



**University of Dundee**

**Methodology on Quantification of Sonication Duration for Safe Application of MR Guided Focused Ultrasound for Liver Tumour Ablation**

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*Published in:*  
Computer Methods and Programs in Biomedicine

*DOI:*  
[10.1016/j.cmpb.2017.09.006](https://doi.org/10.1016/j.cmpb.2017.09.006)

*Publication date:*  
2017

*Licence:*  
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*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Mihcin, S., Karakitsios, I., Le, N., Strehlow, J., Demedts, D., Schwenke, M., Haase, S., Preusser, T., & Melzer, A. (2017). Methodology on Quantification of Sonication Duration for Safe Application of MR Guided Focused Ultrasound for Liver Tumour Ablation. *Computer Methods and Programs in Biomedicine*, 152, 125-130.  
<https://doi.org/10.1016/j.cmpb.2017.09.006>

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1                   **Methodology on Quantification of Sonication Duration for Safe Application of MR**  
2                   **Guided Focused Ultrasound for Liver Tumour Ablation**

3  
4  
5   **Abstract**

6   **Background and Objective:** Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for liver  
7   tumour ablation is a challenging task due to motion caused by breathing and occlusion due the  
8   ribcage between the transducer and the tumour. To overcome these challenges, a novel system for  
9   liver tumour ablation during free breathing has been designed.

10 **Methods:** The novel TRANSFUSIMO Treatment System (TTS, EUFP7) interacts with a Magnetic  
11 Resonance (MR) Scanner and a focused ultrasound transducer to sonicate to a moving target in liver.  
12 To meet the requirements of ISO 13485; a quality management system for medical device design,  
13 the system needs to be tested for certain process parameters. The duration of sonication and, the  
14 delay after the sonication button is activated, are among the parameters that need to be quantified  
15 for efficient and safe ablation of tumour tissue. A novel methodology is developed to quantify these  
16 process parameters. A computerised scope is programmed in LabVIEW to collect data via  
17 hydrophone; where the coordinates of fiber-optic sensor assembly was fed into the TRANSFUSIMO  
18 treatment software via Magnetic Resonance Imaging (MRI) to sonicate to the tip of the sensor,  
19 which is synchronised with the clock of the scope, embedded in a degassed water tank via sensor  
20 assembly holder. The sonications were executed for 50W, 100W, 150W for 10 seconds to quantify  
21 the actual sonication duration and the delay after the emergency stop by two independent  
22 operators for thirty times. The deviation of the system from the predefined specs was calculated.  
23 Student's-t test was used to investigate the user dependency.

24 **Results:** The duration of sonication and the delay after the sonication were quantified successfully  
25 with the developed method. TTS can sonicate with a maximum deviation of 0.16s (Std 0.32) from the

1 planned duration and with a delay of 14ms (Std 0.14) for the emergency stop. Student's T tests  
2 indicate that the results do not depend on operators ( $p>0.05$ ).

3 **Conclusion:** The evidence obtained via this protocol is crucial for translation- of-research into the  
4 clinics for safe application of MRgFUS. The developed protocol could be used for system  
5 maintenance in compliance with quality systems in clinics for daily quality assurance routines.

6 **Keywords:**

7 MR guided FUS; Computer control of laboratory machines and device; Safety; Protocol  
8 Development; Quality Management Systems; Experiment and Measurement Technics, Medical  
9 Device Legislation; Sonication duration.

