Recommendations for reporting therapeutic ultrasound treatment parameters

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Abstract

These recommendations are intended to provide guidance and to encourage best practice in reporting therapeutic ultrasound treatment parameters. Detailed uniform reporting will allow testing of therapy ultrasound systems and protocols, cross-comparison of studies between different teams using different systems, and validation of therapeutic bioeffects. These recommendations have been divided in two sets, one for clinical, and one for preclinical studies, each with stratified reporting categories, to account for the disparities in expertise and access to equipment between sites. They are intended to be useful for clinicians and researchers, for ethical and funding review boards and for the editors and reviewers of scientific journals.

Keywords: Therapy ultrasound; HIFU; FUS; exposure parameters; intensity; acoustic pressure; acoustic cavitation; histotripsy
Rationale

This paper’s intent is to provide guidelines for reporting therapeutic ultrasound treatment parameters. It is a companion paper, and extension to, previously published guidance on reporting ultrasound exposure conditions for bio-effects studies (Haar et al. 2011).

Detailed uniform reporting is necessary for testing therapy ultrasound systems and protocols, for cross-comparison of studies between different teams using different systems, and for validation of therapeutic bioeffects. Two separate sets of recommendations are proposed, for clinical, and preclinical studies, respectively, since the question being addressed may be slightly different for these two applications. For clinical studies, the guidelines reflect what is needed to repeat or compare treatments, whereas for preclinical studies the reporting should also aid the understanding of the mechanisms of action behind the response to treatment. Clinical treatment reporting should therefore include details of the system - including the transducer, guidance method, details of exposure parameters (and their monitoring, regimes and placement), percentage of target covered, and outcome measures such as imaging or histology. Pre-clinical treatment reporting should include more detail about the acoustic exposure and treatment monitoring, and would be expected to include more detailed outcome measures including imaging, histology, functional studies and/or biomarkers.

The list of characteristics to be reported is largely informed by an understanding of the bio-effects that produce therapeutic effects, the extensive pre-clinical research literature that is available, and, to a lesser extent, by existing clinical experience. As the clinical database grows, and the number of clinical devices in use expands, it is expected that these guidelines will need periodic
At the time of writing, the number of clinical applications of therapeutic ultrasound is expanding rapidly, with the most common being thermal ablation of uterine fibroids, prostate cancer and the ventral intermediate nucleus (Vim) in the treatment of essential tremor. A number of trials are underway to establish, for example, the use of therapeutic ultrasound for delivery of drugs across the blood brain barrier, the mechanical disruption of tissue for the treatment of cancer and the stimulation of the immune system. The Focused Ultrasound Foundation’s website maintains a comprehensive list of these applications that is updated annually, and it is to be expected that the range will change over time as clinical need varies, and competing techniques come in and out of favour.

Reporting categories

We propose a stratification of the reporting into categories, to account for the disparities in expertise and access to equipment between sites.

3 reporting categories are defined:

- **Minimum**: as the name suggests, this category provides the minimum level of detail that is acceptable for reporting (at conferences & for publication). This is intended for sites using clinical equipment without access to calibration facilities, and for which the only information available about treatment parameters is that given on the machine used, and by the manufacturer;

- **Medium (or standard, intermediate...)**: a more inclusive list of details is required, with some measure of the acoustic field. This is intended for research oriented clinical units, and some, more biological, laboratories;
• **Optimum**: a counsel of perfection! This category provides extensive details of the treatment parameters. This may be difficult to achieve for many clinical units, but research labs should be aiming for this level of reporting.

For pre-clinical applications, we propose that only the two last categories should apply. It is generally expected that more information about the characteristics of pre-clinical equipment will be available than for a commercial clinical system, and/or that calibration measurements would be more easily accessible, even for commercial systems.

The details of each category are given in the Table 1 below, and the following sections describe what should be reported in more detail.
Reporting recommendations

FUS transducer & system

Characteristics of the therapeutic system should include, at a minimum, information about the transducer geometry, its fundamental frequency and bandwidth.

What should be reported?

- Transducer geometry
  - plane v. focused, single v. multiple elements,
  - diameter,
  - focal length, f-number,
  - positioning of elements if multiple,
  - backing material (or air backing)

- Transducer material (PZT, other ceramics...)

- Transducer characterization
  - impedance, use of matching circuit,
  - center frequency, frequency bandwidth

- When using non-commercial or clinical systems:
  - Drive electronics: references to function generator, amplifier (including manufacturer)
Power and intensity measurements

Power and intensity should always be reported, as they give information about potential bioeffects. While it may not be possible for commercial entities to report some of the information listed below precisely, since they may be proprietary, information about the efficiency of the transducer and the acoustic power delivered for specific treatment settings, at least, should be provided.

