 10° angular step.

The accuracy of robotic motion was then evaluated using MR imaging as initially proposed. In brief, a plastic marker was robotically moved by specific motion steps, and MR images were acquired after each step. The various images were superimposed into one image for visualization of the motion pattern. As expected, the motion errors estimated using digital callipers were significantly smaller than those obtained by MRI (ranged from 0.171 ± 0.191 to 0.352 ± 0.179 mm), in which the size of the imaging voxels determined the finest possible accuracy. Fortunately, there wasn't any evidence of magnetically induced shift of the mechanical components that could compromise the accuracy of ultrasound delivery to the target. Thereby, it was concluded that the motion accuracy is excellent during full operation of the system in the MRI environment.

Advantageously, a third visual method was implemented for motion accuracy assessment. This method involved performing multiple ablations on a transparent plastic film. Discrete melted spots were formed on plastic film, being spaced by the commanded step. Accordingly, excellent motion repeatability was evidenced by equally spaced spots. Well-defined areas of discrete and overlapping lesions were achieved by varying the spatial grid step and sonication time, proving that the system can precisely ablate a large tissue volume by overlapping lesions.

In the framework of WP6, six navigation algorithms were investigated for their performance based on two indicators: the amount of induced heating in the near-field region and the total treatment time for complete elimination of the pre-focal heating. For each algorithm, sonications were performed in a grid (10×10 with 2 mm step) using the same ultrasonic protocol (110 J acoustic energy at each point) while the time delay between adjacent sonications was varied from 0 to 60 s to examine its effect on the above indicators. The Random algorithm resulted in safe temperatures and a safe thermal dose accumulation in the near-field at the shorter delay of 40 s, and also in the shortest treatment time of about 81 min. However, the effects of this algorithm are considered unpredictable due to its random nature. The sequential algorithm, which is the most commonly used algorithm, requires a longer delay of 60 s for eliminating pre-focal heating and achieving a thermal dose within the permitted limits, which corresponds to a treatment time of 110 min. Advantageously, for the Euler's and Triangular algorithms, this is achieved at a shorter delay of 50 s and a quite shorter treatment time of about 95 min.

Finally, early validation of the system’s safety in rabbits led to some initial experiments in pets with superficial mammary tumours. The pets were treated and the effects of FUS therapy were examined by histological examination of the dissected tumours (n=3), with the results being very promising for the following pet experiments.

A.3. EXPLANATION OF THE WORK CARRIED OUT PER WORK PACKAGE (WP).

(Maximum Recommended 3 pages per WP)

Work Package Number:	**1**	**Start Month:**	**1**	**End Month:**	**36**
Work Package Title	**Project Management**				
Work Package Leader	**MEDSONIC LTD**				

Partner Role	**HO** **CUT**	**PA1** **MEDSONIC LTD**	**PA2** **LINAC**	**PA3** **DEMS**	
Person Months	**2.7**	**1**	**3.8**	**-**	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

The aim of this package is the scientific, financial, and legal management of the program. Although the number of researchers involved is small (this is limited by the size of the grant), it will follow management principles as if it was a large size grant.

Work Description and Key Results

Describe the activities undertaken relating to project management (e.g. preparation of Progress Reports, coordination meetings, decision making procedures etc.) and networking (i.e. exchange of visits between partners including timeframe and purpose of each visit). Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner.

Task 1.1 Management (CUT, M1-36)

Project coordinator duties

During the first reporting period, the Project coordinator:

- Served as the contact point with the responsible officer of the Research Promotion Foundation (RPF) and provided any requested information.
- Prepared the consortium agreement and sent to all partners the objectives to be fulfilled in accordance with the Consortium Agreement, as well as a detailed plan of the program.
- Managed all financial issues. Specifically, the coordinator collected financial material from all partners and monitored that they follow financial obligations according to the consortium agreement. He also managed payments of staff and informed partners about the funding spent.
- Ensured proper communication flow between partners, as well as with other organizations or individuals. In this framework, he prepared the minutes of all scientific and any other meetings.

The interim report was prepared by the coordinator at the end of the first reporting period.

Scientific coordinator duties

The scientific coordinator was responsible for everything related to the scientific aspect of the program. He monitored and collected scientific and dissemination material from all the partners.

Scientific committee

- The scientific committee included: C. Damianou, C. Ioannides, M. Giannakou, and C. Euthivoulou, who made decisions on any scientific-related matter by voting following a full discussion of the matter.

Management of knowledge

- A file was created that contains information on the experience and skills of all researchers to be used for enhancement of the program quality.
- Information about the program were distributed by the project coordinator to other academic organizations that carry out research in the same field. The coordinator also sent information to associations related to the disease under research, as well as to business and industrial organizations.

Communication among partners

The communication between partners was done mainly by email and via the platform zoom. The consortium used three different email addresses for network communication. The first address concerned technical issues and the second one financial issue, whereas the third email was dedicated to dissemination and exploitation activities. Other means of communication were the telephone, videoconferencing via Internet, and regular mail.

Deliverables

List and describe the Deliverables of this WP for the reporting period.

D1.1 Interim report (CUT, report, M18).

Work Package Number:	2	Start Month:	1	End Month:	36
Work Package Title	**Dissemination Activities**				
Work Package Leader	**CUT**				
Partner Role	**HO** CUT	**PA1** MEDSONIC	**PA2** LINAC	**PA3** DEMS	
Person Months	**2**	**-**	**0.26**	**2**	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

Dissemination and commercialization plan at national and international level.

Work Description and Expected Key Results

Describe the activities regarding the dissemination of research results (e.g. Publications, Scientific Information Days, Conference Presentations etc.). Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner.

Describe any problems encountered and how they were resolved. Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule.

Task 2.1 Dissemination (ALL, M1-36)

The dissemination activities during the 1st reporting period (Interim report) included the following:

Creation of logo

A visual identity/ logo (Figure 1) was created for the SOUNDPET project under the guidance of professional designers to be used by all project partners in dissemination activities, thus securing a strong and unique brand.

Figure 1: Project Logo.

Creation of Website

A dynamic website has been created, giving many researchers of the project access to upload information. The website will serve as the main communication tool for dissemination of project information. Promotional information about the developments and benefits of SOUNDPET, as well as a demonstration video of the system, are available on the website. The newsletters produced during the first reporting period were also uploaded. The domain of the website is www.soundpet.eu.

Creation of social networks

Pages were created on Facebook, LinkedIn, and Twitter about the SOUNDPET project. This proved to be effective in promoting discussion and generating awareness of the project and its associated activities since we have received numerous messages requesting additional information

about the project. The project was also disseminated through the Facebook page of partners (GOC, MEDSONIC).

Production of brochure and newsletters

A **brochure** was created presenting the main features and intended use of the developed technology. The brochure may be used in future mail campaigns for informing customers or as handout at events or tradeshows.

Newsletters (3) were produced in English. The first newsletter was produced 3 months after beginning of the project to present the project, partner organizations, and participants. The second newsletter focused on the developed robotic system and its efficacy in terms of MRI compatibility and motion accuracy, whereas the third one presented the development of the ultrasonic transducer, as well as the assembly of all electronic devices in a modern medical cart.

Public Events

Opening Event: A virtual opening event took place, in which key stakeholders (researchers, health and social care professionals, veterinarians, purchasers, and companies) and project participants were informed about the program. The event was held virtually due to the COVID-19 pandemic.
Other Events (2): The project was presented by the project coordinator in a local event organised by the Cyprus Cancer Research Network. The technology and its major benefits over existing therapeutic solutions was showcased at another local event, in front of a big audience including government executives and foreign ambassadors.

Publications (2) in scientific journals

- Drakos T, Giannakou M, Menikou G, Constantinides G, Damianou C, "Characterization of a soft tissue-mimicking agar/wood powder material for MRgFUS applications," *Journal of Ultrasonics*, 113:106357, 2021, doi: 10.1016/j.ultras.2021.106357.

- Antoniou A, Drakos T, Giannakou M, Evripidou N, Georgiou L, Christodoulou T, Panayiotou N, Ioannides C, Zamboglou N, Damianou C, "Simple methods to test the accuracy of MRgFUS robotic systems," *International Journal of Medical Robotics and Computer Assisted Surgery*, 17(4): e2287, 2021, doi: 10.1002/rcs.2287doi: 10.1002/rcs.2287.