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## 1 **1. Introduction**

2 Magnetic Resonance guided Focused Ultrasound (MRgFUS) is a technique enabling the monitoring of  
3 the thermometry in real time while applying FUS. MRgFUS has been CE (Conformité Européene)  
4 marked, and Food & Drug Administration (FDA) approved for the treatment of uterine fibroids and  
5 the treatment of pain for bone metastasis [1]. However, the application of Focused Ultrasound  
6 (FUS) in upper abdominal organs is particularly challenging due to complexity of breathing motion, a  
7 multitude of risk structures and possible occlusions through the rib cage. TRANS-FUSIMO Treatment  
8 System (TTS TRANS-FUSIMO, EU FP7 project) is a newly developed system with a dedicated software  
9 to enable the application of MRgFUS in upper abdominal organs such as in liver. This novel software  
10 is based on the mathematical models describing the motion due to breathing, the propagation of the  
11 ultrasound waves through the rib cage and into the targeted tumour destination, and the multi-base  
12 line algorithm to read the temperature during ablation [2]. Virtual reality simulations prove to be  
13 promising in achieving an accurate prediction of a real patient scenario [3]. However, safety and  
14 efficiency of the application still depend on the successful configuration of the hardware and the  
15 efficient control of the process parameters [1]. For these reason, the most important process  
16 parameters for successful ablation of liver tumour have been identified with pre-defined specs  
17 based on the best known clinical practice by TRANSFUSIMO consortium [4]. These identified process  
18 parameters are as follows; delivered acoustic power (with an efficiency of 70-90 %), actual  
19 sonication duration (with less than 1 second of deviation), delay after an emergency stop (less than  
20 200 ms), sonicating to a certain location (within 1 mm accuracy) and reaching to a desired  
21 temperature (with less than 10% of deviation) [4]. Each of these parameters needs to be controlled  
22 by the TTS software reliably. For this reason, it is important to design a protocol to measure the  
23 deviations and provide evidence by providing supportive data for safety before clinical applications.  
24 Due to the high level of energy delivery during treatment, the TTS software is classified as class 3/C  
25 high risk software, where serious injury or death is possible according to the international standard

1 IEC 62304. For this reason, it is crucial to develop a reliable protocol following the requirements of  
2 International Organisation for Standardization, ISO 13485 Quality Management System (QMS). This  
3 is a mandatory step for CE marking approval for clinical use. The CE mark is a legal designation that a  
4 medical product has met the requirements of all relevant Medical Device Directives in the EU. To  
5 achieve this status, as a first step, effective and safe acoustic power delivery of this novel system was  
6 cross validated against the best available clinical standard by applying a dedicated testing protocol in  
7 compliance with ISO 13485 quality management system for medical device design [1]. Based on the  
8 successful evaluation, the next step is to develop a methodology for the quantification of sonication  
9 duration and the delay after the emergency stop. Quantifying sonication duration is important both  
10 in static and dynamic application of the MRgFUS, however due to breathing motion, control of  
11 sonication duration and being able to stop sonication in case of an emergency, is very crucial. In case  
12 of a delay in an emergency stop, there is a risk of sonicating to vital structures, such as arteries or  
13 sonicating to healthy tissues; instead of the targeted tumour tissue only. Sonicating less than the  
14 planned duration might cause inefficient treatment, and can have adverse effects on the response of  
15 autoimmune system [5]. In compliance with ISO 13485, a novel protocol is developed which  
16 consisted of design and development plans, risk assessment forms, risk assessment matrices and  
17 traceability matrices. This study differs from the other studies in literature [6-8], as it aims to  
18 translate science into a clinical application by following the requirements of quality management  
19 systems from the beginning. Whereas, the other published work [5-9] only provides information on  
20 quality assurance for the systems which already received clinical approvals, and these studies only  
21 aim to provide guidance on reliable and safe use in clinics. Vicari *et al.* [8] also mentions the  
22 importance of pre-clinical testing, however, their study only investigates the system efficiency in  
23 pre-clinical settings with no reference to sonication duration verification. Although Bucknor *et al.* [9]  
24 investigates the duration, they investigate the combined effect of power and sonication duration for  
25 optimum clinical applications with a system which already received clinical approval. Obtaining a  
26 clinical approval for a new methodology is a very challenging task and demands evidence for safety

