FOCUSED ULTRASOUND FOUNDATION

Guidelines for treatment reporting

Introduction

The guidelines outlined in this document aim to fulfill three main objectives:

- To ensure consistency in reporting FUS treatment parameters, in order to allow cross-comparison of studies performed by different groups and/or with different systems
- To provide guidelines for assessing and reporting bioeffects associated with different FUS treatment regimens, necessary for (1) cross-comparison of studies, (2) validation of therapeutic bioeffects
- To provide guidelines for testing the FUS systems and protocols

The guidelines are divided into five sections: (1) overall recommendations for important reporting parameters, (2) detailed methodologies for measuring/simulating FUS system and field parameters, (3) detailed methodologies for assessing bioeffects, (4) dosimetry quality assurance (DQA) procedures for FUS equipment, and (5) relevant standards and references.

While these guidelines were written for both pre-clinical and clinical studies, some of the treatment information described below may be more useful and would be more readily provided for pre-clinical rather than clinical studies, especially if there is a commercial entity involved, and will have to be adapted on case by case basis.

These guidelines were drafted by the Focused Ultrasound Foundation with input from several focused ultrasound scientific and technical experts. They were disseminated via the Foundation's newsletter and website, and have been made open for public comments, and were revised following reception of these initial comments. We envision these guidelines to remain a living document that will be regularly updated based on users feedbacks.

Recommendations

1. Operational parameters reporting

The following must be considered:

- FUS transducer & system
  - See **Reporting on FUS transducer & system**
  - See **Reporting DQA procedures**
- Frequency (Hz or equivalent), bandwidth
- Axial and radial beamplots of the acoustic pressure field (Pa) and/or quantification of the Intensity (W/m^2 or equivalent unit of Power/Area)
  - See **Reporting acoustic output parameters: power and intensity**
  - See **Reporting acoustic field: hydrophone measurements**
  - See **Reporting numerical simulation**
- Acoustic output power (W or equivalent unit of Energy/time)
  - See **Reporting acoustic output parameters: power and intensity**
  - See **Reporting numerical simulation**

2. Treatment parameter reporting

The following must be reported:

- Treatment duration (s or equivalent)
- Total treatment time vs actual treatment delivery (on) time
- If pulsed: pulse repetition rate and pulse duration (or number of acoustic cycles per pulse or duty cycle), and any appropriate complementary description of the pulsing regime, or for histotripsy the number of pulses per treatment spot
- Acoustic Pressure/Intensity/Power levels used for the treatment
- Target tissue type(s)
- Depth of treatment
- Position of transducer relative to tissue/anatomy
- If multiple spots are treated: sequential positioning of the treatment spots, duration at each spot, waiting time between spots if any. If using handheld probe system, treatment spot positioning strategy, duration, waiting time if any.
- If microbubbles or other cavitation agents are used, composition, dose, method of injection
  - See **Reporting use of microbubbles**

3. Treatment bio-effect reporting

The following should be given:

- If using thermal effects: Thermal dose, peak and average temperature, temperature maps, recorded over time
  - See **Recommendations for temperature monitoring**
- Localization, monitoring method, type and level of cavitation activity
  - See **Recommendation for reporting on cavitation monitoring**
- Targeting accuracy, lesion formation, changes in biomarkers
  - See **Recommendation for validation of induced bio-effects**

Detailed Methodologies

1. Reporting on methodologies used to measure/simulate/derive FUS system and field parameters

The guidelines on how to report FUS treatment parameters follow the guidelines published in reference [1] to determine and report the exposure conditions used in studies.

Reporting on FUS transducer & system

- Transducer geometry (plane v. focused, single v. multiple elements, diameter, focal length, f-number, positioning of elements if multiple, backing material v. air-backed), material (PZT, other ceramics…), and characterization (impedance, use of matching circuit, center frequency, frequency bandwidth). At minima: transducer geometry, center frequency and bandwidth
- When using non-commercial or clinical systems: Drive electronics: references to function generator, amplifier (including manufacturer)

Reporting acoustic field: hydrophone measurements

- Hydrophone manufacturer and modeln hydrophone type (e.g., membrane, needle, capsule, fiber optic …)
- Hydrophone characteristics: diameter, sensitivity (frequency response for the range of therapeutic frequencies, or at least center frequency of the hydrophone), dynamic range, hydrophone calibration, hydrophone precision/accuracy
- Scanning grids: interval between steps, dimensions of the grid
- Hydrophone data collection: sampling rate, filtering, amplifier or preamplifier
- Spatial-variation of peak-negative and peak-positive pressure: as a minimum measured along three orthogonal axes, one of which being the direction of propagation of the ultrasound beam.
- Temperature at which the measurements were performed
- At minima, ensure that the information included in the documentation follow specifications of measurement standards (such as the 60601 series, see the “Standards” section at the end of the guidelines)