What should be provided?

- Frequency, and pulsing or scanning regime (including pulse length & pulse repetition frequency).
- Acoustic power as a function of voltage to the transducer. Description of the radiation force balance system where used, including accuracy/precision
- Transducer efficiency (include method of measurement of the electrical power)
- Acoustic intensity:
  - spatial variation of temporal-average and peak intensities of the field, 3D or axial + radial beamplots of the acoustic pressure field (Pa) and/or quantification of the intensity within the region of interest,
  - or, at a minimum, the spatial-peak temporal-average intensity at the target site (and the distance from the transducer at which these measurements are taken)
- Uncertainty in all measurements
- Derated values: estimate of in-situ values, accounting for absorption losses caused by propagation through overlying tissues
Acoustic field (hydrophone measurements)

Measurements should be made to determine at least the maximum values of peak negative and peak positive acoustic pressures. 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. Where the pressure is expected to be sufficiently high that hydrophone damage might be expected, measurements should be made at a reduced (‘safe’) level, and extrapolated. The method of extrapolation should be described.

What should be reported?

- Spatial-variation of peak-negative and peak-positive pressure:
  - as a minimum measured at targeted treatment position (and the distance from the transducer at which these measurements are taken), or
  - along three orthogonal axes, one of which being the direction of propagation of the ultrasound beam, over a distance covering the main focus and the first lobe of the transducer’s pressure field or
  - spatial variations in 2D or 3D

- Hydrophone
  - manufacturer
  - model and 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 and calibration,
• Scanning grids: interval between steps, dimensions of the grid

• Hydrophone data collection:
  o  sampling rate, filtering, amplifier or preamplifier
  o  Temperature at which the measurements were performed

• Methods employed (if any) to correct (i.e., deconvolve) for the distorting effects of
  frequency-dependent sensitivity and spatial averaging

• At a minimum, 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)

• Derated values: estimate of in-situ values accounting for absorption losses caused by
  propagation through overlying tissues

**Numerical simulations**

Numerical simulations of acoustic fields are a useful tool for designing a treatment scheme
and/or validating experimental measurements. Reporting should allow other groups to
reproduce similar computations and should contain information on the model, its numerical
implementation, parameters used and simulation validation.

**What should be reported?**

• Model equation (linear or non-linear?)

• Numerical implementation (for example, finite difference or finite element method?)

• Code verification methodology
• Parameters modeled (pressure or displacement, fluid or solid model)
• Coupling of the acoustic field simulation with thermal or streaming
• Software used
• System discretization (spatial mesh uniform or non-uniform, simulation timepoints…)
• Material parameters and transducer characteristics
• Sensitivity analysis
• System geometry
• System conditions, including initial and boundary conditions
• Outputs simulated at each point
• Limitations of the model

**Quality assurance (QA) procedures**

A QA procedure should be used to provide a rapid and efficient method of assessing the FUS transducer output stability. Wherever possible, use of a phantom approved by the FDA as a “medical device development tool” (MDDT) will enable a more streamlined regulatory pathway for the treatment device in the USA (the report entitled “MDDT Qualification Decision Summary (Q180407)” is available online on the FDA website).

**What should be reported?**

• Specifications of the QA processes
  o Use of phantom, hydrophone or RFB measurements, ...
  o Specifications of phantom, hydrophone...
• Frequency/schedule for performing QA
• Metrics assessed (lesion formation, thermometry, ...)
Cavitation monitoring

Cavitation monitoring should provide information about the presence/absence of cavitation activity, the cavitation behavior such as sustained inertial or non-inertial, and potentially its localization and spatial distribution.

What should be reported?

If using passive cavitation devices (PCDs):

- PCD specifications: frequency bandwidth, number, positions, frequency & spatial response at the depth of measurement
- PCD signal acquisition: sampling frequency, number of points acquired, sampling mode, characteristic of amplifier if used, description of signal processing method applied (for example, how frequency spectra are 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 are used to assess presence/absence of cavitation activities, method of determination of background signal level, where possible (e.g. if not proprietary for commercial entities)
- Where possible, the spatio-temporal distribution of cavitation activity should be reported, along with the ultrasound exposure leading to this distribution

If mapping cavitation:
• Specifications of the experimental system, such as the imaging array, multiple PCDs etc

• Description of the algorithms used to process the signal and localize cavitation, where 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 are used to assess presence/absence of cavitation activity, method of determination of background signal level, where possible (e.g. if not proprietary for commercial entities)

Histotripsy:

• Type of histotripsy being used – intrinsic or boiling?

• 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)

Thermal dosimetry

Temperature monitoring should provide information on temporal and spatial temperature changes induced by the treatment. These temperature changes should be recorded over a time span that covers a pre-measurement period (to estimate noise), the treatment duration and the cool-down phase.
What should be reported?