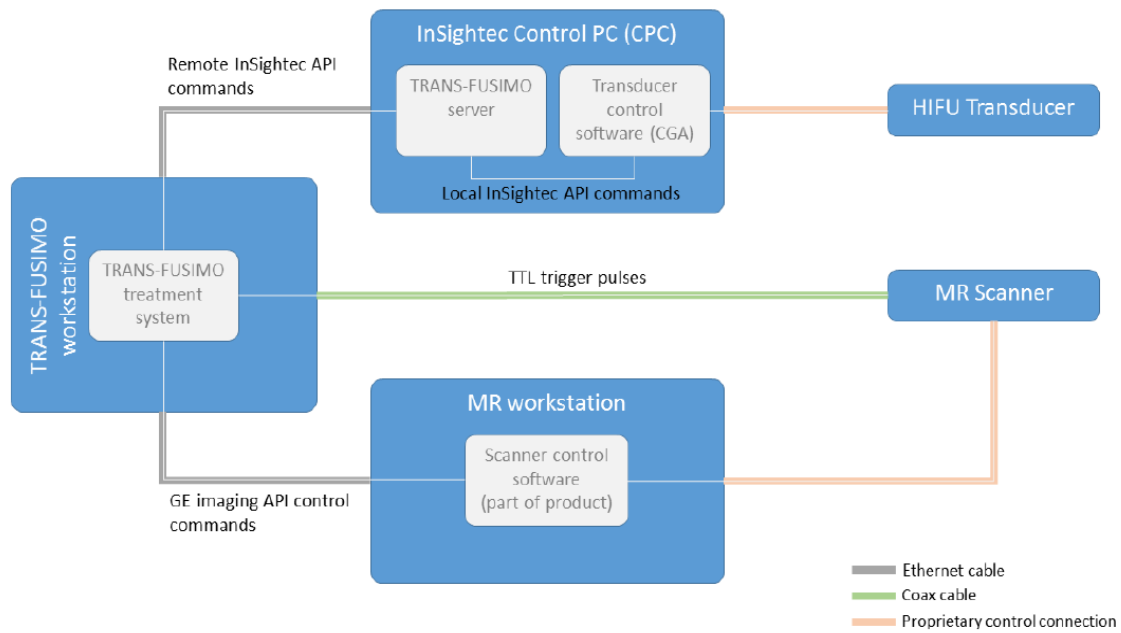
1 and efficiency. For this reason, it is important to develop and design protocols for assessing each  
2 process parameters individually.

3 Below the TTS is explained briefly and the current protocol is described in detail in the methodology  
4 section.

## 5 **2. Background**

6 The evaluated version of the TTS is installed on a desktop PC. It communicates with the user  
7 interface of Signa 1.5 T MR Scanner (GE Healthcare, Milwaukee, MN, USA) and the transducer of  
8 Conformal Bone System 2100 (CBS) (Insightec Ltd, Tirat Carmel, Israel) as shown in Figure 1. This  
9 structure is similar to the structure of ExAblate 2100 TTS (Insightec Ltd, Tirat Carmel, Israel)  
10 however, the system has a completely novel software controlling the transducer of the CBS. The  
11 software itself is its first kind in ablating to a moving target; aiming at obtaining a CE mark status for  
12 clinical applications for liver tumour applications. TTS has a user interface which provides  
13 commands for operator to follow in using the MR scanner. TTS is synchronised with the MR scanner  
14 by using the Transistor Transistor Logic (TTL) pulse. The system can deliver the electrical power and  
15 convert it to the acoustic power within 70-90 % efficiency [1]. The developed power delivery  
16 assessment protocol proves to be repeatable and applicable for power measurements. However,  
17 there is still a need for robust, repeatable protocol for quantifying the duration of sonication and the  
18 delay after emergency stop both for CE marking purposes and for routine maintenance of the  
19 system in clinical settings.