Hydrophone measurements

Measurements should be made to determine at least the maximum values of peak negative and positive acoustic pressures. The pressure variations should be measured along at least three orthogonal axes, one of which should be the direction of propagation of the ultrasound beam. The spatial interval between sample points may be different on each axis; but the interval should be sufficiently small to demonstrate the main features of the spatial variation.

A key requirement on acoustic measurements made by hydrophone is a report of the overall uncertainty.

The description of the hydrophone set-up will include hydrophone diameter, sensitivity (frequency response for the range of therapeutic frequencies, or at the transducer driving frequency for CW), dynamic range, its calibration (how and where), precision/accuracy; description of the data collection methods including sampling rate, filtering (if filters used), amplifier or preamplifier.

Treatment reports should include methods employed (if any) to correct (i.e., deconvolve) for the distorting effects of frequency-dependent sensitivity [17,18] and spatial averaging [19]. If no methods were employed, that should be stated also.

For precise recommendation on the use of hydrophones to characterize acoustic fields for medical applications, refer to the IEC standards[1]. Particularly, these standards provide recommendations on relevant hydrophone characteristics given specifications of the therapeutic transducer, the acoustic parameters to be measured, the derived intensity parameters, and the definition of measurement procedure that may be used for the determination of acoustic pressure parameters.

Commercial scanning tanks are available[2], and in-house systems can be designed. The FUS Foundation for example will publish a blueprint for how to build one's own 3D-printed, computer-driven motorized system to be used with hydrophones for acoustic field calibration.

Because of the technical difficulty of measuring these acoustic outputs with a hydrophone and force balance, some laboratories may not be able to undertake these measurements themselves. In that case, we recommend contacting laboratories who do have the necessary expertise, or companies providing these services, and the need to involve one of these should be factored into a study from the start. A list of potential sites is provided in Annex 1 (Medical Ultrasound Test Measurement Laboratories), and the Focused Ultrasound Foundation can connect you with appropriate laboratories if needed.

Measurements for characterization of the acoustic field pressure and intensity should be performed in water to allow comparisons between centers. If estimated values of in situ acoustic pressure or intensity are reported (for instance, by using a derating factor), the method for calculating the in situ value should be fully explained and a worked example given. Note that it is generally not correct to use a derating factor of 0.3 $dB.cm^{-1}.MHz^{-1}$ to estimate the in situ values of intensity or acoustic pressure that are relevant to the occurrence temperature rise, cavitation or other mechanical effects. An estimate of the transmission loss of the propagation path should be used instead.

If high pressures are to be measured, the use of a fiber optic or membrane hydrophone [2] will be necessary to assess whether nonlinear propagation and the associated phenomenon of acoustic saturation are significantly affecting the in situ exposure levels.

[1] IEC 62127-1:2007+AMD1:2013 CSV ; IEC 62127-2:2007+AMD1:2013+AMD2:2017 CSV ; IEC 62127-3:2007+AMD1:2013 CSV

[2] Examples of commercially available scanning systems: Onda http://www.ondacorp.com/products_testingsol_scanningsystem.shtml; Precision Acoustics https://www.acoustics.co.uk/product/ums3-scanning-tank/

Temperature and water quality will affect the measurements. Water should conditioned, highly filtered (0.2 um, preferably) and degassed. While a physiological temperature of 37 C° would be preferable, it is often practically easier to perform the measurement at room temperature, and this should be reported.

Reporting acoustic output parameters: power and intensity measurement

The following are needed:

- Description of the radiation force balance system, including accuracy/precision
- Acoustic power as a function of voltage to the transducer
- Frequency, pulsing or scanning regime
- Transducer efficiency
- Acoustic intensity
- Uncertainty of these measurements

Power and intensity measurement

Measurements should be made to determine at least

1. the total output power
2. the spatial-peak temporal-average intensity of the field (and the distance from the transducer at which these measurements are taken)

Radiation force will provide a measurement of the acoustic output power for a given set of electrical inputs. Reports should include a description of the radiation force balance system, including its accuracy/precision, and how acoustic power measurements were performed. For details on the procedure for force balance measurements, refer to the IEC standards (see IEC 61161 or IEC 62555.)