Presentations at a scientific conferences

- Giannakou M, Drakos T, Evripidou N, Evripidou G, Antoniou A, Damianou C, "MRI-guided focused ultrasound robotic system for preclinical use of small and large animals," *International Society for Therapeutic Ultrasound* (ISTU 2021), 6-9 June, Gyeongju, Korea .
- Marinos Giannakou, Nikolas Evripidou, Anastasia Antoniou, Christakis Damianou, Robotic device for MRgFUS applications in veterinary medicine, 2021 International Conference on Medical Imaging Science and Technology (MIST 2021), December 1-3, 2021, Virtual Conference.
- Marinos Giannakou, Nikolas Evripidou, Anastasia Antoniou, Christakis Damianou, MRI compatible FUS robotic device for treatment of canine and feline mammary tumors, International Conference on Animal Health, November 22-23, 2021, Dubai, UAE
- Marinos Giannakou,Nikolas Evripidou,Anastasia Antoniou, Christakis Damianou, MRI compatible robotic device for fus therapy of canine and feline mammary tumours, VI International scientific conference industry 4.0, 08 – 11.December 2021, Borovets, Bulgaria

- Marinos Giannakou, Nikolas Evripidou, Anastasia Antoniou, Christakis Damianou, Andreas Georgiou, Robotic device for veterinary applications of MRgFUS VI International scientific conference industry 4.0, 08–11 December 2021, Borovets, Bulgaria
- T. Drakos, M. Giannakou, G. Menikou, G. Constantinides, C. Damianou, "Characterization of an agar/wood powder soft tissue-mimicking material for MRgFUS therapies". 12th Annual Scientific Symposium, Ultrahigh Field Magnetic Resonance: Clinical Needs, Research Promises and Technical Solutions, Berlin, Germany, 2-3 September 2021.

Task 2.2 Exploitation (MEDSONIC, M1-36)

A patent application relating to the developed MRgFUS device was prepared. A FTO analysis was carried out by searching patent literature worldwide and obtaining legal opinion as to whether our product may be considered to infringe any patent owned by others. Currently, there is no similar patent application on the subject. The application will be submitted when financial resources are secured.

Deliverables

List and describe the Deliverables of this WP for the reporting period.
Provide information regarding the publications submitted to open access journals and deposited in relevant repositories.

DISSIMINATION

D2.1 Website (ALL, website, M3).
D2.2 Opening event (CUT, report, M3).
D2.3 Publication in a scientific journal (CUT, report, M12).
D2.4 Presentation at a scientific conference (CUT, report, M12).

EXPLOITATION

D2.10 Preparation of patent application (MEDSONIC, report, M12).

Work Package Number:	3	Start Month:	1	End Month:	18
Work Package Title	**Hardware design**				
Work Package Leader	**MEDSONIC LTD**				
Partner Role	**HO** **CUT**	**PA1** **MEDSONIC**	**PA2** **LINAC**	**PA3**	
Person Months	23	12.1	1.7	-	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

Finalize the design of all the necessary hardware of the system (robotic system, ultrasonic transducer, electronic system, and medical cart).

Work Description and Expected Key Results

Describe the activities implemented in the frame of this specific WP. Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner (including Foreign Research Organisations).

Describe any problems encountered and how they were resolved. Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule.

All the relevant tasks were completed during the 1st reporting period of the project.

Task 3.1-Four DOF robotic system (MEDSONIC, CUT, GOC, M1-18)

Three versions of the SOUNDPET robotic system have been developed. All three versions offer motion of a single element spherically focused transducer in four degrees of freedom (DOF). Specifically, the positioning mechanism comprises three linear stages for movement in the X, Y, and Z axes, and one angular stage (Θ-axis) that rotates the transducer about its shaft axis. The devices consist of a water enclosure wherein the transducer is actuated for proper acoustic coupling and a mechanism enclosure that accommodates all the mechanical components. Motion is actuated by piezoelectric motors. Jack screw mechanisms are utilized for converting the angular motion of the motors into linear, whereas a series of gears are utilized to reduce the speed of the motors so that smoother positioning is achieved. A set of optical encoders (US Digital Corporation, Vancouver, WA 98684, USA) was incorporated on each axis to ensure highly accurate motion while improving the safety and reliability of the device. The entire systems were designed using the AutoCAD (Autodesk, USA, California) software and manufactured on a 3D printer (FDM400, Stratasys, 7665 Commerce Way, Eden Prairie, Minnesota, 55344, USA) using acrylonitrile styrene acrylate (ASA) thermoplastic.

Robotic system Version 1

In the first version of the system, the USR30-S3 piezoelectric motors (Shinsei Kogyo Corp., Tokyo, Japan) were employed. Figure 2A shows a computer-aided design (CAD) drawing of the device without upper covers as integrated in the MRI table. This configuration enables a bottom to top ultrasonic delivery to a subject placed in the prone position. Figures 2B and 2C show photos of the front and back views of the manufactured product, respectively.

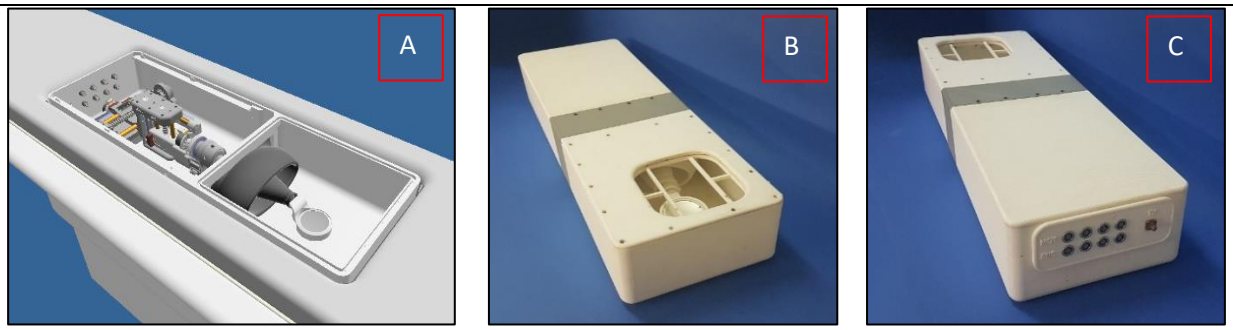


Figure 2: (A) CAD drawing of the 4 DOF robotic device version 1, (B) Front view photo of the manufactured device, and (C) Rear view photo of the manufactured device.

Robotic system Version 2

In the second version of the robotic device, the positioning mechanism was improved in terms of robustness and accuracy. This version comprises larger motors (USR60-S3, Shinsei Kogyo Corp., Tokyo, Japan) that can produce ten times higher torque than the small ones, thus improving the performance of the positioning stages. Several techniques were utilized to arrange the larger motors in a space-saving manner so that the mechanism was fitted in an enclosure of the same size as the previous one. The incorporation of larger motors allowed the creation of a positioning mechanism with significantly tighter tolerances (e.g., nylon inserts were used for tight and smooth connection between plastic and metallic components), since the large motors can operate with reasonably high efficiency without getting stressed. Another major improvement is that the acoustic opening was sealed by a silicone membrane and new techniques were implemented for automatic adjustment of the water volume during movement of the bellow, thus avoiding motion of the target. Figure 3A shows a CAD drawing of the interior view of the device as integrated in the MRI bed. Figures 3B and 3C are photos of the manufactured device from the front and rear sides, respectively.

Figure 3: (A) CAD drawing of the 4DOF robotic device version 2 as integrated in the MRI bed, revealing the interior mechanism, (B) Front view photo of the manufactured device, and (C) Rear view photo of the manufactured device.

Robotic system Version 3

A third version of the robotic system was developed to enable a top to bottom ultrasonic delivery to the target and thereby supine placement of the subject. A support structure with four C-shaped arms was developed for attaching the device on the MRI table. A height adjustment mechanism was incorporated for changing the height of the device depending on the patient's size. The heigh adjustment mechanism is operated by a manual knob located at the top of the device. Supine placement provides the conform required for long-treatment sessions, given also the limited space of the MRI bore. In this version, the air can escape though the top venting opening of the water container, and thus the risk of air bubbles being trapped between the target and transducer is reduced significantly, thus offering a more reliable acoustic coupling. Figure 4A shows a CAD

drawing of the device attached to the MRI table with the assistance of the C-arms. Figure 4B shows photo of the manufactured device attached to a structure with the shape of an MRI bed.

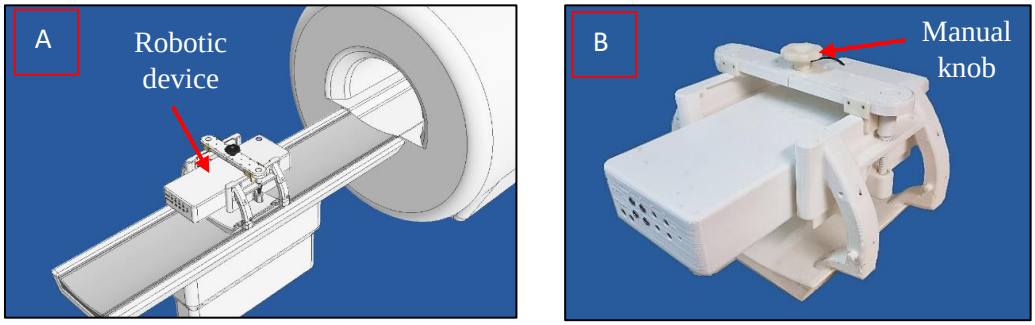


Figure 4: (A) CAD drawing of the robotic device version 3 and (B) Complete manufactured device.