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**Figure1** High-level description of hard- and software components of the TTS

3

### 3. Methodology

4

#### 3.1 Design considerations.

5

A special attention was paid to design a simple protocol which is well documented for all the steps to

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be repeatable by any other operator to measure the actual sonication duration and its deviation

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from the planned duration, as well as the delay after the emergency stop. The system configuration

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and the devices were optimised for its simplicity for the purpose. Risk assessment was conducted to

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eliminate any hardware related failure due to cabling, and any false positives and negatives due to

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experimental errors. A code was written in LabVIEW for data accusation to synchronise the time of

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the sonication command of TTS and the time of the data recording system. Specs were set as such

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that the calculated average standard deviation of the sonication duration from the planned duration

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should be less than 1 seconds and the delay should be less than 200 ms for system to be considered

14

as successful.

15

In this study, sonications were planned for 10 seconds, while sonicating with 50W,100W, and 150W

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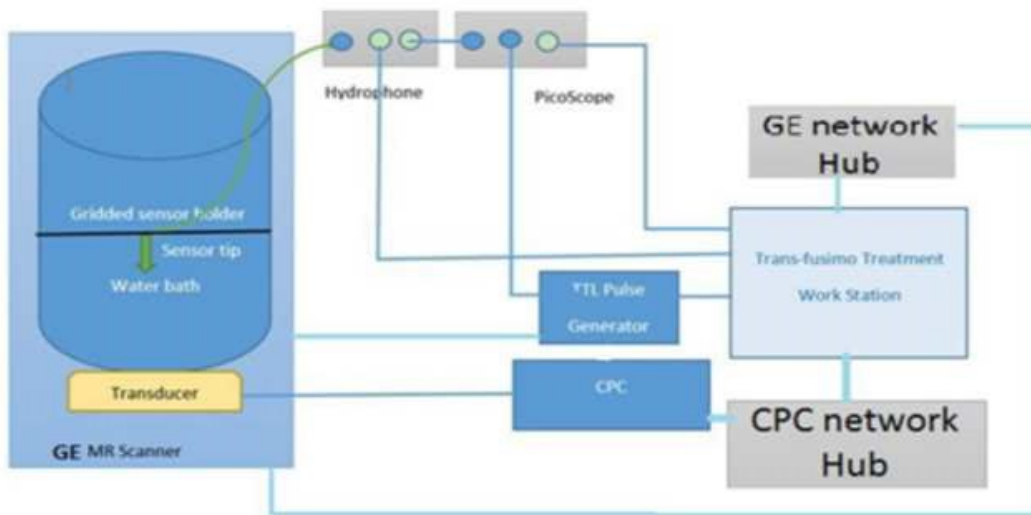
power levels for thirty times by two independent operators to measure the sonication duration.

1 100W sonications were stopped arbitrarily to simulate emergency stops to measure the delay via the  
2 designed protocol; providing evidence for reliability and safe usage of TTS in clinical trials. Student's  
3 T test is required to analyse the user dependency. Any data set producing deviation more than the  
4 pre-defined specs needs to be reported and the system should not be used for clinical purpose until  
5 it conforms to the specs.