Operational parameters, including the acoustic frequency, pulse repetition rate (or an appropriate description of any pulsing or scanning regime), and pulse duration (or number of acoustic cycles per pulse) should be given over the relevant range of output powers.

The acoustic power should be measured for different transducer drive voltages to provide a plot of power versus voltage.

Estimating the transducer efficiency (ratio of output acoustic power to input electrical power) will require a measure of the input electrical power, and its method of measurement should be provided as well.

Quantities such as intensity must be calculated by combining the power measurements with field measurements (e.g. hydrophone or field simulations). The method of calculation of intensity from these measurements should be detailed, including the area over which the intensity is calculated (see for example [9,10].)

All these measurements have uncertainties that must be estimated, and a description of how uncertainty was derived should be provided.

While it may not be possible for commercial entities to precisely report some of these information as they can be proprietary, such as the efficiency of the transducer, information about the delivered acoustic power using treatment settings should be provided.

Reporting numerical simulation

The following are important:

- Model equation
- Numerical implementation
- Code verification
- Parameters modeled
- Coupling of the system
- Software used
- System discretization
- Material parameters and transducer characteristics
- Sensitivity analysis
- System geometry
- Initial and boundary conditions
- Outputs simulated at each point
- Limitations of the model

Numerical simulations

Numerical simulations of acoustic fields are a useful tool for designing a treatment scheme and/or validating experimental measurements.

The FDA has published detailed guidance on reporting the results of simulations[3], from upon which this section is based. The document has sections on both ultrasound propagation modeling and heat transfer, and we strongly recommend referring to these guidelines.

Several tools are available for numerical modeling, some in open format, such as the HITU Simulator developed by the FDA[4] or k-wave developed by University College London and Brno University [5]. Both run on Matlab and include some form of bioheat equation solving to predict heating and calculation of thermal dose in tissues.

Detailed reporting should include:

- Model equations including propagation model (full wave, parabolic, linear or non-linear), frequency dependence of attenuation if modeled, assumptions underlying the propagation model used

[3] https://www.fda.gov/media/87586/download
[4] https://www.fda.gov/about-fda/cdrh-offices/hitu-simulator;
[5] http://www.k-wave.org

- Numerical implementation, such as finite difference method or finite element method
- Code verification, method used to assess the accuracy of the model's predictions (bench methods, experimental data…)
- Parameters modeled (pressure or displacement), fluid or solid model (shear wave taken into account)
- Coupling of acoustic field simulation with thermal effects, streaming, …
- Software used (commercial, user-developed…)
- System discretization: spatial mesh (uniform, non-uniform), simulation timepoints…
- Configurations: material parameters (organ/tissue specifics) including speed of sound, density, absorption, coefficient of non-linearity; and if heat transfer is also modeled (such as bioheat equation) heat capacity, thermal conductivity, perfusion rate, and transducer characteristics (acoustic power, frequency, pressure/phase distribution), dependence of these properties on other variables such as temperature or frequency.
- Sensitivity analysis: if uncertainties are associated with the data, it is relevant to perform a sensitivity analysis to estimate the effect of uncertainties on the simulation results
- System geometry: details about device (single element geometry, where multiple elements include arrangements of the elements, dimensions) and tissue geometry modeled (anatomical features included, if anatomy generated from images, describe the technique used, any scaling or similarities used in the modeling approach)
- System conditions, including initial and boundary conditions
- Outputs simulated at each point (pressure, temperature….)
- Results from the computational modeling, recommended to be provided over a range of parameters
- Limitations of the model and how this might affect the output

Reporting use of microbubbles and other cavitation agents

- Characteristics of the agents (size, composition…) or reference if commercial agents
- Concentration/dilution
- Injection method
- Dose

Microbubbles / Cavitation agents

If the treatment involves the use of microbubbles (MB) for therapeutic effects, such as BBB opening, MB characteristics, dose, injection method has to be reported precisely as they will affect response to ultrasound. This information should include:

- Type of agents: commercial or homemade, size distribution characterization (device used, when was it measured with respect to treatment time, where - straight out of the vial or at the other end of the injection setup), composition including shell and gas
- Agents concentration, dilution if any before injection

- Injection method (bolus v. infusion, single v. repeated injection, injection volume), syringe (gauge), if infusion is used give infusion rate and infusion duration
- Dose, amount of injected agents (such as number of agents /kg)
- Injection volume