Task 3.2-Ultrasonic transducer (MEDSONIC, CUT, M1-12)

A MATLAB-based software was utilized for simulating the HIFU beams and the heating effects of candidate transducers (with different characteristics), from which two were selected for manufacturing. A transducer with a frequency of 2.5 MHz, a 50 mm diameter, and a 65 mm radius of curvature was manufactured for good targeting of shallow tissue. A transducer with a smaller frequency of 1 MHz, a diameter of 60 mm and a radius of curvature of 70 mm was also selected so that deeper malignant regions can be reached as well. The specific diameters were selected so that less space is occupied in the water container. Thus, relatively small radiuses of curvature were chosen for maintaining good focusing. Figure 5 shows indicative simulation results of the axial pressure and temperature distribution for the 2.5 MHz transducer.

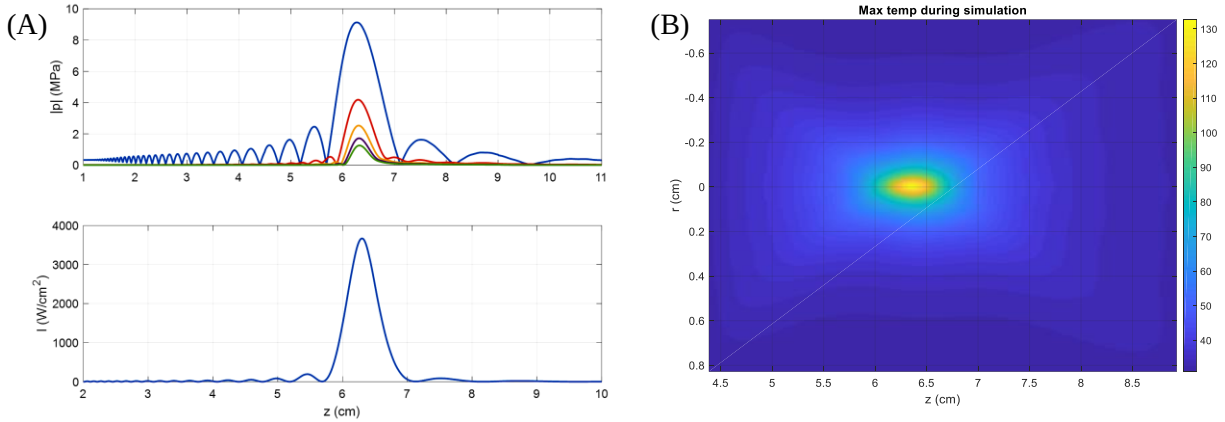


Figure 5: (A) Axial pressure distribution of the first five harmonics and the corresponding intensity of the first harmonic, and (B) Temperature distribution (axial plane) at the time peak temperature occurs (2.5 MHz transducer).

Piezoceramic elements with the specific characteristics were purchased (1 MHz element provided by Ferroperm, Kvistgaard, Denmark & 2.5 MHz element provided by Piezo Hannas, Wuhan, China) and hosted in custom-made housings made of ABS plastic. The elements were sealed with epoxy, which serves as the backing material improving the acoustic performance of the transducers. Their impedance was matched to 50 Ω utilizing a custom-made matching network for maximum power transfer from the amplifier. The selection of all incorporated materials was based on MR compatibility to allow proper operation in the MRI environment. The transducers are connected to extension cables via SMA connectors. A low-pass RF filter (L8959, Anatech electronics, Manhattan, USA) designed in-house is incorporated between the transducer and the amplifier to cut off high-frequency signals and prevent image distortions in MRI. Figure 6 shows photos of the manufactured 1 MHz transducer.

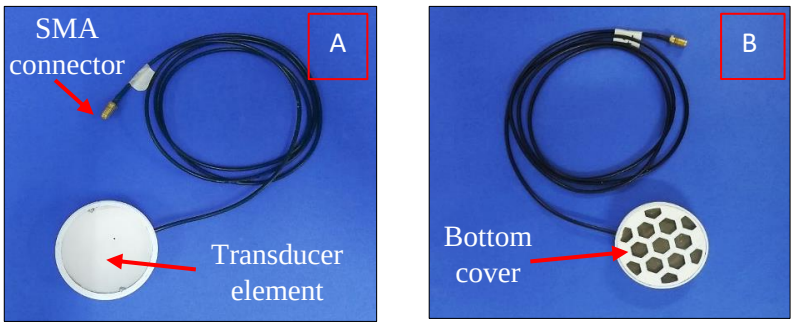


Figure 6: Photo of the manufactured transducer. (A) Front view and (B) Rear view.

Task 3.3-Electronic system (MEDSONIC, DEMS, M7-18)

A modern electronic driving system was developed for controlling the positioning mechanism. The electronic system includes a DC supply, the motor drivers, and a microcontroller card (Arduino cc, Ivrea, Italy). In contrast to previous versions, the present system is controlled by an Arduino UNO that interfaces with a computer via a USB port. Advantageously, its use reduces the operation time of the robot whilst improving the overall performance of the system. The several electronic components were arranged in a compact enclosure for ease integration in the medical cart. Figure 7 shows the developed electronic driving system.

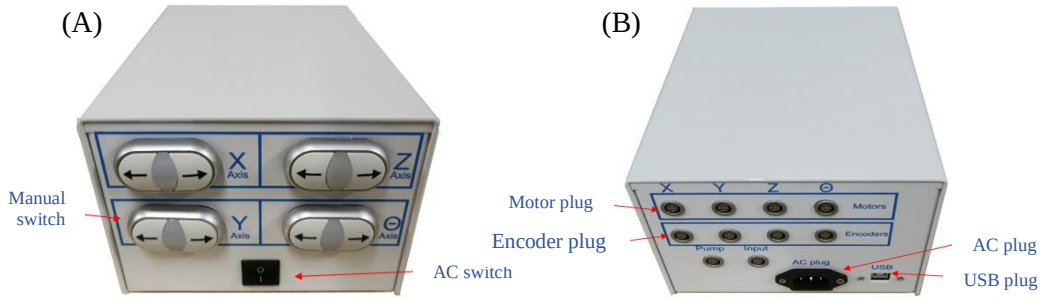


Figure 7: Electronic driving system that controls the robot. (A) Front view and (B) Rear view.

Task 3.4-Design of medical cart (MEDSONIC, DEMS, GOC, M7-18)

A medical cart was developed to host the electronic devices (i.e., driving electronics, RF amplifier, and laptop) of the SOUNDPET system. An existing cart developed by the Haeberle company (Stuttgart Germany) was modified according to the specifications of the present system. The material and thickness of each compartment of the cart assembly were carefully selected based on stress analysis, considering the maximum possible load and predefined safety limits. The final cart is lightweight and thus easily transportable, easy to use, and ergonomic. All wiring is achieved using connectors and plugs. Figure 8 shows the developed medical cart.

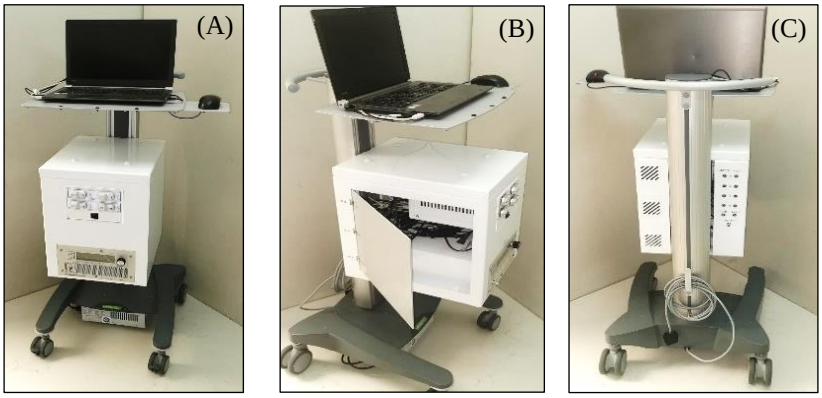


Figure 8: Photos of the developed Medical cart. (A) Front view, (B) Side view, and (C) Back view.