### 6 **3.2 Description of the system and the protocol**

7 To collect data during sonication, fiber-optic hydrophone (Pa Ltd, Dorset, UK) was used. The fiber-  
8 optic hydrophone works on the principle of interferometric detection of changes in the optical thick-  
9 ness of a thin polymer film at the tip of the optical fiber sensor download [10]. The experiment set-up  
10 consisted of a water tank filled with degassed water over which a gridded fibre-optic sensor holder  
11 was placed (Figure2). The fibre-optic hydrophone sensor was mounted in a sensor holder (Figure 3a)  
12 and inserted into a 3D printed grid surface and used as a microphone for recording the sound infor-  
13 mation. The fibre-optic sensor was hard wired to fibre-optic hydrophone system control unit. The hydrophone  
14 system was connected to a PicoScope, a device like an oscilloscope, which is programmed to provide monitoring  
15 on a PC. Hydrophone was connected via the "AC out" connector on the front panel to the PicoScope (Picotech,  
16 UK). PicoScope has two inputs, the first is the output of the hydrophone, and the second is the trigger pulse  
17 coming from the TRANSFUSIMO Treatment Software. To initiate the recording of the data, the TTL pulse which  
18 is generated by the TRANSFUSIMO Treatment system, was utilised. The TTL pulse time was treated as the origin  
19 for recording procedure. The TTL box had a splitter to send the same signal to the MR from the TTS software to  
20 start the monitoring of images in real time and to the PicoScope to start the data recording. When TTL pulse is  
21 activated, a time tag line is created and recorded in the data log file of the TTS software and PicoScope start  
22 recording the data with a resolution of 1 ms. PicoScope is connected to the TRANSUFIMO Treatment Work-  
23 station via USB cable. A code written in LabVIEW is utilised for recording data via PicoScope. Below is the user  
24 interface of the LabVIEW code (Figure 3b) for collecting data from the hydrophone (Channel A) and TTL  
25 box (Channel B) as a trigger pulse to record data. The hydrophone system has its own software to  
26 control its hardware.





1

2 Figure2 Schematic drawing of configuration of the experiment by using hydrophone via PicoScope  
 3 for measuring sonication duration and the delay after 'stop sonication command' is issued.

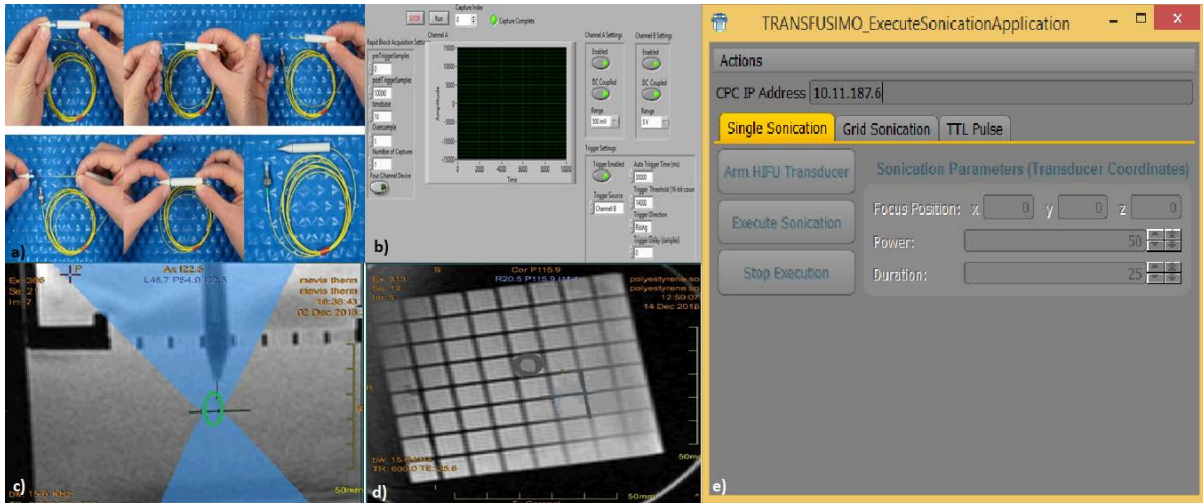
4 Sonicating was performed using the TTS software. MR imaging was used to monitor sonicating to the  
 5 tip of the sensor as shown in sagittal (Figure 3c). and coronal views (Figure 3d). The sonication is  
 6 monitored via single shot EPI MR Sequence of 512 phases, with TE: 26.4, TR: 100, flip angle: 40, freq  
 7 phase: 128 x 106 parameters on the MR machine. A sonication is performed using the user interface  
 8 of TTS software. The operator selects the target on the MR image received by the TTS software as  
 9 the focal spot for the transducer to sonicate, also inputs the magnitude of power and the planned  
 10 sonication duration to the user interface of the TTS software for the treatment planning stage.