2. Reporting on the methodologies to assess bio-effects

Reporting temperature monitoring

If using thermocouple

- specifications (type, size)
- locations
- parameters (temporal sampling, duration)
- accuracy
- artefacts & their mitigation

If using MRI thermometry:

- sequence specifications
- maps of peak temperature over time
- average temperature in the treatment zone over time
- voxel size (spatial averaging resolution)
- accuracy (temperature resolution)
- estimated thermal dose at the treatment location

Thermal dosimetry

Monitoring of the temporal evolution of temperature allows calculation of the thermal dose (or thermal isoeffect dose) delivered, or a cumulative equivalent minutes at 43 °C (CEM43°C), which has been demonstrated as an empirical estimator of induced necrosis. Monitoring and reporting thermal effects induced by a treatment is essential to allow comparison of treatment regimens and to estimate a thermal dose, average, and peak temperature reached. Basic temperature monitoring will include the use of thermocouples, and the use of multiple thermocouples at several locations can give information about the temperature distribution within the tissues. For temperature mapping, MRI thermometry, such as PRF-based MR thermometry [3], seems to be the most reliable option although it is not always available. Temperature maps can be recorded as a function of time, to estimate temporal variation of peak temperature, average temperature in the treatment zone over time, and the thermal dose at the treatment location. These maps should be recorded over a time span which that covers a pre-measurement to estimate noise, the treatment duration and the cool-down phase.

For MRI thermometry, reporting should include:

- specifications of the sequence used to estimate temperature
- resolution of the maps (voxel size)

- method of calculation for each map (what is quoted, average - over which area, or peak?)
- For temperature maps recorded over time:
  - include pre- and post-treatment phases
  - include estimated peak temperature, average temperature in the treatment zone, and the thermal dose at the treatment location
- For thermal dose maps: thermal-dose contour maps, including the threshold value for damage for the organ of interest

For ultrasound image-based systems, options include tissue change monitoring (thermal mapping) [4], and visual changes in the US images during treatment [5].

The use of a thermocouple requires some precautions, as artefacts may give incorrect readings: the presence of a thermocouple changes the environment at the point of interest and may introduce a systematic error. To minimize errors, particularly sources of errors such as thermal conductivity and the effect of the difference in heat capacity between the thermocouple wire and the surrounding tissue, the wire diameter of the thermocouple should remain small, ideally 1/20, of the wavelength of ultrasound field [11].

An important artifact remains however and must be accounted for. This arises from the difference in density between the thermocouple wire and the surrounding tissue leading to relative motion between the two and giving rise to so-called “viscous heating” at the thermocouple-tissue interface [11]. Viscous heating leads to a very rapid increase in the temperature which distorts measurements. The induced artifact can comprise 80% of the measurement when using wire thermocouples [14].
Thermocouples that do not exhibit viscous heating exist, such as thin-film thermocouples (TFT) [14], are not widely available and are not suitable for in-vivo experiments, limiting their use to phantom or ex-vivo experiments.

One common compensation method for the viscous artifact is the “wait then measure” approach; because the temperature rise due to viscous heating initially increases rapidly and then levels off, it is assumed that waiting at the end of the insonification will allow the temperature rise due to viscous heating to decay sufficiently. Different waiting periods have been proposed, from 0.2 to 0.5s after the cessation of FUS exposure [12, 13]. Although such a method will provide more confidence in the results, there is also no consistency as to whether corrections for viscous heating are made or not, and it has been reported that the corrected temperature rise determined with the “wait and see” approach depends on the thermocouple type, beam width of the HIFU beam, and radius of the viscous heating distribution, and should not be used without careful consideration [14].

More complete compensation approaches use numerical simulations to evaluate the viscous heating, the heating due to ultrasound absorption in biological tissues, the temporal behavior of the artifact and the effects of the thermocouple diameter, and then remove the contribution of the viscous heating from experimental temperature rises [15].

Cavitation, and the presence of bubbles, can induce artifacts in temperature monitoring, especially for MR thermometry, and strategies to avoid or compensate for these artifacts

should be reported. Cavitation may also artefactually influence thermocouple reading and should be closely monitored.