Deliverables
List and describe the Deliverables of this WP for the reporting period. D3.1 Four DOF robotic system (MEDSONIC, CUT, prototype/report, M18). D3.2 Ultrasonic transducer (MEDSONIC, CUT, prototype/report, M18). D3.3 Electronic driving system (MEDSONIC, prototype/report, M18). D3.4 Design of medical cart (MEDSONIC, prototype/report, M18).

Work Package Number:	4	Start Month:	7	End Month:	24
Work Package Title	MRI imaging of the thermal exposures				
Work Package Leader	GOC				
Partner Role	HO CUT	PA1 MEDSONIC	PA2 LINAC	PA3 DEMS	
Person Months	2	1	1.02	-	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

To evaluate the MR compatibility of the transducer and to develop MR thermometry for guiding the ultrasound exposures. During the reporting period, agar-based tissue mimicking phantoms were developed. Their critical properties and ability to form lesions were investigated.

Work Description and Expected Key Results

Describe the activities implemented in the frame of this specific WP. Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner (including Foreign Research Organisations).

Describe any problems encountered and how they were resolved. Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule.

Task 4.1 Development of Agar/silica/milk phantom for MRI imaging (CUT, M7-12)

An agar-based TMM doped with wood powder was developed in the laboratory setting at a very low cost to be used in the evaluation process of the robotic system. Instead of using silica, a biological material (wood powder) was used. The agar/wood phantom (2 % w/v agar and 4 % w/v wood powder) was characterized for its acoustical, MR and thermal properties, and the estimated properties agreed sufficiently with the literature values for soft tissue. Since the attenuation and absorption coefficients of the wood-doped phantom were close to those of human tissues, no evaporated milk was used. In addition, the wood phantom resulted in a thermal conductivity value close to that of humans.

Ultrasound, X-ray, and Scanning Electron Microscope images of the phantom were acquired. A photo and MR images of the developed phantom are shown in Figure 9.

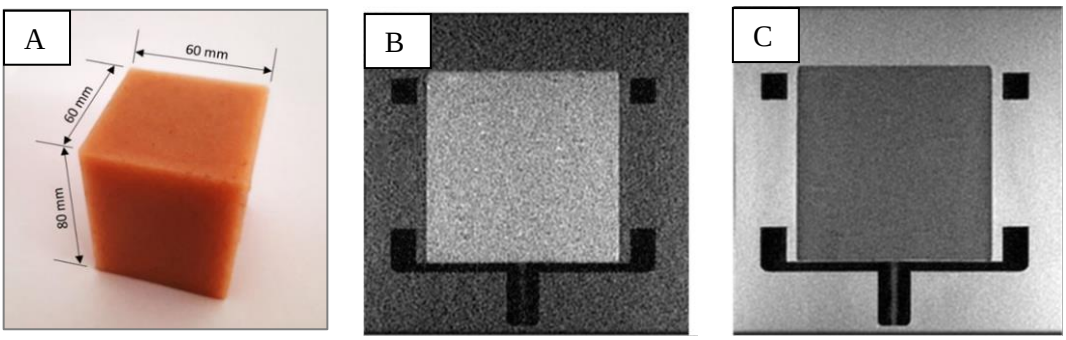


Figure 9: (A)Photo of the developed TMM, (B) Inversion Recovery (IR)-FSE image of the TMM, and (C) T2-weighted FSE image of the TMM.

The phantom was then exposed to high-power sonications to evaluate its ability to form thermal lesions. A special holder accommodated the phantom and the transducer (frequency 2.6 MHz, diameter: 38 mm, focal length: 61 mm, MEDSONIC LTD, Limassol, Cyprus) in a water-filled container with the transducer facing towards the phantom, as shown in Figure 10A.

Initially, temperature measurements were performed in the phantom using a thermocouple (5SC-TT-K-30-36, Omega Engineering, Connecticut, USA). A temperature rise of 63^{o}C was achieved by applying an acoustical power of 44 W for a 30 s duration. The corresponding temperature profile is shown in Figure 10B.

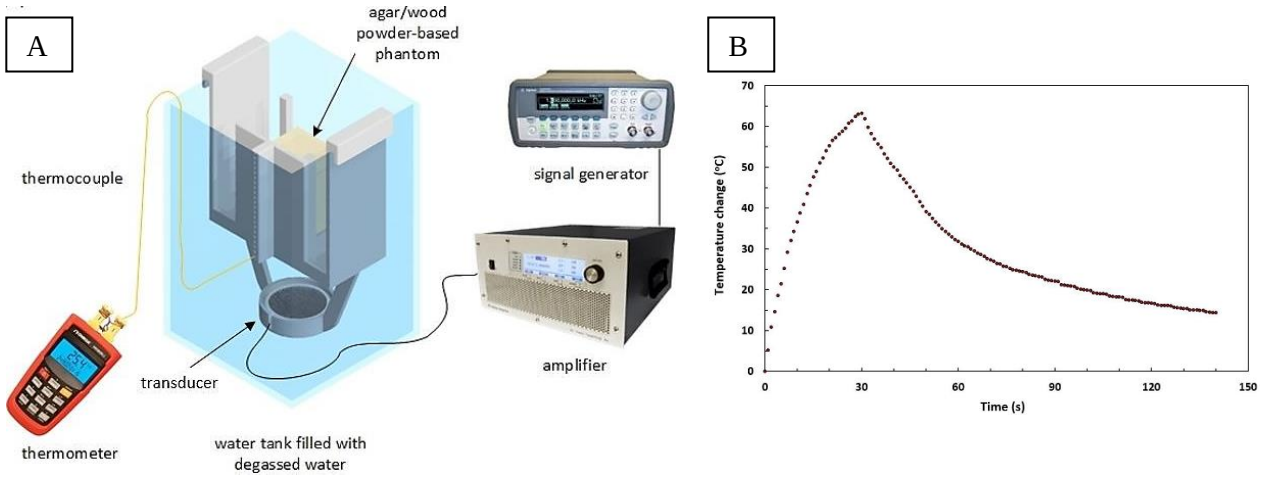


Figure 10: (A) Experimental set up for temperature measurements using a thermocouple, and (B) Temperature change versus time using acoustic power of 44 W for 30 s (2 cm focal depth).

Temperature measurements were then performed in a 1.5 T MR system (Signa Excite, General Electric, Fairfield, CT, USA). MR thermometry was used to calculate the maximum temperature at the focus for the same sonication protocol. Figures 11A to 11C show indicative MR thermal maps that were derived from EPI images obtained in a plane parallel to the focal beam at 2 cm depth. After sonication, a high-resolution Proton Density image was obtained, in which the sonicated area appeared brighter, indicating lesion formation (Figure 11D). The TMM was cross-sectioned after the sonication, and lesion creation was confirmed visually. The temperature change as calculated from the thermal maps reached a value of 66.4 ^{o}C.

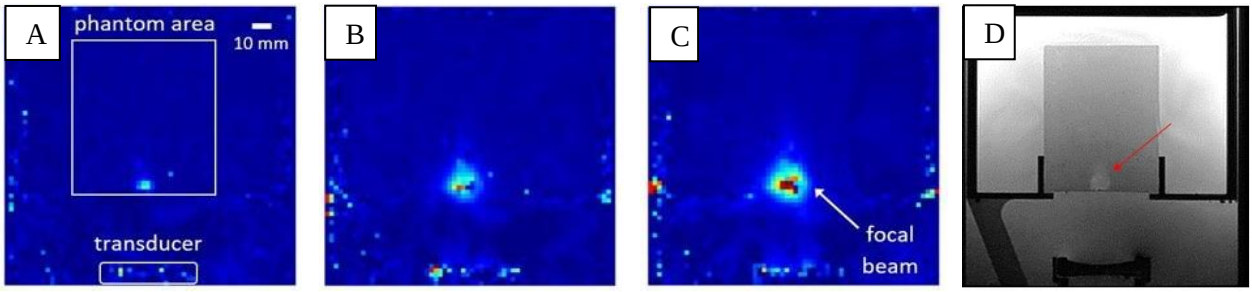


Figure 11: MR thermal maps obtained in a plane parallel to the beam at 2 cm focal depth during sonication at 44 W acoustic power for 30 s, at sonication times of (A) 5 s, (B) 15 s, and (C) 25 s. (D) PD MR image of the TMM after sonication.

Two agar-based tissue/tumour phantoms with superficial mammary tumour models (of 1 and 4 cm depth) were developed. The phantom with the small tumour model can be seen in Figure 12.

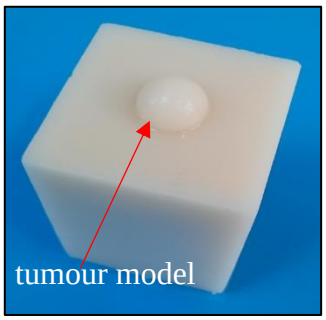


Figure 12: Phantom with small tumour model.