If using thermocouple

- specifications (type, size)
- number and locations
- recording parameters (temporal sampling, duration, type of logger)
- accuracy
- artefacts & their mitigation
- Temperature recorded over time, include pre- and post-treatment phases

If using MR thermometry:

- specifications of the sequence used to estimate temperature including a discussion of the limitations arising from the tissue types being interrogated (for example, MR thermometry in fatty tissue requires a different approach from other soft tissues (Baron et al. 2014))
- method of calculation for each map (what is quoted, average - over which volume, or peak?)
- maps of peak temperature 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
- average temperature in the treatment zone over time
- voxel size (spatial averaging resolution)
- accuracy (temperature resolution)
• estimated thermal dose at the treatment location: thermal-dose contour maps, including the threshold value for damage for the organ of interest

Microbubbles and other cavitation agents

If the treatment involves the use of cavitation agents, such as microbubbles (MB) for opening the blood-brain-barrier, MB characteristics, dose, and injection method must be reported precisely as they will affect response to ultrasound.

What should be reported?

• Type of agent: microbubbles, nanocups, ... commercial or homemade

• Reference if commercial agents

• Concentration/dilution (if any) before injection

• Injection method
  o bolus v. infusion (if infusion, infusion rate and duration)
  o single v. repeated injection
  o injection volume
  o syringe (gauge)

• Dose, amount of injected agents such as number of agents /kg

• Characteristics of the agents
  • Composition including shell and gas
  • If measured, size and size distribution characterization (device used, timing of characterization with respect to usage)
Validation of induced bio-effects

It may be crucial to validate whether the intended bio-effects have been effectively induced, in particular during the phase of pre-clinical technical development, or when treatment monitoring is not easily applicable.

What should be reported?

Targeting accuracy

- Estimate of the actual focal location relative to the desired location
- Explanation of how the focal location was determined

Ablative treatments

- Demonstration and extent of cell death

Non-ablative treatments (that can include drug delivery, hyperthermia...)

- Needs to be a case-by-case assessment on how to demonstrate that the intended bioeffect was effectively induced. This can include imaging, blood biomarkers...

Brief review of how these requirements can be achieved

It is out of the scope of these recommendations to provide guidance on how to perform the proposed characterization of FUS systems, or on how to meet regulatory requirements in the characterization of the treatment systems, and here we only provide suggestions for methodologies.
Power and intensity measurement

Radiation force balances allow 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 of procedures for force balance measurements, refer to the IEC standards (see IEC 61161 or IEC 62555 in Annex 2).

It is important in reporting these measurements that 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) are reported over the relevant range of output powers.

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 (Harris 1985; Zhou et al. 2006)).

All these measurements have uncertainties that must be estimated, and a description of their derivation should be provided.

Hydrophone measurements

For precise recommendations on the use of hydrophones for characterising acoustic field distributions for medical applications, refer to the IEC standards (see Annex 2). In particular, these standards provide recommendations about relevant hydrophone characteristics, for
specific therapeutic transducers, the acoustic parameters to be measured, the derived intensity parameters, and the definition of measurement procedures that may be used for the determination of acoustic pressure parameters. A key requirement for acoustic measurements made with a hydrophone is a report of the overall uncertainty and its determination.

Commercial scanning tanks are available (such as systems from Onda, Sunnyvale, CA, USA, or Precision Acoustics, Dorchester, UK), and in-house systems can be designed. The FUS Foundation for example recently published a blueprint for how to build one’s own 3D-printed, computer-driven motorized system to be used with hydrophones for acoustic field calibration (Clinard et al. 2021).

Because of the technical difficulty of measuring acoustic output with a hydrophone and force balance, some laboratories may not be able to undertake these measurements themselves. In this case, we recommend contact with laboratories who do have the necessary expertise, or companies that provide these services. The need to involve one of these should be factored into a study from the start. A list of potential sites is available in Annex 3: Medical Ultrasound Test Measurement Laboratories.

Acoustic field pressures and intensities should be characterised in water to allow comparisons between centers. Temperature and water quality will affect the measurements. Water should be 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, but the relevant temperature should be reported.
If estimated values of in situ acoustic pressure or intensity are reported (for instance, by using a derating factor), the method for calculating these 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 relevant to the occurrence of 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 (Harris 1985) will be necessary to assess whether nonlinear propagation and the associated phenomenon of acoustic saturation are significantly affecting the in situ exposure levels.

Methods of correcting (deconvolving) for the distorting effects of frequency-dependent sensitivity (Wear et al. 2014; Wilkens and Koch 2004) and spatial averaging (Wear and Howard 2019) have been published.