Reporting cavitation monitoring

If using simple PCDs:

- PCDs specifications: frequency bandwidth, number, positions
- PCD signal acquisition: sampling frequency, number of points acquired, description of signal processing method applied, such as how frequency spectra were derived, filters used
- Specifications of the metrics used to quantify cavitation, such as computation of sub-harmonic power, broadband power, harmonic or ultra-harmonic power, what thresholds or metrics were used to assess presence/absence of cavitation activities

If mapping cavitation:

- Specifications of the experimental system, such as the imaging array, multiple PCDs…
- Description of the algorithms used to process the signal and localize cavitation, when possible (e.g. if not proprietary for commercial entities)
- If imaging cavitation using conventional imaging scanners, specification of the imaging mode used (B-mode, contrast mode…)
- Specifications of the metrics used to quantify cavitation, such as computation of sub-harmonic power, broadband power, harmonic or ultra-harmonic power, what thresholds or metrics were used to assess presence/absence of cavitation activities, when possible (e.g. if not proprietary for commercial entities)

Histotripsy

- Description of the method used to assess bubble activity (US, MRI)
- Description of the method used to assess treatment efficacy/changes in tissue structure (US imaging, optical imaging, histology, MRI imaging)

Cavitation

Cavitation, such as sustained inertial or non-inertial cavitation seeded by microbubbles is now used as a therapeutic mechanism to enable increased delivery and penetration of drugs across the blood-brain barrier or into tumors.

The treatment results will depend on the sonication parameters, the characteristics of microbubbles or other cavitation agents used if any, such as their size, composition, concentration, dose injected, injection method and rate, and the tissue or tumor type and location. All these parameters should be carefully reported.

So-called pulsed-ultrasound also potentially rely on the generation of cavitation bubbles to induce bioeffects.

In addition to reporting treatment characteristics, monitoring of cavitation activity is also required to localize and quantify the effects. Several real-time monitoring strategies have

been proposed that rely on passive cavitation monitoring with a single transducer or hydrophone, or on spatiotemporal monitoring, such as passive cavitation imaging. For histotripsy in particular, image guidance schemes are preferable for quantifying the bubble cloud activity and assessing treatment location.

Tissue liquefaction techniques – cavitational histotripsy, and boiling and shock wave histotripsy – rely on bubble cloud activity to liquefy tissues mechanically. Methods for characterizing histotripsy treatments have been reviewed in detail in [16]. For histotripsy image guidance, assessment of bubble activity and treatment efficacy, B-Mode echogenicity is the most ubiquitous parameter since the bubbles cloud generated will hyper-echoic on a B-mode ultrasound imaging, whereas liquefied tissue appears hypo-echoic.

However, there have been reports of significant variability between patients, preventing quantification of B-mode images. An alternative modality to B-mode imaging for localization of the cavitation cloud is triangulation using PCDs, or so-called passive cavitation imaging (PCI) utilizing an ultrasound imaging array to detect and beam-form acoustic emissions generated by the mechanical oscillations of bubbles.
Bubble clouds can also be visualized using MRI, although the timing between the therapy pulse and the imaging gradients is critical for monitoring cavitation, and the sensitivity of MR sequences to bubble cloud formation is low compared with acoustic methods. Bubble cloud motion, which can be used as a surrogate marker for tissue destruction, can be monitored with color Doppler. Tissue liquefaction however may be better characterized by MRI, as histotripsy ablation zones can be clearly visualized immediately post-insonation with T1- or T2-weighted imaging, or using acoustic elastography since a strong decrease in tissue elasticity occurs during fractionation. After treatment however, acoustic elastography becomes difficult to perform as tracking of the shear wave becomes difficult in the hypo-echoic focal zone. This will limit the accuracy of elastography techniques for delineating the liquefied zone.

Reporting on the validation of induced bio-effects

Targeting accuracy

- Provide an estimate of the actual focal location relative to the desired location
- Explain how the target location was determined

Thermal treatments

- Histology (H&E): for necrosis, especially in case of thermal coagulation
- NADH staining: for early assessment of protein denaturation following thermal FUS
- IHC: for cell death, apoptosis & other death mechanisms
- CEUS to assess loss of perfusion in treated area

Histotripsy

- Histology (H&E) to demonstrate histotripsy-like tissue liquefaction and acellular debris, any hemorrhage or edema

Biomarkers

- When appropriate, monitor expected changes in biomarkers pre- and post-treatment values, such as PSA in prostate cancer treatment
- Other biological markers, such as the number of circulating tumor cells or the frequency/phenotype of immune cells, can also be monitored but will be more relevant for response monitoring than the for validation of treatment efficacy

Bioeffects

The validation of the tissue response is required to clearly demonstrate that the intended bio-effects were effectively induced.