Sonications of 10 s and varying acoustical power were performed using the 2.6 MHz transducer with the focal point approximately adjusted superficial to the lesions. The resultant temperature changes were recorded at the interfaces between the tumour models and the tissue. The objective was to check if the total ultrasonic energy that is intended to be used for ablating superficial small animal tumours is safe in terms of avoiding heating of healthy tissue.

For the larger tumour of 4 cm, the tissue remained safe for high power exposures (460 J) since the temperature change at the tumour/tissue interface was just 1.5 ^{o}C. However, more caution should be given when sonicating smaller superficial lesions given that a remarkably lower acoustic energy (115 W) was needed to achieve a sufficiently small temperature change of 4.1 ^{o}C for the small tumour model.

Finally, in this WP, experimental evaluation of the T1 and T2 relaxation times of different agar-based mixtures was performed. TMMs were developed containing agar (Merck KGaA, EMD Millipore Corporation, Darmstadt, Germany, 2–6 % w/v) as the gelling agent and various concentrations of silicon dioxide (Sigma-Aldrich, St. Louis, Missouri, United States, 2– 6 % w/v) and evaporated milk (Nounou, Friesland Campina, Marousi, Greece, 10 to 30 % volume per volume (v/v)). A series of MR images were acquired in a 1.5 T scanner for T1 and T2 mapping. Figure 13A shows a photo of the phantoms indicating the composition of ingredients, whereas the experimental setup is shown in Figure 13B. As illustrated, the phantoms' container was placed inside a head/neck/spine coil (Signa 1.5T, 16 channel, GE Medical Systems, Milwaukee, Wisconsin, USA). The results suggest that the T2 is mainly affected by varying agar concentration. The addition of silicon dioxide was found to decrease both relaxation times of pure agar gels, whereas a trend towards decreasing T1 was observed with increasing concentration of evaporated milk. Accordingly, the concentration of these additives can be adjusted based on the MR relaxation times of specific body tissues. Figure13C shows the T2 parametric map generated by voxel-based analysis of a series of MultiEcho images of the phantoms.

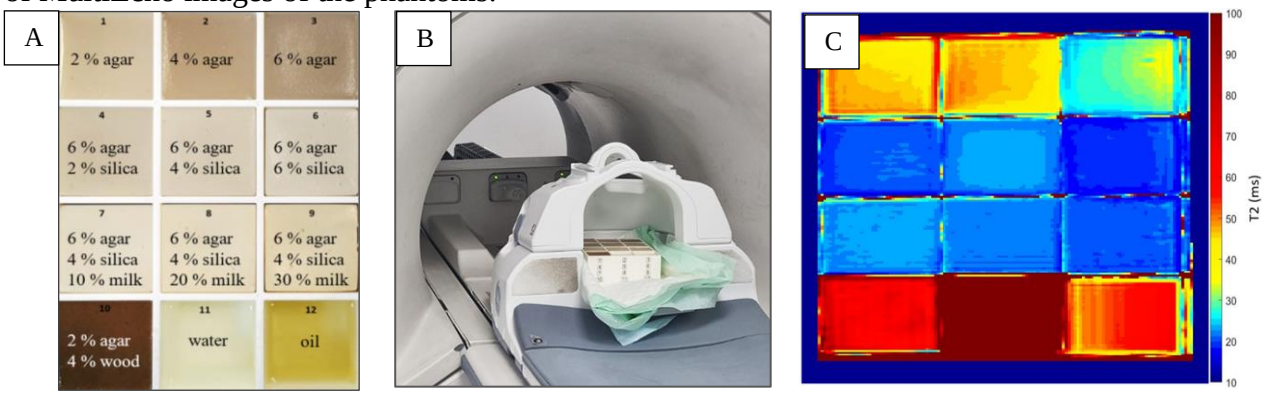


Figure 13: (A) Photo of the TMMs and the composition of additives, including the agar/wood phantom, (B) Experimental set up for T1 and T2 mapping, and (C) T2 parametric map of phantoms generated by voxel-based analysis of a series of 2D coronal MultiEcho images with different echo time values (12 - 250 ms).

Deliverables

List and describe the Deliverables of this WP for the reporting period.

D4.1 Development of Agar/silica/milk breast phantom (CUT, prototype/report, M12).

Work Package Number:	5	Start Month:	1	End Month:	24
Work Package Title	**Software development**				
Work Package Leader	**MEDSONIC LTD**				
Partner Role	**HO** **CUT**	**PA1** **MEDSONIC**	**PA2** **LINAC**	**PA3** **DEMS**	
Person Months	**1.2**	**2**	**-**	**-**	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

A user-friendly program written in C Sharp was developed in order to control the entire system.

Work Description and Expected Key Results

Describe the activities implemented in the frame of this specific WP. Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner (including Foreign Research Organisations).

Describe any problems encountered and how they were resolved. Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule.

Task 5.1 Experiment/animal information(CUT, MEDSONIC, M1-6)

A subprogram was developed for storing experimental information such as the phantom type, excised tissue type, or animal type, gender, and weight depending on the task performed.

Task 5.2 Therapeutic ultrasound control (MEDSONIC, M1-6)

Commands were incorporated into the main page of the software for controlling the ultrasonic exposure by selecting continuous or pulse mode, operating frequency, power, pulse duration, pulse repetition frequency (PRF) and number of exposures.
It should be noted that the SOUNPET system integrates an AG amplifier with a build in generator for powering the transducer, meaning that the user does not need to specify the voltage. Accordingly, software tools were developed for directly selecting the desired power.

Task 5.3-Robotic system control (MEDSONIC, CUT, M7-18)

The commands for controlling the positioning mechanism were also incorporated into the main window of the software. The program allows the user to command movement of the transducer by specifying the distance and direction of motion or customize automatic movement along predefined grid patterns by specifying the grid size, as well as the spatial step and time delay between successive sonications. Furthermore, the software allows the user to select among six different motion algorithms (sequential, Euler, triangular, square, random, and spiral square). The specific subprogram also includes tools for visual monitoring of the grid operation. Figure 14 shows a screenshot of the main window of the software during execution of a 5 x 5 grid pattern indicating the main actions available to the user.

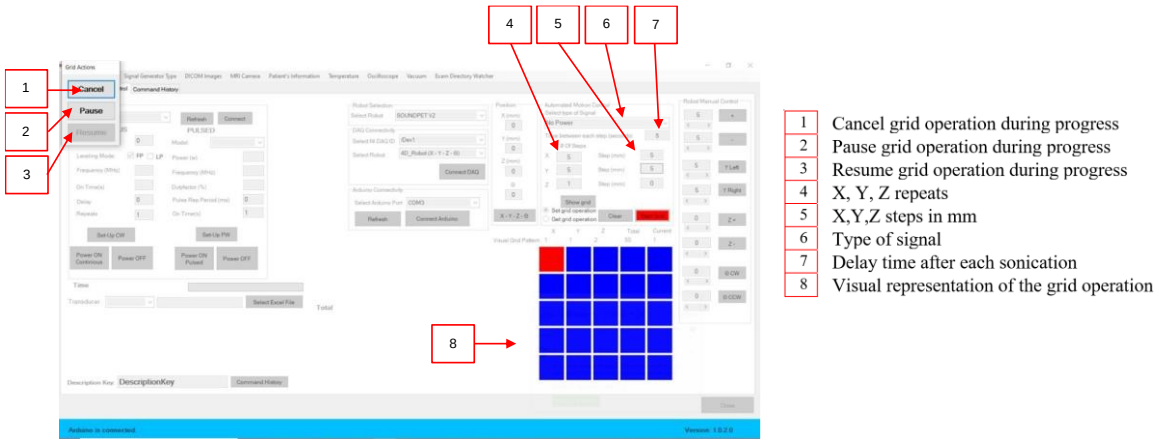


Figure 14: Screenshot of the main window of the software platform (grid operation in progress).

Task 5.4-MRI interfacing (MEDSONIC, CUT, LINAC, M7-12)

The software was interfaced with the MRI system enabling real time transfer and display of DICOM images on the software screen (DICOM viewer page). Accordingly, real time transfer of images enabled development of tools for temperature estimation during scanning (MR thermometry). Tools were also incorporated for controlling an MRI compatible camera.

Task 5.5- Measurements (CUT, MEDSONIC, M7-12)

The user can perform temperature measurement using thermocouples while the temperature readings are displayed on a separate page of the software.