DQA procedure

The FDA has released a report on an Medical Device Development Tools (MDDT)-qualified tissue mimicking material (TMM) for preclinical acoustic performance characterization of HIFU devices (the report entitled “MDDT Qualification Decision Summary (Q180407)” is available online on the FDA website). This is 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 designed 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, since FUS-induced temperature rises in the TMM may differ from that in soft.
tissues. The TMM has acoustic properties in the range of non-fatty soft tissues and is formulated to assist in the design evaluation phase of High Intensity Therapeutic Ultrasound devices classified by the FDA as Class II or Class III devices (with potential moderate or high harms respectively), operating at clinically relevant parameters. The report provides the formulation, a standardized generic recipe, the characteristics, and a guide for use in performing HIFU lesioning tests in the TMM while monitoring using MR thermometry. Cavitation can occur in this phantom, but the threshold is not reported. It is however recommended that a new phantom be used should cavitation occur. Different types of thermo-sensitive phantoms can also be made in the laboratory, using, for example, bovine serum albumin (BSA) as a surrogate marker to ensure that the temperature required for tissue coagulation is reached with the device and treatment parameters (Lafon et al. 2005). 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 (Eranki et al. 2019). 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 the formation of thermal lesions, as coagulated tissues are very easy to distinguish visually in these two types of tissue. Other phantoms are under development. The American Association of Physicists in Medicine (AAPM) has a task force developing and validating a phantom specifically for
MRgHIFU. This phantom is currently being assessed by different laboratories around the USA & Europe and should soon be commercially available through the phantom manufacturer CIRS (Norfolk, VA, USA). 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 in a number of centres.

Phantoms relevant to treatments that do not rely on thermal mechanisms, but rather on mechanical effects, require urgent development, although a simple method for use in pre-clinical studies has been described (Maxwell et al. 2010).

**Numerical simulations**

Several tools are available for numerical modeling, some in open format, such as the HITU Simulator developed by the FDA or k-wave developed by University College London and Brno University (see Annex 4 for freely available simulation tools). Both run on MATLAB and include some form of bioheat equation solution to predict heating, and to calculate thermal dose in tissues.

The FDA has published detailed guidance on reporting the results of simulations, on which our reporting recommendations are based (the document issued on September 21, 2016, and entitled “Reporting of Computational Modeling Studies in Medical Device Submissions », is available on the FDA website). The document has sections on both ultrasound propagation modeling and heat transfer, and we strongly recommend reference to these guidelines.
A description of the simulations should include the propagation model used and its underlying assumptions (full wave, parabolic, linear or non-linear), and the frequency dependence of attenuation if included. Several methods can be used to assess the accuracy of the model predictions, such as bench methods or comparison with experimental data. If uncertainties are associated with the input data or parameters, their effects can be estimated by performing a sensitivity analysis. Similarly, it is often useful to provide the results from computational modeling over a range of parameters. A description of the system geometry should include details about device (single element geometry, or, where multiple elements, arrangements of the elements, and dimensions) and tissue geometry modeled (anatomical features, where anatomy is derived from images, describe the technique used, and any scaling or similarities used in the modeling approach). Other factors that must be included are: material parameters (organ/tissue specifics) including speed of sound, density, absorption, coefficient of non-linearity; and where heat transfer is also modeled (such as bioheat equation) heat capacity, thermal conductivity, perfusion rate, and transducer characteristics (acoustic power, frequency, pressure/phase distribution), and dependence of these properties on other variables such as temperature or frequency.

**Thermal dosimetry**

It is essential to monitor and report thermal effects induced in order to allow comparison of treatment regimens and to estimate the thermal dose, average, and peak temperature reached. Basic temperature monitoring may include the use of thermocouples, with the use of multiple thermocouples inserted in several locations giving information about the temperature distribution at single points within the tissues.
The use of a thermocouple requires some care, 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 (Fry and Fry 1954a).

An important artefact 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 (Fry and Fry 1954a; Fry and Fry 1954b). Viscous heating leads to a very rapid increase in the temperature which distorts measurements. The induced artefact can comprise 80% of the measurement when using wire thermocouples (Morris et al. 2008). Thermocouples that do not exhibit viscous heating, such as thin-film thermocouples (TFT) (Morris et al. 2008), exist but are not widely available and are not suitable for in-vivo experiments, thus limiting their use to phantom or ex-vivo experiments.

One common compensation method for the viscous artefact is the “wait then measure” approach. Since the temperature rise due to viscous heating increases rapidly initially and then levels off, it is assumed that waiting until 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 (Fry and Fry 1954b; Hynynen et al. 1983). 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, width of the HIFU beam, and radius of
the viscous heating distribution, and should not be used without careful consideration (Morris et al. 2008).