Standard histology staining such as H&E can reveal necrosis in treated areas, especially in the case of thermal coagulation. Note that it may take time for the thermal coagulation to be clearly visible on H&E staining, and for early assessment of protein denaturation following thermal FUS, NADH staining is preferable (see [6] for example.) Damage such as tissue liquefaction induced by histotripsy can be clearly identified with standard histology imaging, and H&E stained histological sections of the lesion should contain sharply demarcated homogenized tissue areas.

For drug delivery applications, assessment of efficacy will have to be made on a case-by-case basis, for example using reporters to assess drug distribution and concentration with PET, MRI, fluorescence or bioluminescence imaging post-treatment, or quantification on tissue samples post-mortem using imaging or direct drug quantification such as amount of drug/g. of tissue using HPLC for example..

DQA procedure

Reporting DQA procedures

- Specifications of the DQA processes

    - Use of phantom, hydrophone or RFB measurements, …
    - Specifications of phantom, hydrophone…
- Frequency/schedule of the DQA
- Metrics assessed (lesion formation, thermometry, …)

DQA procedure

A DQA procedure should be used to provide a rapid and efficient method to assess the consistency of the FUS transducer output. When possible, using a phantom approved by the FDA as a "medical device development tool" (MDDT) could enable a more streamlined regulatory pathway for the treatment device in the USA.

The FDA has released a report[6] on a MDDT-qualified tissue mimicking material (TMM) for preclinical acoustic performance characterization of HIFU devices, intended as a standard material that can be used for acoustic performance evaluation during high intensity therapeutic ultrasound (HITU) bench testing. Although the TMM was developed to match literature values of soft tissue acoustic properties, it cannot replicate the complexity or the thermal response of tissue thermal ablation and thus should not be used for these purposes in lieu of ex-vivo or in-vivo tissues, as FUS-induced temperature rises in the TMM may differ from soft tissues. The TMM has acoustical properties in the range of non-fatty soft tissues and is formulated to assist in the design evaluation phase of HITU Class II or Class III devices operating at clinically relevant parameters. The report provides the formulation, a standardized generic recipe, the characteristics and guide for use in performing tests of HIFU lesioning in the TMM under MRI thermometry. Cavitation can occur in this phantom, but the threshold for cavitation is not reported. It is however recommended to use a new phantom should cavitation occur.

Different types of thermo-sensitive phantoms can also be fabricated in the laboratory, using for example bovine serum albumin (BSA) as a surrogate marker to ensure that the temperature for tissue coagulation is reached with the device and treatment parameters [7]. BSA can be coupled with thermochromic ink to make a so-called tissue-mimicking thermochromic phantom (TMTCP) for direct visualization and quantification of HIFU heating [8]. These TMTCP have properties comparable to those of human soft tissues, and upon heating, exhibit incremental but permanent color change for temperatures between 45 and 70°C, allowing post-treatment quantification of a lesion formed, which can also be detected with MRI thermometry and hypointense regions on T2-weighted MRI.

Pieces of fresh chicken breast or bovine liver can also be used in a first pass to monitor formation of thermal lesion, as coagulated tissues are very easy to distinguish in these two types of tissue.

Other phantoms are under development. The AAPM has a task force developing and validating a phantom specifically for MRIgHIFU. This phantom is currently being assessed by different laboratories around the USA & Europe and should soon be commercially available

[6] https://www.fda.gov/media/128803/download

through the phantom manufacturer CIRS[7]. Low cost thermochromic phantoms that can very easily be homemade and used to monitor any drift in a HIFU system's output are also under development (amongst others by the FUS Foundation.)

Treatments that don't rely on thermal mechanisms, but rather on mechanical effects, is an area where the development of phantoms is needed.

Standards

It is not the scope of these recommendations to provide guidance on how to meet regulatory requirements in the characterization of the treatment systems, but below is a list of some of the standards to be followed for measurements and reporting for regulatory submissions in accordance with the IEC 60601 series standards.