More advanced tools relating to therapy planning are currently under development. The software will incorporate functions for defining and segmenting the target volume. Specifically, the treatment zone will be easily selected on the DICOM images (as displayed in the DICOM viewer page) using the computer mouse. The user will also be able to set to the initial location of the robot (zero point). In contrast to our previously developed platforms enabling just square grid operation, the proposed one will enable segmentation along the tumour boundary and a more complicated grid operation, which will be displayed into the respective MR image during execution.
Finally, the tasks described above will be integrated together to form a platform based on commercial standards. The software will be in its final form by month 24, whereas the corresponding deliverable will be submitted by the end of the next reporting period.

Deliverables

List and describe the Deliverables of this WP for the reporting period.

The relevant deliverable (D5.1) will be submitted by CUT in month 36.

Work Package Number:	6	Start Month:	25	End Month:	36
Work Package Title	**Evaluation of the system.**				
Work Package Leader	**GOC**				
Partner Role	**HO** **CUT**	**PA1** **MEDSONIC**	**PA2** **LINAC**	**PA3** **DEMS**	
Person Months	**1**	**1**	**22.08**	**-**	

Work Package Objectives as described in Annex I of the Contract.

Briefly describe the objectives of the WP and the work carried out during the reporting period towards the achievement of each listed objective.

To obtain proof of concept of the therapeutic ultrasound device in an agar based phantom, in freshly excised tissue and in animals. During the reporting period, the MR compatibility of the transducer and the robotic system was assessed. Motion accuracy was also evaluated using benchtop and MRI techniques. In addition, six navigation algorithms were assessed regarding the induced near-field heating and overall treatment time by sonicating an agar-based phantom. In vivo evaluation of the system in rabbits and pets with mammary cancer began.

Work Description and Expected Key Results

Describe the activities implemented in the frame of this specific WP. Where possible, provide quantitative information on activities and results.

Where appropriate, give details of the work carried out per task by each beneficiary involved, indicating the lead partner (including Foreign Research Organisations).

Describe any problems encountered and how they were resolved. Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule.

Task 6.1 MRI compatibility of the transducer and of the robotic system (CUT, MEDSONIC, GOC, M3-M18)

All three versions of the robotic system were evaluated for MR compatibility by comparing the SNR of phantom images acquired under different activation conditions of the various components. Indicative results are next presented.

The experimental setup for the SNR measurements can be seen in Figure 15A (robotic device v2). A homogeneous phantom was scanned using FSE, Fast Spoiled Gradient Echo (FSPGR), and EPI sequences under various activation states in the 1.5 T MRI scanner. Visual assessment of the acquired images did not show any significant effect on image quality between the various activation conditions. Figure 15B illustrates the corresponding effect on the measured SNR. In contrast to the FSE and EPI sequences, the SNR calculated from the FSPGR images seems to significantly decrease when the motor driver is ON, the interface is connected, and the motor is energized. Regarding activation of the transducer, the results showed that as the power is increased, the SNR decreases.

Experiments were also conducted to examine whether the position of the coil with respect to the imaged object affects the image quality. The image quality was visibly improved when the distance between the coil and the imaged object was increased, suggesting that proper coil positioning at a sufficient distance above the subject is essential. In addition, it was proven that coil selection has a major impact on image quality. The body coil (12 Channel, GE Healthcare Coils, Ohio, USA), due to its higher number of channels and higher order shimming capabilities, offers a higher SNR and better image quality compared to the general purpose (GP) FLEX coil (General Electric, Milwaukee,

Wisconsin), when both are used under the same conditions. The coil selection should therefore be considered in future studies.

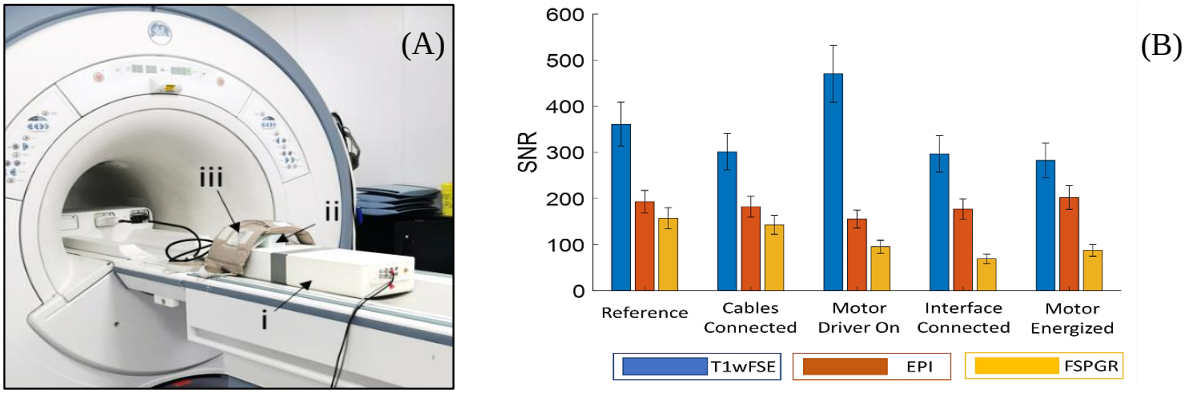


Figure 15: (A) Experimental setup: (i) robotic device version 1, (ii) phantom, and (iii) GPFLEX coil, and (B) Bar Chart of measured SNR (with error bars) for various activation states of the robotic device version 2.

The Robotic System v2 was also evaluated for MR compatibility according to the ACR MRI quality assurance guidelines. Images of an ACR phantom were acquired using a split head coil (General Electric, Milwaukee, Wisconsin, USA) to assess the robot's impact on MRI performance. The following tests were performed: geometric accuracy, high contrast spatial resolution, slice thickness accuracy, slice position accuracy, image intensity uniformity, percent signal ghosting, and low contrast object detectability. Figure 16 shows an MRI image of the ACR phantom at the location of the resolution insert, which is used for assessing the high contrast spatial resolution visually. Assessment is based on the distinguishability of holes (arranged in arrays) that appear as points of brighter signal intensity. Overall, the results from all tests were well within the permitted limits given by the ACR, suggesting that the system is MR compatible under the conditions described in this experiment.

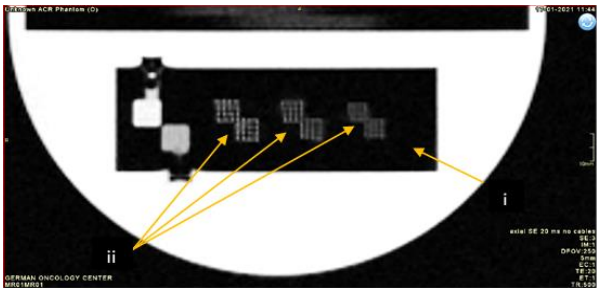


Figure 16: ACR phantom image showing the (i) resolution insert and (ii) three pairs of hole arrays.

Task 6.2 Evaluation of the motion of the robotic system using MRI imaging (CUT, MEDSONIC, DEMS M3-M18)

Caliper-based method: Firstly, the motion accuracy of the robotic device was evaluated using digital calipers, which were mounted on the motion stages under evaluation using specially designed 3D printed structures, as shown in Figure 17A. Bidirectional motion steps of 1, 5, and 10 mm were commanded through the controlling software. The actual displacements as measured by the caliper were then compared to the commanded (intended) steps. Figure 17B shows the mean measured distance (n=20) versus the intended distance for the X-axis forward and reverse directions.

The mean error of linear motion varied from 0.042 ± 0.032 mm for the 1 mm step in the X axis forward direction to 0.123 ± 0.082 mm for the 10 mm step in the Y axis right direction. Accordingly, the mean error of angular motion varied from a minimum value of 0.100 ± 0.077^{o} for the 1^{o} step to a maximum value of 0.320 ± 0.225^{o} for the 10^{o} step (counterclockwise rotation). Notably, the mean error was found to be increasing with increasing motion step for all four axes.

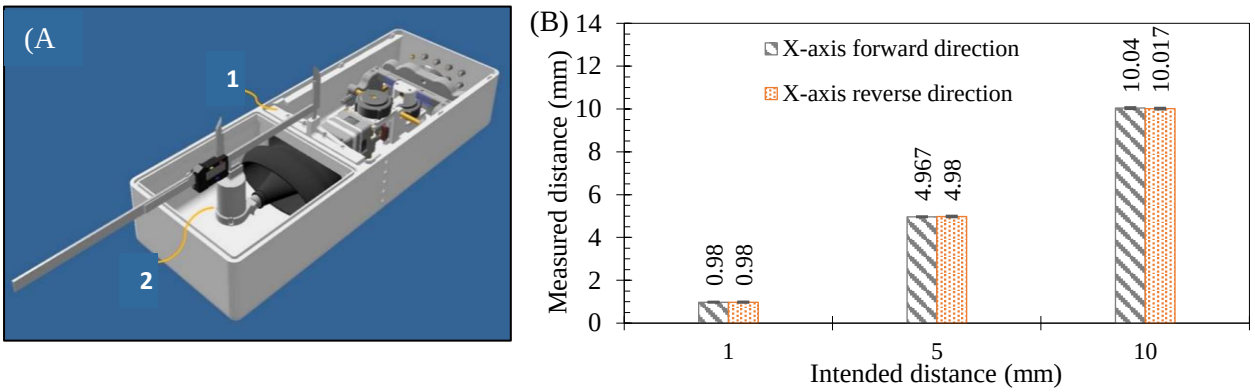


Figure 17: (A) CAD drawing of the setup used for the X axis motion accuracy estimation showing the 3D printed mounting structures (1,2). (B) Mean value of the measured distance versus intended distance.