11 Before sonication starts, the operator activates the arm command, enabling the transducer to send  
 12 almost zero power sonication for a safety check for sonication to start in full power. The tag lines  
 13 are generated in the data log of TTS software, when the arm command is activated and for the time  
 14 information when the sonication ends.

15 Once the setup is tested for feasibility, experiments are executed for the planned sonication  
 16 duration of 10 seconds while applying sonication power levels of 50 W, 100W, and 150 W. To

1 produce a meaningful data set, experiments are planned to be repeated for 30 times by two  
2 independent users. To eliminate long treatment planning and monitoring using MR step and for  
3 regular quality assurance (QA) purposes, the TTS software has a Trans-Fusimo Execute Sonication  
4 Application (TESA). With the recorded coordinate values after the first successful feasibility test, the  
5 TESA application is used to eliminate MR monitoring and imaging time. This protocol enables  
6 repeatability experiments to take place in shorter amount of time with a faster sonication  
7 procedure. TESA requires only the magnitude of electrical power, the focal position, and the  
8 duration of planned sonication as an input and does not use MR monitoring (Figure 3e).

9 In the user interface of TESA application, pressing the 'Arm HIFU Transducer' button initialises the  
10 transducer and makes it ready for instant sonication, i.e., the transducer is powered up and the  
11 elements are configured to random phases with almost-zero output power. Once arming is  
12 complete, the sonication is executed by pressing the 'Execute Sonication' button. The sonication  
13 duration is completed by running a loop of 250-ms sonication intervals (due to safety reasons) until  
14 the planned duration time is reached. Once this loop is complete, sonication is stopped  
15 automatically. The 'Stop Sonication' button is used to simulate emergency stop button by providing an  
16 input power of 100 W. This button is activated randomly to measure the delay after sonication is  
17 stopped by pressing this button. A tagline is recorded with the time information into the database  
18 of the TTS software. The same experiment set-up was used by two independent operators and the  
19 sonications are repeated for 30 times.



1

2 **Figure3 a)** Mounting the tip of the sensor into the sensor pen shaped sensor holder **b)** User interface  
 3 of the Labview code for collecting data via Picoscope using the fiber optic sensor of the hydrophone  
 4 initiated by the TTL pulse **c)** Sagittal and **d)** Coronal views of the sensor during sonication **e)** TRANS-  
 5 FUSIMO execute sonication applying, enabling sonication with the coordinates obtained from the  
 6 MR images initially, eliminating the MR monitoring for repeatability experiments to be performed in  
 7 shorter time for a realistic time frame.

8

9 **3.3 Data Processing**

10 The time information for the TTL pulse, the ‘execute’ command and the ‘stop’ commands were  
 11 recorded as a tag line with the computer clock time information in the log book of the TTS software.  
 12 This information is also recorded in the user interface of the PicoScope when the sonication is  
 13 executed as demonstrated in Figure4a. The TTL pulse time is used as an origin to calculate the actual  
 14 duration of the sonication signal in Pico scope’s time frame. The deviation is calculated by  
 15 subtracting the actual sonication duration from the planned sonication duration [Eq1]. Actual  
 16 duration is defined as defined by Eq2.