- IEC 60601-2-5 Ed. 3.0. Medical Electrical Equipment – Part 2-5: Particular requirements for the safety of ultrasonic physiotherapy equipment. 2009.
- IEC 60601-2-36 Ed. 1.0. Medical Electrical Equipment – Part 2-36: Particular requirements for the safety of equipment for extracorporeally induced lithotripsy. 1997.
- IEC 60601-2-37 Ed. 2.0. Medical Electrical Equipment – Part 2-37: Particular requirements for the safety of ultrasonic medical diagnostic and monitoring equipment. 2007.
- IEC 60601-2-62: Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment
- IEC 61161:2013 Ultrasonics - Power measurement - Radiation force balances and performance requirements
- IEC 62555: Ultrasonics - Power measurement - High intensity therapeutic ultrasound (HITU) transducers and systems
- IEC/TS 62556: Ultrasonics - Field characterization - Specification and measurement of field parameters for high intensity therapeutic ultrasound (HITU) transducers and systems
- IEC 61846 Ed. 1.0. Ultrasonics – Pressure pulse lithotripters – Characteristics of fields. 1998.
- IEC 62359 Ultrasonics Ed. 2.0. Field characterization - Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields. 2010.
- IEC 61689 Ed. 2.0 Ultrasonics – Physiotherapy systems – Field specifications and methods of measurement in the frequency range 0.5 MHz to 5 MHz. 2007.
- IEC 61847 Ed. 1.0 Ultrasonics – Surgical Systems - Measurement and declaration of the basic output characteristics. 1998.
- EN45502-1 Section 22.1: Active implantable medical devices. 1998

[7] https://www.cirsinc.com

- ISO14708 1: 2014 - Implants for surgery -- Active implantable medical devices -- Part 1: General requirements for safety, marking and for information to be provided by the manufacturer.
- AIUM NEMA UD3 Standard for real time display of thermal and mechanical acoustic output indices on diagnostic ultrasound equipment. 2004 – Revision 2
- AIUM NEMA UD2 Acoustic output measurement standard for diagnostic ultrasound equipment. 2007

References

1. ter Haar, G. *et al.* Guidance on Reporting Ultrasound Exposure Conditions for Bio-Effects Studies. *Ultrasound Med Biol* **37,** 177–183 (2011).
2. Zhou, Y., Zhai, L., Simmons, R. & Zhong, P. Measurement of high intensity focused ultrasound fields by a fiber optic probe hydrophone. *J. Acoust. Soc. Am.* **120,** 676–685 (2006).
3. Rieke, V. & Butts Pauly, K. MR thermometry. *J Magn Reson Imaging* **27,** 376–390 (2008).
4. Sanghvi N, Chen W, Carlson R, Weis C, Seip R, Uchida T, Marberger M. Clinical validation of real-time tissue change monitoring during prostate tissue ablation with high intensity focused ultrasound. Journal of Therapeutic Ultrasound (2017) 5:24 DOI 10.1186/s40349-017-0102-2
5. Illing RO, Leslie TA, Kennedy JE, Calleary JG, Ogden CW, Emberton M. Visually directed high-intensity focused ultrasound for organ-confined prostate cancer: a proposed standard for the conduct of therapy. BJU Int. 2006;98:1187–92.
6. Hijnen, N. *et al.* Thermal combination therapies for local drug delivery by magnetic resonance-guided high-intensity focused ultrasound. *Proc. Natl. Acad. Sci. U.S.A.* **114,** E4802–E4811 (2017).
7. Lafon C , Zderic V, Noble ML, Yuen JC, Kaczkowski PJ, Sapozhnikov OA, Chavrier F, Crum LA and Vaezy S. Gel phantom for use in high-intensity focused ultrasound dosimetry. Ultrasound Med Biol. 2005, 31(10): 1383-1389.
8. Avinash Eranki, Andrew S. Mikhail, Ayele H. Negussie, Prateek S. Katti, Bradford J. Wood & Ari Partanen (2019) Tissue-mimicking thermochromic phantom for characterization of HIFU devices and applications, International Journal of Hyperthermia, 36:1, 518-529, DOI: 10.1080/02656736.2019.1605458
9. Harris, G. R. A discussion of procedures for ultrasonic intensity and power calculations from miniature hydrophone measurements. *Ultrasound Med Biol* **11,** 803–817 (1985).
10. Zhou, Y., Zhai, L., Simmons, R. & Zhong, P. Measurement of high intensity focused ultrasound fields by a fiber optic probe hydrophone. *J. Acoust. Soc. Am.* **120,** 676–685 (2006).
11. Fry W J and Fry R B 1954a Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes: Theory *J. Acoust. Soc. Am.* **26** 294–310
12. Fry W J and Fry R B 1954b Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes *J. Acoust. Soc. Am.* **26** 311–7
13. Hynynen K, Martin C J, Watmough D J and Mallard J R 1983 Errors in temperature measurement by thermocouple probes during ultrasound induced hyperthermia *Br. J. Radiol.* **56** 969–70
14. Morris, H., Rivens, I., Shaw, A. & Haar, ter, G. Investigation of the viscous heating artefact arising from the use of thermocouples in a focused ultrasound field. *Phys Med Biol* **53,** 4759–4776 (2008).
15. Tiennot, T., Kamimura, H. A. S., Lee, S. A., Aurup, C. & Konofagou, E. E. Numerical modeling of ultrasound heating for the correction of viscous heating artifacts in soft tissue temperature measurements. *Appl. Phys. Lett.* **114,** 203702 (2019).