Visual method: Visual assessment of the accuracy and repeatability of motion was conducted by performing multiple ablations on a transparent plastic film, as illustrated in Figure 18A. An acoustic power of about 10 W was applied at each grid point and the sonication time varied from 1–4 s to control the lesion size. Sonications were performed with varying spatial step while the time delay was set at 30 s. A representative result of discrete lesions formed on the film is shown in Figure 18B. The centers of almost all the spots were equally spaced. Grid sonication with a smaller spatial step and three times longer sonication time resulted in a well-defined square area of overlapping lesions (Figure 18C). It should be noted that lesion creation was a result of sound reflection at the plastic/ air interface.

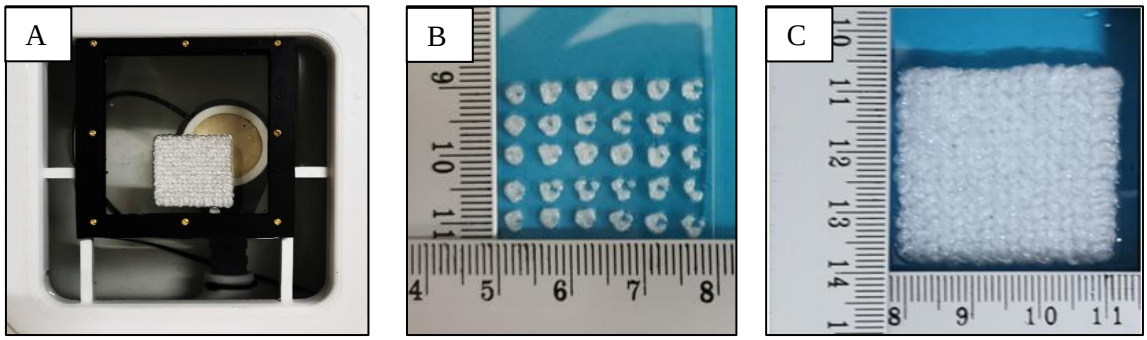


Figure 18: (A) Plastic film secured to the acoustic opening, (B) Lesions formed after exposure at acoustic power of 10.5 W for 1 s and 5 mm step, and (C) Lesions formed after exposure at same acoustic power for 3 s and 2 mm step (1.1 MHz transducer).

MRI method: The system was then evaluated in the MRI environment that is intended to be used. The robotic device was placed on the table of the 1.5 T MRI system, as shown in Figure 19A. The focused transducer was replaced by a 3D-printed plastic structure with a tip of 2 mm thickness (Figure 19B), which served as a marker in the MR images, and was covered with the GPFLEX coil. Bidirectional movements of the transducer with steps of 3 and 5 mm were tested (in the X and Y directions). An MR image was acquired after each step movement to detect the tip location (pixel with the lowest signal intensity). The change in pixel number after a step reflected the shift in the transducer's position. The shift in millimeters was calculated by multiplying the pixel difference with the pixel size (0.5469 mm). Finally, the series of acquired images were superimposed onto one image for visualizing the motion patterns. Figure 19C shows the superimposed image for the X-axis, whereas Figure 19D shows the mean value of the measured distance plotted against the intended distance. Note that the spatial positioning errors estimated in the MRI setting are significantly larger than those obtained by benchtop evaluation. However, given the MRI resolution of about 0.55 mm per pixel, the estimated motion errors are within a reasonable range.

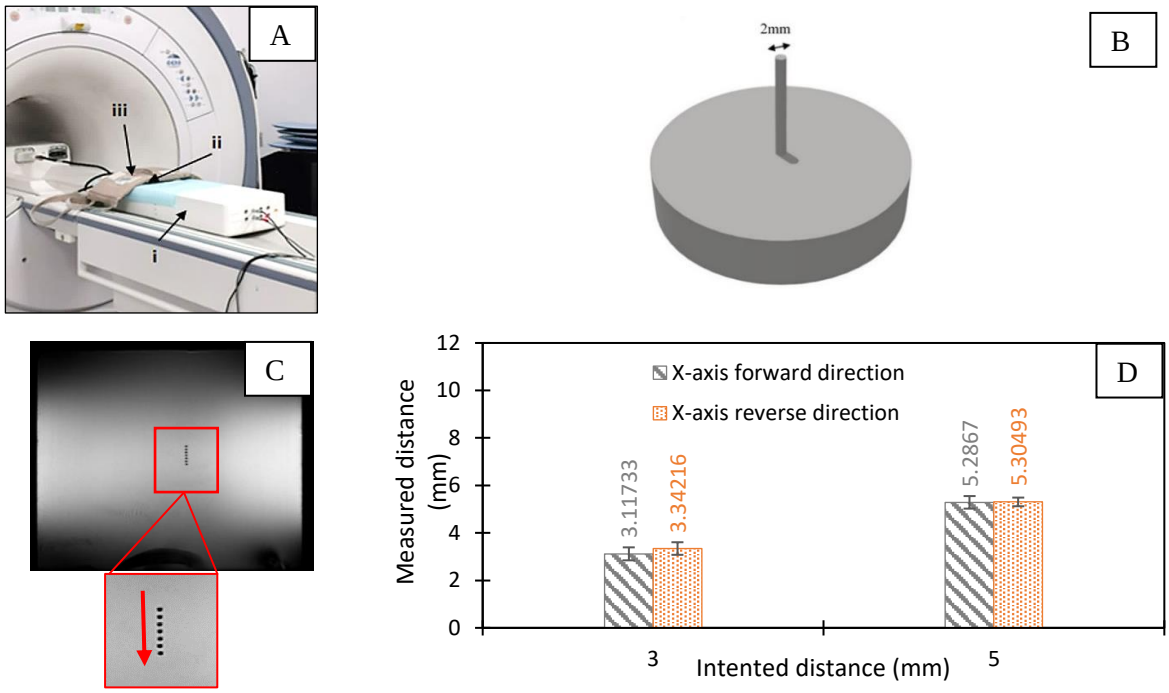


Figure 19: (A) Experimental setup: (i) Robotic device, (ii) Plastic marker, and (iii) GPFLEX coil, (B) CAD drawing of the plastic marker, (C) Minimum Intensity Projection from a combination of images that indicates motion in the X-axis reverse direction (3-mm step), and (D) Mean value of the measured distance versus intended distance for the X-axis. Error bars indicate the standard deviation.

Task 6.4 Evaluation of navigation algorithms for reducing the near-field heating and the treatment time (CUT, MEDSONIC, M6-M12) 0 PMS - synergy with PROSTASONIC

Six navigation algorithms (Sequential, Euler's, Spiral, Square, Random, and Triangular) were evaluated for their performance regarding the amount of heating induced in the pre-focal region and the overall treatment time by sonicating an agar-based phantom. The phantom was fitted in a 3D printed holder that was securely attached to the acoustic opening, as illustrated in Figure 20, with the transducer facing towards its bottom surface. The holder allowed easy vertical insertion of thermocouples in the near-field (at 1 depth) and far-field (7 cm depth) regions. The 1.1 MHz transducer was moved in a 10 x 10 square grid with a 2 mm step according to the motion pattern of each algorithm. An acoustical power of 22 W was applied at each grid point for a sonication time of 5 s. For each algorithm, time delays of 0 s (no delay), 10 s, 20 s, 30 s, 40 s, 50 s, and 60 s between successive sonications was tested. As shown in Figure 20, the controlling software allowed for varying the time delay and the motion algorithm.

Figure 21 shows indicative temperature profiles recorded in the near field at various time delays. As expected, all six algorithms produced intense heating (>10 ^{o}C) with no delay. A minimum of 40 s delay was required for the Spiral, Square, Random, and Triangular algorithms for reducing pre-focal heating to 4 ^{o}C maximum, whereas the Euler's and Sequential algorithms required longer delays of 50 and 60 s, respectively. Regarding the accumulated thermal dose, a value of 30 cumulative equivalent minutes (CEM) or smaller was considered safe. The Random algorithm results in safe temperatures and thermal dose in the near field at the shortest delay of 40 s. A 50 s delay is needed for the Eulers and Triangular algorithms, whereas the rest algorithms require a longer delay to achieve thermal doses in the permitted limit.