For temperature mapping, MRI thermometry, such as PRF-based MR thermometry (Rieke and Pauly 2008), seems to be the most reliable option, although it is not always available. Temperature maps can be recorded in the voxel of interest as a function of time in order to estimate the temporal variation of peak and average temperature in the treatment zone over time, and thus the thermal dose at the treatment location. There is an inevitable trade off between spatial and temporal resolution using this method, an increase in one decreasing the resolution in the other.

Monitoring of the temporal evolution of temperature can allow calculation of the thermal dose (or thermal isoeffect dose) delivered, defined in terms of cumulative equivalent minutes at 43 °C (CEM43°C), which has been demonstrated as an empirical estimator of induced necrosis.

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 artefact and the effects of the thermocouple diameter, and then remove the contribution of the viscous heating from experimental temperature rises (Tiennnot et al. 2019).

Cavitation, and the presence of bubbles, can also give artefacts in temperature monitoring, especially for MR thermometry, and strategies for avoiding, or compensating for these artefacts should be reported. Cavitation may also artefactually influence thermocouple readings and should be closely monitored.
Cavitation monitoring

Several real-time cavitation monitoring strategies have been proposed that rely on passive emission monitoring (with a single transducer or hydrophone), or on spatiotemporal monitoring, such as passive cavitation imaging. For histotripsy in particular, cavitation imaging can be used for both quantifying extent of bubble cloud activity and assessing treatment location (Bader et al. 2017).

Tissue liquefaction techniques – intrinsic cavitation histotripsy, 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 (Bader et al. 2019). For histotripsy image guidance, assessment of bubble activity and treatment efficacy, B-Mode echogenicity is the most ubiquitous parameter since the bubble clouds generated appear hyper-echoic on a B-mode ultrasound image, whereas liquefied tissue appears hypo-echoic.

An alternative method for localization of the cavitation cloud is triangulation using PCDs, or so-called passive cavitation imaging (PCI), using 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 histotripsy 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 by 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 this region.

Cavitation is now used as a mechanism to enable increased delivery and penetration of
drugs across the blood-brain barrier, or into tumors, or to mechanically ablate tumor tissue
with histotripsy. Blood-brain barrier opening brings specific challenges for transcranial
cavitation monitoring, where aberration corrections related to the thickness of the skull are
needed. Cavitation monitoring is key to the safety of these treatments, and is also often
employed to verify BBB opening. The details of the strategies employed for cavitation
monitoring and for decisions on safety and efficacy thresholds will have to be reported,
including the frequency bandwidths analyzed. The results of cavitation-based treatments
will depend on the sonication parameters (peak negative pressure, pulse length and pulse
repetition frequency), the characteristics of microbubbles (or other cavitation agents used),
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.

Finally, novel treatment strategies are being deployed that are using cavitation control.
These rely either on open-loop controllers, often to meet an acoustic emissions threshold,
or on closed-loop controllers that aim to maintain the acoustic emissions at a target level.
These cavitation regulation strategies should also be reported.
Validation of bio-effects induced \textit{in vivo}

Several methods can be used to demonstrate the efficacy and spatial extent of an ablative treatment. 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 after exposure for the thermal coagulation that is clearly visible on H&E staining to develop, and, for early assessment of protein denaturation following thermal FUS, NADH staining is preferable (see (Hijnen et al. 2017) for example.) Damage such as tissue liquefaction induced by histotripsy can be clearly identified with standard histological techniques, and H&E stained histological sections of the lesion should contain sharply demarcated homogenized histotripsy-like tissue liquefaction and acellular debris tissue areas, and any hemorrhage or edema. More generally, immunohistochemistry (IHC) can be used to assess cell death mechanisms such as apoptosis.

Imaging, such as perfusion imaging using ultrasound contrast agents (CEUS) can be used to assess perfusion loss in treated areas (Serres-Créixams et al. 2021).

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

Finally, when appropriate, monitoring the expected changes in biomarkers pre- and post-treatment values can be indicative of treatment efficacy. An example of this is the monitoring of prostate specific antigen (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 are more relevant for response monitoring than for the validation of treatment efficacy

Summary and conclusions

This paper is intended to provide guidelines, and to encourage best practice for reporting therapeutic ultrasound treatment parameters.

The parameters described in this document are important for describing a treatment, whether clinical or pre-clinical. Measurements made in water are essential for describing the field incident on the patient (or sample). However, in assessing biological effect, whether for therapeutic benefit or for safety considerations, it is important to know the pressure and/or intensity in the target tissue volume itself. This requires derating (reducing) the value measured during calibration in a water bath to account for attenuation (transmission loss) in the tissue path overlying the target. Conventionally, for diagnostic ultrasound, a constant derating factor of 0.3 dB.cm⁻¹MHz⁻¹ has been used. This may lead to an overestimate of the in situ value, but, while for imaging this is a wise precaution where the concern is for safety, it may lead to a lack of benefit where therapeutic effects are sought. Here, the actual attenuation should be estimated as accurately as possible in order to perform an effective treatment. This requires accurate knowledge of the thickness of the tissue layers, and their attenuation coefficients.