16. Bader K B, Vlaisavljevich E, Maxwell A, Review FOR WHOM THE BUBBLE GROWS : PHYSICAL PRINCIPLES OF BUBBLE. 45 (2019) 1056–1080. doi: 10.1016/j.ultrasmedbio.2018.10.035.

17. Wilkens V and Koch C, “Amplitude and phase calibration of hydrophones up to 70 MHz using broadband pulse excitation and an optical reference hydrophone,” J. Acoust. Soc. Amer., 115, pp. 2892–2903, 2004.

18. Wear K A, Gammell P M, Maruvada S, Liu Y, and Harris G R. Improved Measurement of Acoustic Output Using Complex Deconvolution of Hydrophone Sensitivity, IEEE Trans Ultrason. Ferroelectr., and Freq. Contr. 61, 62-75, 2014.

19. Wear K A and Howard S M. Correction for spatial averaging artifacts in hydrophone measurements of high-intensity therapeutic ultrasound: an inverse filter approach, IEEE Trans Ultrason. Ferroelectr., and Freq. Contr. 66, 1453-1464, 2019.

ANNEX 1: Medical Ultrasound Test Measurement Laboratories

National Physical Laboratory (NPL)
Hampton Road, Teddington, Middlesex, TW11 0LW, UNITED KINGDOM
Tel: 020 8977 3222
https://www.npl.co.uk/acoustics

Physikalisch-Technische Bundesanstalt (PTB)
Bundesallee 100
38116 Braunschweig, GERMANY
https://www.ptb.de/cms/en/research-development/subject-areas-in-metrology/acoustics-ultrasound-acceleration.html

Acertara Acoustic Laboratories
1950 Lefthand Creek Lane
Longmont, CO 80501, USA
Tel: +1 303.834.8413
https://www.acertaralabs.com/

ONDA Corporation
1290 Hammerwood Avenue
Sunnyvale, CA 94089, USA
Tel: +1 408.745.0383
http://ondacorp.com/
http://www.ondasonics.com/

Precision Acoustics Ltd
Hampton Farm Business Park
Higher Bockhampton
Dorchester, Dorset DT2 8QH, UNITED KINGDOM
+44 (0) 1305 264669
https://www.acoustics.co.uk/

Schaffer Acoustics Inc.
943 Embury St. Los Angeles, CA 90272, USA
Tel: +1 310-459-6463
http://www.schaffer-acoustics.com

TUV SUD
TÜV SÜD Aktiengesellschaft

Westendstraße 199
80686 München, GERMANY
Phone: +49 (0)89 5791-0
info@tuev-sued.de
https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/medical-devices-and-ivd/medical-device-testing/physical-testing-of-medical-devices/ultrasound-testing

F2labs
26501 Ridge Rd
Damascus, MD 20872, USA
301-253-4500
https://f2labs.com/medical-equipment-testing-certification?gclid=CjwKCAjw5Ij2BRBdEiwA0Frc9bgEF2D7xG1WQnYSHQk2Q601MvrTH_ZMXzfvx6nT2zE42LOPqoaHTRoC3WEQAvD_BwE

Istituto Nazionale di Ricerca Metrologica (INRIM)
Strada delle Cacce, 91
10135 Torino, ITALY
tel: +39 011 3919 1
https://www.inrim.eu/services/metrology-services

TÜBİTAK National Metrology Institute (TÜBİTAK UME)
TÜBİTAK Gebze Yerleşkesi
P.K. 54 41470 Gebze/KOCAEL, TURKEY
(262) 679 50 00
http://www.ume.tubitak.gov.tr

National Institute of Metrology Standardization and Industrial Quality (INMETRO)
BRAZIL
https://www4.inmetro.gov.br/