17 Deviation= Planned Sonication duration (10 seconds) -Actual Sonication Duration [Eq. 1]

18 Actual Sonication Duration=(t2- t1) [Eq. 2]

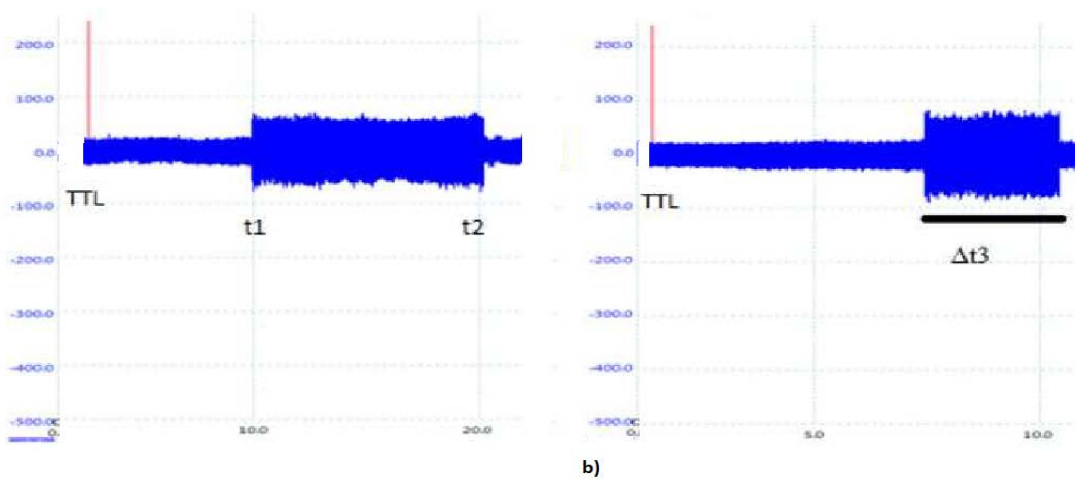
1 where; t2 is the time of the final signal recorded by the PicoScope when TTS stops sonicating, and t1  
2 is the initial time of the peak signal after TTS starts executing sonication, shown as Figure 4a.

3 To calculate the delay, after the sonication stop button was pressed, the synchronised TTL pulse  
4 time was used as an origin again; both in the time frame of PicoScope and in the log book of TTS  
5 software for the time values of execute sonication tag data and stop sonication tag data. The delay is  
6 calculated by the length of the signal on PicoScope ( $\Delta t3$ ) minus the log t [Figure 4 b, Eq. 3].

7 
$$\text{Delay} = \Delta t3 - (-\Delta t1 + \Delta t2) \text{ [Eq. 3]}$$

8 where  $\Delta t3$  is the length of the signal on PicoScope,  $\Delta t2$  is the length of the sonication stop tag and  
9  $\Delta t1$  is the execute sonication tag info in the log book of the TTS software.

10 The data files were extracted from the PicoScope in the form of CSV files for post processing. The x  
11 axis to record the time value when reaching a peak value on the y axis is recorded at the start of  
12 actual sonication data. The values of t1 and t2 were read from the excel files where the signal passed  
13 the threshold noise signal level. The same also applies to calculation of delay for emergency stops.  
14 The graphs are provided in the scale of seconds for demonstration purposes to cover the full signal  
15 length in Figure4, however, the data is collected in the scale of milliseconds.



16 a)  
17 **Figure 4 a)** Picoscope signal recorded by using the fiber-optic hydrophone, red vertical line

1 representing the TTL pulse execution time, serving as an origin for 10 seconds of sonication. **b)**  
 2 Emergency stop signal with an arbitrary duration to measure the delay after stop button is pressed.

3 **4. Results**

4 Using the processed data, average duration and standard deviations were calculated for each soni-  
 5 cation power value; 50 W, 100W, and 150W for 10 seconds and for each independent operator. For  
 6 emergency stops, the results show that the average emergency stop time delay is 14 ms (Std 0.16) by  
 7 the first operator and 13 ms (Std 0.14) by the second operator 2, meeting the specs set previously;  
 8 less than 200 ms. The two-paired T test show that the results do not have user dependency  $p > 0,05$ .

9

10 **Table 1.** Results for planned '10 second' sonication duration for (50, 100, and 150 W) of sonication  
 11 by two independent operators.