A more challenging problem is presented when trying to account for changes that arise because of non-linearities that occur in high pressure acoustic fields. Non-linear propagation
introduces high frequency components into the ultrasonic wave. These are absorbed in tissue more rapidly than their lower frequency counterparts. Thus an ultrasound beam that is highly non-linear while propagating through water becomes gradually more linear in appearance as it travels through tissue and its high frequencies are attenuated. The problem that presents itself is therefore in interpreting the in situ pressure at the target from that measured in water under free field non-attenuating conditions.

In practice, the beam pressure/intensity is derated as if non-linearity had not been present. In reality, combined effects of diffraction and nonlinearity can lead to asymmetric pressure waveforms, with large peak positive components (containing a large number of harmonics) and a smaller peak negative component that is primarily at the fundamental component of the pulse and can be derated as described. In some cases, where a shock is formed, this may lead to an over-estimate.

A challenging problem with the presence of non-linear propagation remains the possible formation of shock waves at the focus. In the presence of shock waves, the heat deposition in tissues will be increased relative to that for linear harmonic waves at similar intensities. This is a difficult issue to tackle, but theoretical models and software that simulate non-linear propagation (see Annex 4) can be helpful in predicting the presence of absence of shock waves in situ.

Detailed uniform reporting is necessary for testing therapy ultrasound systems and protocols, for cross-comparison of studies between different teams using different systems, and is essential for validation of therapeutic bioeffects. It is expected that these guidelines will be useful for clinicians and researchers, for review boards of ethical and funding committees and for editors and reviewers of scientific journals.
Acknowledgements

An earlier version of these guidelines has been made open for public comment through the Focused Ultrasound Foundation’s newsletter and website. The authors would like to acknowledge the involvement from ultrasound scientific and technical experts for the comments received, these were taken into account in these revised and completed guidelines.

Conflict of interest

GtH has no conflict of interest to declare.

FP has no conflict of interest to declare.

References


**TABLE 1: Reporting categories**

<table>
<thead>
<tr>
<th></th>
<th>Clinical studies</th>
<th>Pre-Clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimum</strong></td>
<td>Technical details of the clinical system as provided by the manufacturer</td>
<td></td>
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<tr>
<td></td>
<td>Treatment protocol, including:</td>
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<td></td>
<td>- Position of transducer relative to tissue/anatomy</td>
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<tr>
<td></td>
<td>- Treatment planning strategy</td>
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<tr>
<td></td>
<td>- Treatment settings: power, duration</td>
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<tr>
<td></td>
<td>- Transducer geometry, center frequency &amp; focal length range</td>
<td></td>
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<tr>
<td></td>
<td>- Where cavitation agents are used: types, quantity, injection mode</td>
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<td></td>
<td>If data monitoring is provided by the system</td>
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<td></td>
<td>- When appropriate based on the known mechanism of action, peak temperature or thermal dose, presence or absence of cavitation</td>
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<td></td>
<td>DQA procedure</td>
<td></td>
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<tr>
<td><strong>Medium / Standard / Intermediate</strong></td>
<td>Minimum level reporting requirements + More detailed information about treatment parameters, transducer and acoustic field:</td>
<td>Treatment protocol, including:</td>
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<tr>
<td></td>
<td>- power, intensity, pressure at focus</td>
<td>- Position of transducer relative to cell or tissue sample/anatomy</td>
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<tr>
<td></td>
<td>- measurement system (RFB, hydrophone)</td>
<td>- Treatment planning strategy</td>
</tr>
<tr>
<td></td>
<td>- transducer characteristics (number of elements, frequency bandwidth...)</td>
<td>- Transducer characteristics: geometry, frequency response, number of elements ....</td>
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<tr>
<td></td>
<td>Detailed temperature information, including details of methodology used</td>
<td>- Where cavitation agents are used: types, quantity, injection mode, methods of characterization</td>
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<tr>
<td></td>
<td>- Thermal dose and temperature maps</td>
<td>- power, intensity, pressure at focus, including details of measurement system used (RFB, hydrophone)</td>
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<td></td>
<td>Treatment monitoring highly recommended. Where performed, details of methodology should be given:</td>
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<tr>
<td></td>
<td>- Temperature, thermal dose &amp; temperature maps where possible and appropriate</td>
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</tbody>
</table>
| Optimum       | Medium level reporting requirements  
|              | + Detailed characterization of the acoustic field, that should include  
|              | - 3D or Axial + radial beamplots of the acoustic pressure field and/or quantified spatial distribution of the intensity within the region of interest. Where intensity is reported, details of the intensity type (peak, average etc)  
|              | Detailed description of monitoring methodologies, including hardware and methods for acquiring  
|              | - Thermal dose, peak and average temperature, temperature maps, recorded over time  
|              | - Localization, monitoring method, type and level of cavitation activity  
|              | If simulations used in treatment planning  
|              | - Model used, software, materials parameters  

|          | Medium level reporting requirements  
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|          | - Model used, software, materials parameters  