Based on the estimated minimum delay for achieving a safe thermal dose accumulation, the total treatment time varied from approximately 81 min for the Random algorithm to 113 min for the Spiral algorithm (except for the square that requires more than 116 min), accounting for the robot's time, sonication and scanning time.Figure 21

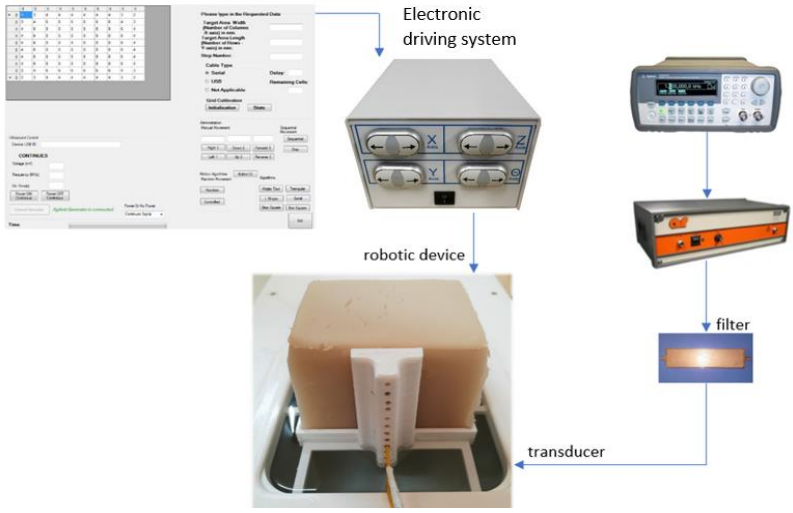


Figure 20: Schematic diagram of the experimental setup for near- and far-field heating evaluation.

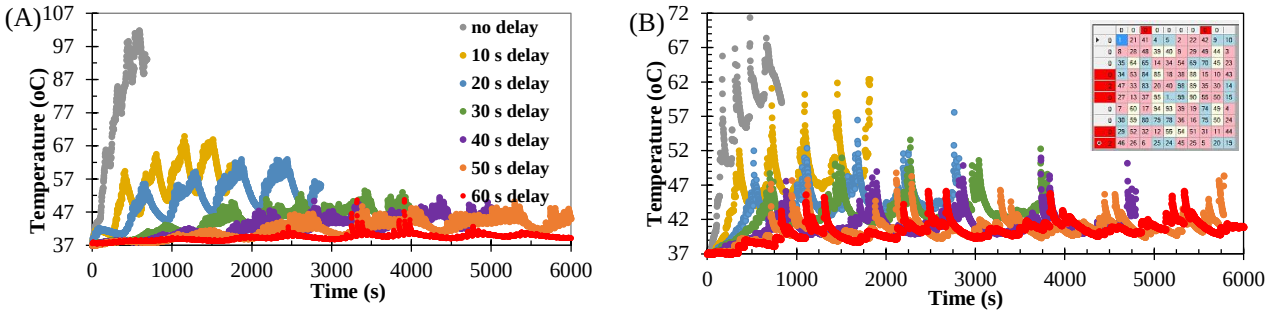


Figure 21: Temperature versus time in the near-field (1 cm depth) for sonication in a 10 x 10 grid using acoustical power of 22 W for 5 s, and varying delays. (A) Sequential algorithm and (B) Spiral algorithm (Software screenshot during execution of the algorithm is shown).

Task 6.5 Evaluation of the system in animals (GOC, CUT, MEDSONIC, M12-M27).

Feasibility studies were performed in rabbits for assessing the safety of the system with the ultimate goal to convince pet owners to give us the green light for treating their pets.

Task 6.6 Evaluation of the system in dogs and cats (GOC, CUT, MEDSONIC, M15-M36).

Safety validation of the system in rabbits allowed some initial experiments in pets to be conducted. Pets with superficial mammary tumours were treated according to the proposed therapeutic protocol and the surgically dissected tumours were analyzed using hematoxylin and eosin (H&E) staining for assessing the effects of FUS therapy (n=3). A picture of a dog placed on the robotic device with the tumour directly above the transducer, as well as indicative histopathological results are shown in Figure 22. The safety and efficacy of the developed system and therapeutic protocol will be further assessed in pets during the second half of the program. The relevant deliverable will be submitted by the end of the project. Notably, all the experiments were approved by the authorities of the Veterinary Services, Ministry of Agriculture (CY/EXP/PR.L01/2020).

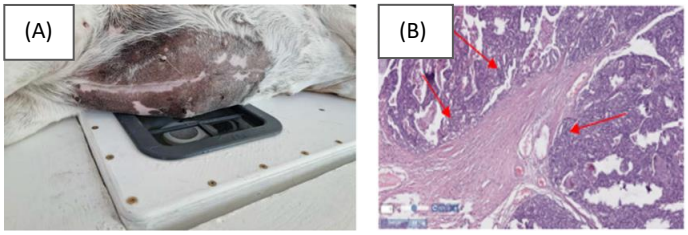


Figure 22: (A) Dog placement on the robotic device and (B) Histological slide revealing necrotic area.

Deliverables
List and describe the Deliverables of this WP for the reporting period. D6.1 MRI compatibility of the transducer and robotic system (CUT, report; M18). D6.2 Evaluation of the accuracy of the robotic system (CUT, report; M18) D6.4 Evaluation of navigation algorithms for reducing the near-field heating and the treatment time (CUT, report, M12).

A.4. TABLE OF WORK PACKAGES

		Contract		Actual Implementation	
Work Package	Work Package Title	Start Month	End Month	Start Month	End Month
WP1	**Project Management**	1	36	1	36
WP2	**Dissemination Activities**	1	36	1	36
WP3	**Hardware design**	1	18	1	18
WP4	**MRI imaging of the thermal exposure**	7	24	3	24
WP5	**Software development**	1	24	1	24
WP6	**Evaluation of the system**	25	36	3	36

A.5. EXPLOITATION OF RESULTS AND ADDED VALUE (This section only applies for final reports)

Provide a brief description regarding the added value of Project results and exploitation measures[1]. Where possible, the measures should be consistent with the expected impact described in Annex I of the contract and the plan for the exploitation of the results.

As a result of the Project and if applicable, provide information regarding:

- Number of Patent and/or Industrial Designs Applications filed
- New job positions (as Full Time Equivalent) created or retained
- Number of spinoffs created
- Collaboration with organisations abroad (for the participation in follow-up R&D projects, technology / know-how transfer, commercial collaboration, etc).
- Number of new Products / Processes / Services (prototype, demonstration, pilot, testing and validation of new products processes or services in environments representative of real-life operating conditions)
- Number of proposals submitted under Horizon 2020 and/or any other European Programme
- Amount of funding received from Horizon 2020 and/or any other European Programme
- Number of standards in which project results were incorporated, indicating the Standardisation Body for each one

As a result of the project, a four DOF robotic device, an electronic driving system, and a medical cart were manufactured. Regarding recruitment of personnel, 2 new job positions were created, whereas 1 position was retained.

A prototype robotic system and its associated software were developed. So far, the efficacy of the system in terms of MRI compatibility and motion accuracy was demonstrated through extensive experimentation, which also proved its feasibility to form lesions in gel phantoms and plastic films.

A patent application relating to the developed MRgFUS robotic device was prepared based on a FTO analysis but has not been filed yet. Extensive patent search (USA, EPO, WIPO) revealed that there is no similar patent on the subject. The application will be submitted after completion of the project when financial resources are secured.

Prof. C. Damianou served as the coordinator in 5 national research grants (under Horizon 2020 and other programmes) including this one.

[1] Please note that all participating organisations will be requested to submit a Report on the impact of the project results two (2) years after completion of its implementation.

B.1. ADDITIONAL INFORMATION (OPTIONAL)

Provide, where deemed necessary, any additional information regarding the Project.

Include explanations on deviations of the use of resources between actual and planned use of resources based on the project contract (if applicable).

Include explanations on transfer of costs between categories (if applicable).

B.2. FOLLOW-UP OF RECOMMENDATIONS AND COMMENTS FROM PREVIOUS PROJECT EVALUATION (Only applicable for the Final Report of Large Projects)

Include in this section the list of recommendations and comments from the interim project evaluation and give information on how they have been followed up.

Notes:

Collection and processing of personal data is carried out according to the RIF's Policy for the Protection of Personal Data. The RIF's Policy is posted on IRIS.