Operator 1	Power Values for 10 seconds		
Power	50 W	100 W	150 W
Measured Actual Duration	9.84	9.85	10.05
Deviation	-0.16 (Std 0.33)	-0.15 (Std 0.35)	0.05 (Std 0.22)
Operator 2	Actual Sonication Duration		
Measured Actual Duration	50 W	100 W	150 W
10 seconds	9.85	9.83	10.02
Deviation	-0.15 (Std 0.35)	-0.17 (Std 0.33)	-0.02 (Std 0.24)

12

13 **5. Discussions**

14 The procedure and the set-up is simple enough for any other user to implement the same technique  
 15 in any other lab or in clinical settings. The strength of TESA application is that it enables quality assur-  
 16 ance time to be minimised leaving more time for clinical usage. By analysing the signal forms, we were  
 17 able to identify errors in the system and make corrections in the phase id numbers and correct  
 18 memory allocations by refreshing the memory information in the TTS software during the feasibility  
 19 tests. The designed methodology enabled fixing the errors when multiple sonications were performed  
 20 by the operator and memory allocation problems were resolved. By using the TTL pulse as an origin  
 21 for recording the data, enabled us to calculate the deviation between the planned sonication duration

1 and the actual sonication. The results show that there is a decrease in deviation of sonication duration  
2 for power values more than 100 W. This could be explained that system has higher inertia for high  
3 power values.

4

5 Before using this system, in clinical settings, it is strongly recommended to perform this protocol and  
6 report any deviations from the specifications. This recommendation is also in line with the studies  
7 conducted in literature which were mainly used for evaluation of already approved clinical systems in  
8 clinical settings [5-9] for maintenance purposes according to quality management system. The pro-  
9 tocol can identify the faults in the system easily, as it is possible to observe the changes in signal in-  
10 formation from the screen of the PicoScope. The weakness of the protocol is the post processing time.  
11 To eliminate this problem, TESA application was enabled to extract special tag line information from  
12 the database of the software; such as arm command, execute sonication command and stop soni-  
13 cation command information. This enabled faster post-processing of the data.

14

15 In clinical applications, emergency stop is executed mostly when the operator or the patient needs to  
16 stop the treatment. This study is also unique in measuring the delay after the emergency stop button  
17 is pressed, drawing attention to important steps in translation of science into clinical applications dif-  
18 ferent than other studies available in literature [5-9]. For this reason, the tolerance value for emer-  
19 gency stop delay was set as 200 ms by the clinicians of the TRANS-FUSIMO consortium according to  
20 the best clinical practice. The experiment results show that the delay after stop command is executed  
21 is 14 ms (std 0.16), meeting the predefined specifications for a safe application in clinical settings.

22

## 23 **6. Conclusion**

24 Results provide evidence that with the used methodology TTS can successfully drive the transducer of  
25 CBS Exablate 2100. The developed protocol is capable of measuring duration of sonication as docu-  
26 mented according to the requirements of ISO 13485 standards. The TTS can control the duration of

1 sonication within the defined specs for the planned and emergency stops. The evidence collected by  
2 the designed protocol proves that TTS meets the safety standards for controlling the sonication dura-  
3 tion. After proving that the system can control sonication duration, the next step is to develop meth-  
4 odologies for other process parameters, such as thermometry which requires strict MR imaging to  
5 collect thermometry information using the multi-baseline thermometry methodology and also soni-  
6 cating to a desired spot with a certain accuracy.

7 After successful evaluation of the TTS software, confirming to the ethical guidelines, the next step is  
8 the testing of the system on animals. This study demonstrates the importance of detailed testing to  
9 prevent sacrifice of animals without demonstrating enough evidence for the expectation of a success-  
10 ful outcome from the clinical trials.

## 11 **7. Acknowledgements**

12 This work was supported by the European Community's Seventh Framework Programmes  
13 (FP7/2007-2017) and (FP7/2014-2019) under grant agreement numbers 270186 (FUSIMO project)  
14 and 611889 (TRANS-FUSIMO project).

## 15 **8. Funding**

16 This work was supported by the European Community's Seventh Framework Programmes  
17 (FP7/2007-2017) and (FP7/2014-2019) under grant agreement numbers 270186 (FUSIMO project)  
18 and 611889 (TRANS-FUSIMO project).

## 19 **9. Competing interests**

20 Authors declare that they have no competing interests.

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