- cavitation  
Assessment of bioeffects (histology, ...)  
DQA procedure if any
ANNEX 1  Worked example of reporting for each category

The following examples have been inspired by published reports, but have been modified to provide complete sample texts for each category. The values given below have no clinical relevance.

Minimum level of reporting – Clinical study

The procedure was performed on an MRI guided focused ultrasound system, consisting of a 3 Tesla MRI system (Model, Manufacturer) and the XX FUS system (Model, Manufacturer), which includes a hemispheric, 1024-element, phased-array transducer, (Elias et al. 2013) 30-cm diameter, 15-cm focal length transducer operating at a frequency of 670 kHz. A reference scan was performed in order to position the transducer relative to the target. A series of anatomical MRI scans were fused with the preoperative CT scan for the skull-correction algorithm. After treatment planning, a series of low power sonications (typically, 150 to 250 acoustic W, 10 seconds) that produced temperatures of 40 to 45°C determined by magnetic resonance (MR) thermography confirmed the position of the focus in three orthogonal planes. Therapeutic sonications of 10 to 20 seconds were then performed, gradually escalating the power (starting at 300W, and in steps of 50W) and monitoring the temperature, up to a final sonication which gave temperatures from 55 to 63°C in the maximal voxel as measured using MR thermometry.
Intermediate level of pre-clinical reporting.

Example of reporting the treatment parameters, microbubble usage and cavitation monitoring.

A therapeutic transducer was used. It was a spherically focused 1.1 MHz transducer, 64 mm in diameter with a central opening of 20 mm, 15-cm focal length, 3.3-mm 3-dB beam width at focus (Model, Manufacturer). For treatment planning, an ultrasound linear imaging array was used (center frequency 5 MHz, model AA, Manufacturer YY) and positioned in the central opening of the transducer, so that the focus lay at the center of the tumor imaging plane. For treatment, the focus was positioned at the center of the tumor. The sonication scheme consisted of 50 x 0.1-ms-long pulses spaced 1 ms apart, repeated at 20-s intervals for a duration of 2 mins. Peak negative pressures at the focus were 1.65 +/- x.xx MPa, as measured with a calibrated 0.2-mm needle hydrophone (Model, Manufacturer). The US pulsing sequences began 10 s after the intravenous injection of a 50-mL mixture of diluted MBs (Model, Manufacturer) followed by a 100-mL saline flush. This procedure was repeated once more after a 10-mins interval.

Cavitation levels were assessed in a subset of mice (n = 4) using a focused 15 MHz PCD transducer (2.5-cm diameter, 7.5-cm focal length, broadband 5-15 MHz, Model, Manufacturer) with its focal zone situated within the tumors, overlapping the therapy transducer focus. Received signals were digitized at a 100-MHz sampling rate (Model, Manufacturer), both baseline (pre-injection) and post-injection cases. A 100 MHz sampling frequency ensured reliable representation and avoidance of signals received over the PCD bandwidth. Signals were processed by extracting 50 µs windows from the time trace, and were analysed in the frequency domain using fast Fourier transforms. By implementation of
suitably centred 20kHz bandwidth digital filters around the harmonics of the central
frequency, each trace was separated into its fundamental, harmonic and broadband noise
components. An increase in the broadband noise to greater than 6 standard deviations
above the noise level was considered significant, and indicative of the onset of inertial
cavitation.

To validate that the intended bioeffects had been induced, namely a blood flow stoppage in
the treated area, the tumors were imaged 30 minutes before and 30 minutes after the
treatment with Doppler ultrasound. For Doppler imaging, a high frequency imaging
ultrasound system was used (Model, Manufacturer) with a 30 MHz center frequency
transducer (Model, Manufacturer). 3D volumes were acquired with a step size of 0.2 mm.
The Power Doppler settings were as follows: a clutter-filter cut-off of 1.0 mm/s, a scan
speed of 0.8 mm/s, a pulse repetition frequency of 4 kHz, a power Doppler gain of 20 dB, a
frame rate of ~10 fps.

The microbubbles (MB) used in this study were an experimental agent obtained from
Manufacturer. They have octafluoropropane gas cores encapsulated by pegylated
phospholipid shells. These MBs have number- and volume-weighted mean diameters of 1.1
and 3.7 µm, respectively, based on Coulter counter measurements in the size range 0.7 - 20
µm. After reconstitution with saline, the MBs are at an initial concentration of 3.6x10^8
MB/mL, and were administered in bolus form in a 50-µL injection corresponding to a dose of
9.6 x 10^8 MBs/kg, assuming a 20g weight mouse.
Optimum level of reporting:

Example of acoustic field characterization with hydrophone measurements:

Hydrophone measurements were made across a range of power levels to assess changes in acoustic pressures. A fiber-optic hydrophone (Model, Manufacturer) was attached to a 3-D positioner (Model, Manufacturer). A customised MATLAB (MathWorks, Natick, MA, USA) program was used to control the 3-D positioner, acquire hydrophone signals using a digitizer (Model, Manufacturer), synchronize data acquisition, and process the acquired data. The HIFU system was controlled to generate ultrasound pulses with different acoustic powers (500, 550, 600, or 650 W) at 1.2 MHz frequency, 10 Hz PRF, and 40 cycles/pulse. 2D scans with a 0.5mm step size were acquired initially to localize the position of the focus. 3D scans with a step size of 0.25 mm were then acquired over a 3x3x3 mm cubic volume. At each position, and the peak positive and peak negative pressures were recorded. After completion of the scan, the customised MATLAB program positioned the hydrophone at the position of the detected peak in the volume. Three repeated pressure measurements were then performed at the focus for each power setting to obtain average peak positive and peak negative free field pressure values.
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 60601-2-62: 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

• 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
ANNEX 3 – Medical Ultrasound Test Measurement Laboratories

National Physical Laboratory (NPL)

Hampton Road, Teddington, Middlesex, TW11 0LW, UNITED KINGDOM
Tel: 020 8977 3222
Relevant information can be found on the NPL in the Research area, category “Acoustics”

Physikalisch-Technische Bundesanstalt (PTB)

Bundesallee 100
38116 Braunschweig, GERMANY
Relevant information can be found on the PTB website in the Research and Development category, under the subject area in Metrology “Acoustics, ultrasound, acceleration”

Acertara Acoustic Laboratories

1950 Lefthand Creek Lane
Longmont, CO 80501, USA
Tel: +1 303.834.8413
Relevant information can be found under the “Services” category on the Acertara website.

ONDA Corporation

1290 Hammerwood Avenue
Relevant information can be found under the “Services” category on the Onda website.

Precision Acoustics Ltd

Hampton Farm Business Park

Higher Bockhampton

Dorchester, Dorset DT2 8QH, UNITED KINGDOM

+44 (0) 1305 264669

Relevant information can be found under the “Services” category on the Precision Acoustics website.

TUV SUD

TÜV SÜD Aktiengesellschaft

Westendstraße 199

80686 München, GERMANY

Phone: +49 (0)89 5791-0

Relevant information can be found in the “Indutries/ healthcare-and-medical-devices” section of TUV website, under the “Testing of medical device” category.

F2labs

26501 Ridge Rd
Relevant information can be found in the “Medical Devices” section.

Istituto Nazionale di Ricerca Metrologica (INRIM)
Strada delle Cacce, 91
10135 Torino, ITALY
tel: +39 011 3919 1
Relevant information can be found under the “Services/Metrology” section of the INRIM website.

TÜBİTAK National Metrology Institute (TÜBİTAK UME)
TÜBİTAK Gebze Yerleşkesi
P.K. 54 41470 Gebze/KOCAEL, TURKEY
(262) 679 50 00
Relevant information can be found under the “Industrial services / Calibration” section of the TÜBİTAK UME website.
All the tools listed below are freely available, and can be used to simulate non-linear propagation of ultrasound:

**HITU Simulator, developed by the FDA**

Accessible directly from the FDA website: [https://www.fda.gov/about-fda/cdrh-offices/hitu-simulator](https://www.fda.gov/about-fda/cdrh-offices/hitu-simulator)

**k-wave developed by University College London and Brno University**

Accessible directly from the dedicated k-wave website: [http://www.k-wave.org](http://www.k-wave.org)

See also (Treeby et al. 2020; Treeby and Cox 2010)

**HIFU Beam software**


See also (Yuldashev et al. 2021)

**FOCUS, developed by Michigan State University**
Accessible directly from a dedicated website: https://www.egr.msu.edu/~fultras-web/

See also (Zeng and McGough 2008)

mSOUND

Accessible directly from the dedicated mSOUND page on Github: https://m-
sound.github.io/mSOUND/home

See also (Gu and Jing 2021)